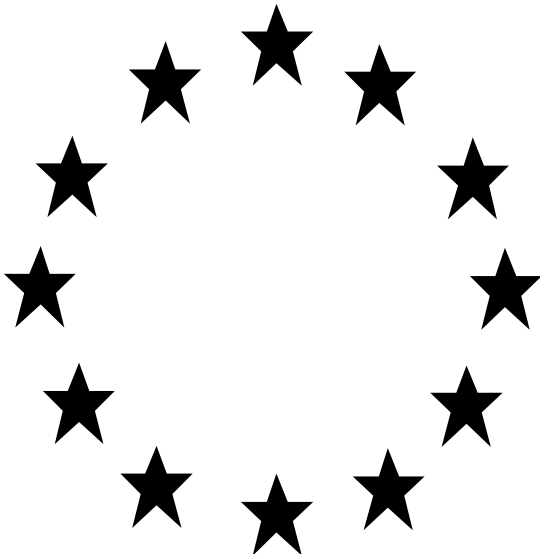

Final addendum to the

Draft Assessment Report (DAR)

- public version -

Initial risk assessment provided by the rapporteur Member State Italy for the existing active substance

CAPTAN

of the second stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC

part 1

January 2006

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Captan

Addendum to Draft Assessment Report:

Environmental fate and behaviour

Rapporteur Member State: Italy

EU review under Directive 91/414 EEC

Relating to Annex B (Volume 3) of the DAR

January 2005

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B.8 Environmental fate and behaviour

Introduction

This document is an Addendum to the Draft Assessment Report (DAR) for the EU review of **captan**. The aim of this Addendum is to address 'Open points' and 'Data requirements' as raised in the official Reporting Table (dated 17.01.05) and Evaluation Table (dated 19.01.05) in the area of **Environmental fate and behaviour**.

This Addendum includes summarisation and evaluation of new studies and risk assessments submitted by Makhteshim Chemical Works Ltd and *Calliope (*formerly, Tomen France S.A.S.).

Section numbering in this Addendum is in line with Annex B (Volume 3) of the DAR.

The Good Agricultural Practice (GAP) uses proposed by the Notifier for consideration under the review are specified in Table 1.

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Table 1: Critical Good Agricultural Practice for captan in the EU review

Crop	Member state or country	Product name	F, G or I	Pests or group of pests controlled	Formulation		Application			Application rate per treatment			PHI (days)	Remarks:
					Type	Conc. of a.s.	method kind	growth stage/ timing	number[b] (max.)	kg a.s./hL (max.)	water L/ha	kg a.s./ha (max.)		
Pome fruit	North EU	'Merpan' 80 WDG / 'Malvin' WDG	F[a]	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 53 / April	9 - 10	0.125	1000	1.25	14	
	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69 / April	9 + 3 [c]	0.125 0.24	1000 1000	1.25 2.4	14	
Tomatoes	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Foliar spray; down-wards	From BBCH 60 to 87	4	0.15	1200	1.8	14	
Peaches/ nectarines	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69: petal fall	4	0.25	1000	2.5	7	

[a] F = field.
[b] Applications at a minimum of 7 days for all crops.
[c] Nine applications at 1.25 kg a.s./ha (scab control) followed by three applications at 2.4 kg a.s/ha (*Nectria* control).

B.8.1 Route and rate of degradation in soil (Annex IIA 7.1.1; Annex IIIA 9.1.1)

B.8.1.1 Aerobic studies

The following is stated in the Evaluation Table:

Data requirement 4.1	Two new laboratory aerobic soil degradation studies. These studies should cover the ranges of pH 4.5 to 5 and pH 8. Metabolites THCY and THPAI should be addressed as well with separate studies if necessary.
Data requirement 4.2	Adequate kinetic analysis of degradation data should be provided for the soil degradation studies (kinetic model employed, goodness of fitting).
Data requirement 4.3	Relevance of field USA study with respect to EU conditions should be assessed.
Data requirement 4.4	DT_{50} values estimated in the laboratory studies for the metabolites THPI and THPAM using first order kinetics should be provided for modelling purposes.

In the Reporting Table, significant issues were raised (comments 4(16), 4(17), 4(18), 4(19), 4(20), 4(23), 4(25), 4(26), 4(27), 4(33), 4(34), 4(35), 4(36), 4(37), 4(38), 4(39), 4(40), 4(51), 4(52) and 4(54)) on the adequacy of the soil degradation studies in the submitted dossier to address the fate and behaviour of captan and its degradation products in soil. The substantive concerns can be summarised as:

- The pH range of the soils employed in the laboratory to investigate soil degradation under aerobic conditions was too narrow,
- Adequate kinetic analysis of degradation data (DT_{50} values, kinetic model employed, goodness of fit) for the soil degradation studies was not provided,
- The relevance to European conditions of the field degradation studies conducted in the USA should be assessed.

The Notifier has submitted an expert review (by Cambridge Environmental Assessments, UK) to address these points and some of the other questions raised in the reporting table, and to address the Data Requirements in the Evaluation Table (as quoted above). This review has been summarised below:

Report: *Terry, A. and Price, O. (2005). Fate of captan in soil under aerobic conditions: A Review. CEA, unpublished report January 2005.*

The report brings together the results of all the fate and behaviour studies conducted on captan and its metabolites that, together (hydrolysis, laboratory soil degradation and field dissipation studies), define the fate and behaviour of captan in soil under aerobic conditions. In addition, where possible DT_{50} values have been calculated using first order kinetics and goodness of fit coefficients given. The relevance of the individual field dissipation studies to European conditions have been evaluated and values recommended for use in PEC_{soil} and PEC_{gw} calculations. Each of these areas is set out below.

Hydrolysis studies

Five hydrolysis studies were briefly summarised (three conducted on captan and one each with THPI and THPAM). The hydrolysis DT_{50} values derived from these studies are summarised in Table B.8.1.1.8. Captan consistently hydrolysed very rapidly (DT_{50} values of 3.6 minutes to 18.8 hours). The fastest degradation rates occurred at alkaline pH values, but even at a pH value of 5, the degradation was very fast (DT_{50} maximum value of 18.8 hours). Given this rapid hydrolysis at all investigated pH values it is very likely that chemical hydrolysis would be a significant degradation pathway in all environmental compartments for captan. The hydrolysis data for the two metabolites, on the other hand, indicated that hydrolysis was likely to be significant only at specific pH's (pH 9 for THPI and pH 4 for THPAM).

Table B.8.1.1.8: Summary of results of hydrolysis studies on captan, THPI and THPAM

			DT_{50}					
		Temp (ºC)	**25**	**29**	**39**	**50**	**60**	**70**
Compound	**Study**	**pH**						
Captan	7.2.1.1/01	5	11 hr					
		7	2.6 hr					
		9	3.6 min					
	7.2.1.1/02	5	18.8 hr					
		7	4.9 hr					
		9	8.3 min					
	7.2.1.1/03	5	11.7 hr					
		7	4.7 hr					
		9	8.1 min					
THPI	7.2.1.1/04	4*	>1 year					
		7*	152 days			137 hr	43.5 hr	14.5 hr
		9*	3 days			5.5 hr	2 hr	1 hr
THPAM	7.2.1.1/05	4*	4 days	53 hr	11.5 hr	3 hr		
		7*	360 days			507 hr	177 hr	70 hr
		9*	>1 year					

*DT_{50} at 25ºC extrapolated from results obtained at other temperatures

Aerobic Laboratory Soil Degradation Studies

Five aerobic soil laboratory degradation studies were summarised (three conducted on captan and one each with THPI and THPAM). The soil DT_{50} values derived from these studies, together with the goodness of fit and soil properties are summarised in Table B.8.1.1.9. Details of the kinetic analysis undertaken for each study were reported in the form of appendices to the report. For all (except study *7.1.1.1.1/03*: *Pack, D.E. 1974 Soil metabolism of [carbonyl-^{14}C] captan*) this analysis took the form of minimising the sums of the squares of the residuals between experimental values and values derived assuming first order decline, using the SOLVER function in EXCEL.

Table B.8.1.1.9: Summary of results of laboratory soil degradation studies on captan, THPI and THPAM

Substance	Study	DT_{50} (days)	Coefficient of fit (r^2)	Soil texture	pH	Organic carbon (%)
Captan	*7.1.1.1.1/01*	0.60	0.87	Sandy loam	7.7	0.41
	7.1.1.1.1/02	0.44	0.99	Sandy loam	7.2	0.7
	7.1.1.1.1/03	1.09	1.00	Sandy loam	6.8	1.03
THPI		8.98	1.00			
THPAM		6.97	0.99			
THPI	*7.1.1.2.1/07*	14.37	0.98	Sand	6.3	0.4
		6.94	0.99	Loamy sand	6.0	2.2
		5.87	0.98	Sandy loam	7.1	1.9
THPAM	*7.1.1.2.1/08*	11.07	0.98	Sand	6.3	0.4
		7.14	0.99	Loamy sand	6.0	2.2
		6.00	0.98	Sandy loam	7.1	1.9

For *7.1.1.1.1/03*, a more sophisticated approach was required to model the formation and decline of THPI and THPAM following application of captan to soil. For this, Modelmaker4 was used with the multi-compartmental first order model given in Figure B.8.1.1.1. The resulting fit of modelled against experimental values was very good (r^2 values of 0.99-1.00 were obtained) and is shown in Figure B.8.1.1.2. The derived DT_{50} values for captan, THPI and THPAM are presented in Table B.8.1.1.9. It was also possible to derive kinetic fractions for the pathways modelled and these are presented in Table B.8.1.1.10.

Figure B.8.1.1.1 Multi-compartmental model used in Modelmaker4 to analyse data from study *7.1.1.1.1/03*

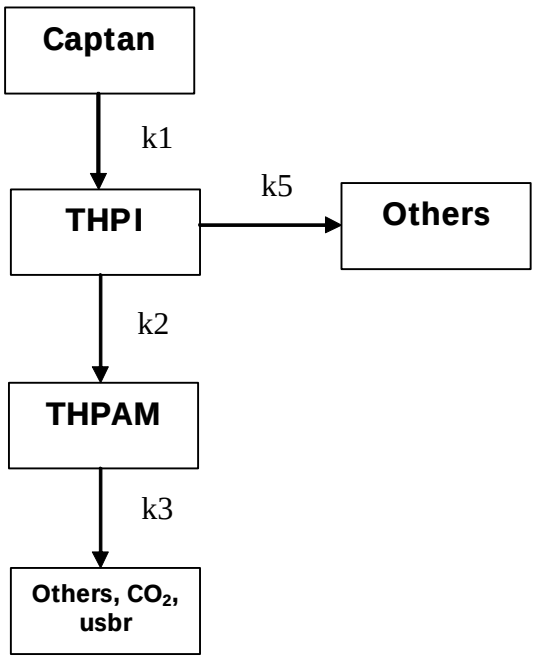
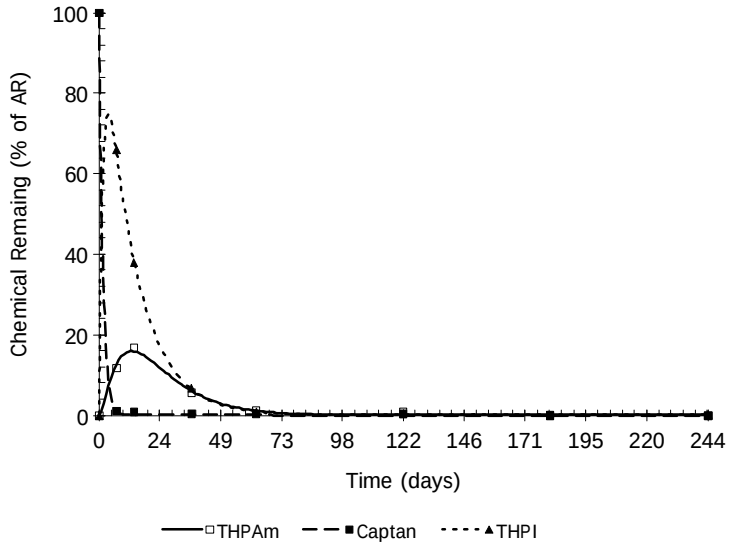


Table B.8.1.1.10: Derived kinetic fractions for the pathways modelled using Modelmaker4 and data from study *7.1.1.1.1/03*

Compound	Kinetic Fraction
Captan	To THPI 1.0
THPI	To THPAM 0.502 To CO_2 etc. 0.498
THPAM	NR

Figure B.8.1.1.2 Plot of modelled against experimental values from study *7.1.1.1.1/03*



Captan was found to degrade very rapidly in soil under aerobic conditions in the laboratory. The derived DT_{50} values for captan were 0.44, 0.60 and 1.09 days. Further, captan degraded *via* THPI to THPAM and then to carbon dioxide. These major soil metabolites in turn degraded rapidly with derived DT_{50} values of 5.87 to 14.37 days (THPI) and 6.00 to 11.07 days (THPAM). Given the similarity of the rate of captan degradation in soil and in aqueous solution and the products of degradation, it is clear that chemical hydrolysis is the most significant process of degradation of captan in soil. Although the aerobic soil degradation studies conducted with captan were in soils with a narrow range of pH values (6.8-7.7), the results of the hydrolysis studies indicate that captan would also be expected to degrade very rapidly in soils of other pH's.

USA Field Dissipation Studies

Investigations under laboratory conditions indicated that degradation of captan and its major soil metabolites did not trigger field dissipation studies (DT_{50lab} <60 days). However, a total of six field dissipation studies were conducted at different locations across the USA and reported in six reports and these studies do provide useful information with respect to the degradation of captan in soil. Each study involved multiple applications of captan (as a formulated product) to a crop at 7 day intervals. All applications were in spring or summer. Processing and analytical procedures were the same for all studies. Levels of captan and THPI were monitored in the soil for variable time periods depending on how rapidly degradation occurred. Generally, significant residues were only found in the top 7.5 cm of soil. The studies were carried out according to USEPA guideline 164-1 and under GLP. The soil properties at each location varied, with soil types ranging from clay to sand and pH values ranging from 4.9 to 7.8.

The results were re-analysed for the review (see Table B.8.1.1.11). Generally, captan and THPI degraded rapidly under field conditions. DT_{50} values for captan were calculated starting from the residues measured from the last application of captan. For THPI, however, calculations started from the maximum residue value for THPI (which varied from 0 days following the last application of captan to 28 days after the last application). This is likely to result in an over estimate for the THPI DT_{50} value. Best-fit values were obtained by applying a first-order decay optimised for both initial concentration (C_0) and the rate constant against the square of the residual using EXCEL SOLVER.

The DT_{50} values for captan ranged from 0.33 to 7.04 days and for THPI ranged from 2.63 to 33.94 days. There was no correlation between the DT_{50} values and the pH of the soils. Captan degraded readily in soils of all pH's.

An analysis was also carried out to determine the relevance of each field study location in the USA to possible locations in the EU. The climatic classification system developed by the geographer Köppen (Köppen, 1923) was used to determine the climate descriptors for each of the locations of the US field studies. Corresponding locations within the EU (where they existed) were then identified. In this way it was possible to determine that for five of the six US locations there were indeed corresponding locations/regions in the EU that had very similar climates (see Table 8.1.1.11). Only the field dissipation study conducted in Lakeland, Florida did not correspond (climatically) with an area in the EU. Four of the field studies were conducted at locations corresponding to climates similar to various locations in Southern Europe, but one (conducted at Waterloo, New York) had a climate corresponding to Helsinki, Finland. This also had the longest field DT_{50} for captan (7.04 days).

Table B.8.1.1.11: Summary of USA field dissipation studies, associated re-calculated DT_{50} values, goodness of fit coefficients and examples of climatically similar locations in the EU

Location (*study*)	Soil pH	Soil organic carbon (%)	Soil texture	Treated crop	Application details (first application)	Köppen classification	Similar EU locations	Captan DT_{50} days (r^2 coef.)	THPI DT_{50} days (r^2 coef.)
Lakeland, Florida (*7.1.1.2.2/07*)	4.9	1.2	Sand	Tomato	4 x 4.48 kg a.s./ha (11 April)	Am	None	3.28 (0.99)	7.41 (0.89)
Waterloo, New York (*7.1.1.2.2/02*)	5.5	1.2	Loamy sand	Apples	8 x 4.48 kg a.s./ha (14 April)	Dfb	Helsinki (Finland)	7.04 (0.91)	2.63 (0.98)
Hillsboro, Oregon (*7.1.1.2.2/04*)	5.6	2.2	Silt loam	Grapes	6 x 2.24 kg a.s./ha (3 June)	Csb	Porto (Portugal), La Coruna (Spain)	3.38 (0.94)	33.94 (0.91)
Gilroy, California (*7.1.1.2.2/06*)	6.9	0.9	Loam	Tomato	4 x 4.48 kg a.s./ha (21 July)	Csb	Porto (Portugal), La Coruna (Spain)	4.21 (0.91)	16.70 (0.87)
Fresno, California (*7.1.1.2.2/03*)	7.1	0.3	Loamy sand	Strawberry	8 x 3.36 kg a.s./ha (14 May)	Csa	Granada (Spain), Badajoz (Spain), Palermo (Italy), Toulon (France)	4.12 (0.98)	4.62 (0.97)
Center Point, Texas (*7.1.1.2.2/05*)	7.8	1.4	Clay	Canteloupe	7 x 2.24 kg a.s./ha (23 June)	Cfa	Toulouse (France), Milano (Italy)	0.33 (1.00)	3.44 (1.00)

Selection of DT_{50} values for calculation of PEC_{GW}

Laboratory DT_{50} values are preferred for the calculation of PEC_{GW} using FOCUS models. According to FOCUS guidance (FOCUS 2000), a mean value is suitable, once the laboratory derived DT_{50} values have been normalised for incubation temperature and soil moisture. The required normalisation process has been carried out for the laboratory values derived for captan, THPI and THPAM (and presented in appendices in the review). The conditions of incubation for study *7.1.1.1.1/03* were not given in the study report, and so for the purposes of the normalisation process it was assumed that conditions often encountered for studies conducted in USA were appropriate (i.e. at 25°C and 1/3 bar). The calculated mean DT_{50} values for THPI and THPAM (mean of four values) were **9.05** and **7.80** days, respectively. For captan there were only three laboratory DT_{50} values available and as such the highest normalised DT_{50} value should be selected (FOCUS 2000). This value was **1.10** days.

Selection of DT_{50} values for calculation of PEC_{soil}
Field DT_{50} values are suitable for use in calculating PEC_{soil} values. In this case, there were five field dissipation studies conducted in the USA which are also applicable to the EU. It is generally considered appropriate to use the longest field DT_{50} value, which in the case of captan corresponds to that found at the Waterloo, New York location which was determined to correspond to conditions in Helsinki, Finland. This DT_{50} value was **7.04** days.

Overall conclusions of the Review
It has been demonstrated that taken all together, the laboratory and field studies in the fate area allow a coherent and credible picture of the fate and behaviour of captan and its major metabolites in soil under aerobic conditions to be constructed, without the need for further studies. For captan and THPI potential influence of soil pH has been fully addressed.

Other issues raised in the Reporting Table but not covered by the above report are addressed below by the following statements provided by the Notifier (ref: Terry, A. 2005. Responses to questions raised in the Reporting Table on fate and behaviour of captan):

Comment 4(16) EFSA: the initial parent concentrations in the soil studies are between six to ten times those intended by the representative uses.

The equivalent application rates quoted in some of the studies were apparently not calculated according to the methods in current use (i.e. assuming uniform distribution into a soil depth of 5 cm and a soil density of 1.5 g/cm^3). As such, the values quoted are significantly higher than would be arrived at now. The actual soil concentrations in the studies are more suitable for use for comparison purposes. In the three captan soil laboratory degradation studies the initial soil concentrations were 8.67 mg/kg, 4.6-6.1 mg/kg and 5.33 mg/kg. The maximum single application rate, according to the proposed GAP, 2.5 kg a.s./ha corresponds to an initial soil concentration of 3.3 mg/kg (without crop interception), but the captan soil concentration arising from the maximum total application (in 12 applications to pome fruit in Southern Europe assuming no degradation) would be 18.45 kg a.s./ha corresponding to 24.6 mg/kg. It is customary to conduct soil laboratory degradation studies at close to worst case test substance concentrations and it can be seen from the considerations presented here that the concentrations used in the laboratory studies were reasonable and no concentration degradation dependence is evident.

The RMS supports the above statement from the Notifier.

Additional comment from Germany (in a letter dated 29.10.04), 4(16): The non-GLP study with carbonyl-^{14}C-labelling is very old (Pack 1974) and the method of differentiation of metabolites is not indicated (TLC?). The validity of the study is questioned. Since the formation of THPI and THPAM is crucial for the evaluation, a repetition of the study is suggested.

The *Pack, 1974* study is old, but was apparently conducted to a high scientific standard. Analytical methods were summarised in some detail in the report and analysis was based on two dimensional TLC with up to 3 different solvent pairs. The results of the study have been subjected to a multi-compartmental kinetic analysis which enabled DT_{50} values for captan, THPI and THPAM to be derived with a very good fit to the experimental data (r^2 values of between 0.99 and 1.00). This analysis is presented in *Terry, A. and Price, O. (2005). Fate of captan in soil under aerobic conditions: A Review,* (see above) which also indicates that the findings of the study are fully consistent with the other fate and behaviour studies. It was clear that hydrolysis of captan was the major route of degradation in all matrices. Taken together,

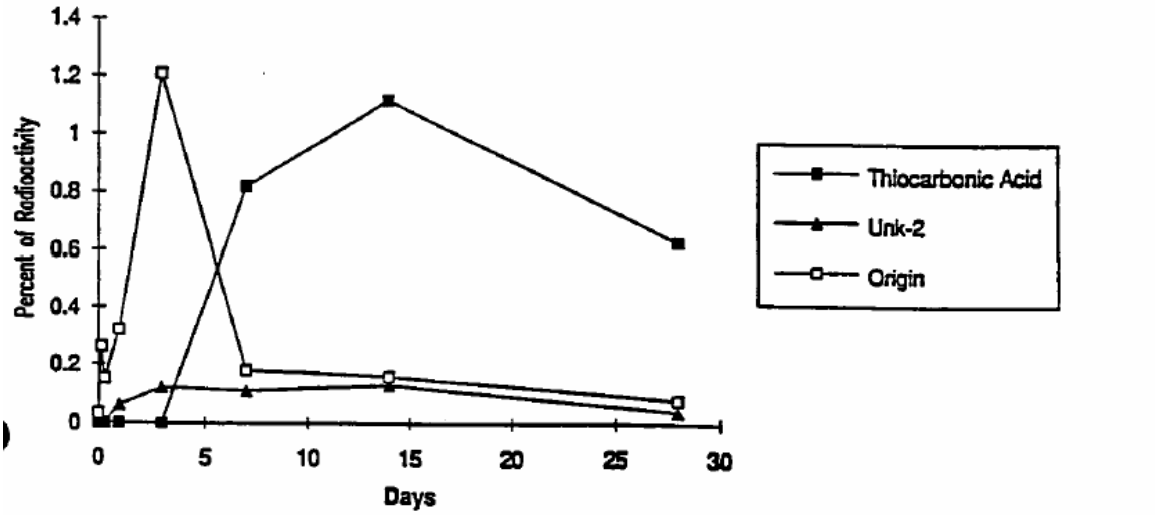
these considerations indicate that the knowledge of the fate of captan in soil is such that further degradation studies are not necessary.

The RMS supports the above statement from the Notifier.

Additional comment from Germany (in a letter dated 29.10.04:, The proposed metabolic pathway (Vol. 3, Fig.8.1.2.1, p. 85) is unclear with respect to the formation of 'thiocarbonic acid' and in relation to the study summaries. With the rapid separation of the ^{14}C-labelled side chain from the nitrogen (e.g. by hydrolysis under sterile conditions?), occurrence of the thiocarbonic acid would be expected earlier.

In *Diaz and Lay, 1992 (7.1.1.1.1/01),* thiocarbonic acid reaches a maximum of 1.12% of applied after 14 days (see Figure B.8.1.1.3). It is a very minor metabolite. The major route of degradation for the side chain clearly rapidly leads to generation of carbon dioxide (50% of applied after 1 day). A more detailed examination of the results presented in this study suggests that the thiocarbonic acid was generated from more polar material that did not chromatograph in the TLC system used (it was 'origin' material). Given that the major route of degradation very rapidly generated carbon dioxide it is clear that the generation of thiocarbonic acid was *via* a very minor side route generating a very small amount of thiocarbonic acid which in turn rapidly degraded. As such, it is considered that the formation and decline of thiocarbonic acid was too minor to warrant inclusion on the proposed metabolic pathway.

Figure B.8.1.1.3: Formation and decline of thiocarbonic acid under aerobic conditions (from 7.1.1.1.1/01)



The RMS supports the above statements from the Notifier.

Overall Response from RMS on the route and rate of captan degradation in soil under aerobic conditions:

The review (Terry, A and Price, O. 2005) evaluates the experimental data on the fate of captan in soil under aerobic conditions, and hydrolysis. The RMS agrees with the conclusion of the expert review that the available data confirm that the dominant transformation route for captan in soil is *via* chemical hydrolysis. As such, captan degradation in soil is very rapid at all pH values. Although the main route of degradation study is old (*Pack, 1974*) close examination of the study report leads to the conclusion that it was conducted to a high standard. This is especially with respect to the analytical procedures followed, as shown by the very good fit to experimental data achieved in the kinetic analysis reported. The RMS agrees with the conclusion of the expert review, that the available data are sufficient to characterise the fate and behaviour of captan (and its metabolites) in soil. Additional data are not necessary. The route of degradation of captan has been adequately defined for risk assessment purposes.

Whilst there are not four *laboratory* DT_{50} values available for captan (there are three) the *field* dissipation data strongly corroborates the laboratory data. As such, and given the rapid degradation of captan in all studies, it is not necessary to request further studies to increase the number of laboratory DT_{50} values available for captan. The Notifier has selected the longest laboratory DT_{50} for use in PEC_{GW} calculations. This is in accordance with FOCUS guidance and is a sufficiently conservative approach.

As stated in the expert review, the field dissipation studies conducted in the USA were very useful for confirming the fate of captan in soil. It should be noted that the undertaking of field studies is not triggered by the laboratory degradation studies for captan nor for the major soil metabolites (DT_{50} <60 days). Hence, field studies are not strictly necessary for the risk assessment process. However, the Notifier has re-calculated the DT_{50} values for captan and THPI and analysed for correspondence of climatic conditions at the field locations with locations in the EU. Five of the six field studies were conducted under conditions similar to those at locations in the EU, with one corresponding to a location in Northern Europe (the study conducted at Waterloo, New York corresponding to conditions in Helsinki, Finland). The Notifier has proposed that the captan DT_{50} derived from this site (7.04 days) be selected for use in PEC_{soil} calculation. The RMS considers this approach to be conservative and appropriate.

B.8.1.2 Supplementary studies

Anaerobic metabolism

Data requirement 4.5	Notifier to provide clarification on deviations of the anaerobic degradation studies(Lay (1992) and Pack et al. (1988b)).

Open point 4.9:
RMS to assess if the anaerobic degradation studies (Lay (1992) and Pack et al. (1988b) are acceptable and essential for the risk assessment. If anaerobic studies are finally considered not acceptable and not essential this information should be removed from the end points list.

Open point 4.11:

RMS to clarify on the information available on the degradation of anaerobic metabolite THCY under aerobic conditions.

In the Reporting Table, various concerns were raised regarding the quality of the anaerobic studies in the dossier and the significance of several major anaerobic soil metabolites for the risk assessment process (4(20), 4(25), 4(28), 4(29) and 4(48)).

RMS comments:

Captan is only used in the spring and summer and not in the autumn and winter. In addition, captan and its major soil metabolites degrade with laboratory DT_{50} values of between 0.4 and 14 days. Therefore, it is very unlikely that significant amounts of these substances will be present in soil during times when anaerobic conditions might be experienced (autumn/winter) following use according to the GAP. Therefore, the anaerobic degradation studies are not required for risk assessment purposes and significant anaerobic metabolites (which are not major metabolites under aerobic conditions: THCY and THPAI) need not be considered in the risk assessment. Given the lack of need to evaluate fate of captan under anaerobic conditions, it is also unnecessary to address potential concerns arising from the submitted anaerobic degradation studies.

B.8.1.2 Supplementary studies

Laboratory soil degradation studies on soil metabolites

Open point 4.12:
RMS to clarify which DT_{50} are relevant for the risk assessment of metabolite THPI.

Comments in the Reporting Table have been addressed by statements from the Notifier (ref: Terry, A. 2005. Responses to questions raised in the Reporting Table on fate and behaviour of captan). These statements are provided below.

Comment 4(26), 4(27) The small range of pH values associated with the soils used to investigate the soil degradation of THPI and THPAM was questioned and it was requested that DT_{50} values be recalculated with associated coefficients of goodness of fit. The Notifier has re-calculated these values (see Table B.8.1.1.9).

The RMS agrees with the above statement.

Comment 4(26) EFSA: the pH of the three soils used in the study to investigate the rate of degradation of THPI were very similar.

The kinetic analysis of *Pack, 1974* (*7.1.1.1.1/03*) allowed the derivation of a fourth DT_{50} value for THPI. In addition, the field dissipation studies conducted in the USA (five of six locations were found to correlate with locations in the EU, climatically) included the analysis of THPI residues and DT_{50} values were re-calculated (see Table B.8.1.1.11). THPI DT_{50} values ranged from 2.63 to 33.94 days. The pH range of the field soils was very wide (pH 4.9-7.8) and there was no correlation between the DT_{50} values and the pH of the soils.

The RMS agrees with the above statement.

Comment 4(27) EFSA: the pH of the three soils used in the study to investigate the rate of degradation of THPAM were very similar.

The kinetic analysis of *Pack, 1974* (*7.1.1.1.1/03*) allowed the derivation of a fourth DT_{50} value for THPAM. Although the pH range of the four soils was narrow (6.00 to 7.1), there was no indication of pH dependency within this range. In addition, THPAM hydrolysis proceeds very much faster under acidic conditions than under neutral or alkaline (DT_{50} of 4 days at pH4, DT_{50} of 365 days at pH7) which would suggest that soil degradation under acidic conditions would be more rapid. It is unlikely that additional studies would improve the understanding of the degradation of THPAM in soil.

The RMS agrees with the above statement.

Overall response from RMS: It is clear that the range of soil pH values investigated for the degradation of THPI is sufficient, if the field dissipation studies are included. It appears to be reasonable to include the field dissipation studies and no correlation between pH and degradation was evident for THPI soil degradation. For THPAM (which reached a maximum of 16.8% of applied captan in the laboratory study) there was less data available. Never the less, there was no indication of any pH dependency for THPI degradation in soil in the data that was available and the more rapid hydrolysis at lower pH values might indicate that degradation is likely to be more rapid for THPAM at more acidic pH values. Consequently, additional data on the soil degradation of THPAM is not required for the risk assessment.

B.8.1.3 Field studies

a) *Confined rotational crop study of [ring - ^{14}C] and [trichloromethyl - ^{14}C] - captan with beet, lettuce and wheat. (Ewing, A., Krauter, G. and Ruzo, L. 1990; IIA, 7.1.1.2.2/01)*

RMS comment: This study has been found to be not reliable and not essential for the risk assessment process.

Data requirement 4.3	Relevance of field USA study with respect to EU conditions should be assessed.

In the Reporting Table, two main concerns were raised with respect to the field dissipation studies conducted in the USA (4(33), 4(34), 4(35), 4(36), 4(37), 4(38), 4(39) and 4(40)).

- For the $DT_{50field}$ values reported no measure of the goodness of fit was reported,
- The relevance of the data generated to climatic conditions in the EU

The Notifier has submitted an expert review of the fate and behaviour of captan in soil under aerobic conditions and this has been summarised above (see B.8.1.1). The sections of the expert review that relate to the re-calculation of the field DT_{50} values, generation of coefficients of goodness of fit and assessment of climatic relevance of field locations are reproduced below:

Report: *Terry, A. and Price, O. (2005). Fate of captan in soil under aerobic conditions: A Review. CEA, unpublished report January 2005.*

USA Field Dissipation Studies
Investigations under laboratory conditions indicated that degradation of captan and its major soil metabolites did not trigger field dissipation studies (DT_{50lab} <60 days). However, a total of six field dissipation studies were conducted at different locations across the USA and reported in six reports and these studies do provide useful information with respect to the degradation of captan in soil. Each study involved multiple applications of captan (as a formulated product) to a crop at 7 day intervals. All applications were in spring or summer. Processing and analytical procedures were the same for all studies. Levels of captan and THPI were monitored in the soil for variable time periods depending on how rapidly degradation occurred. Generally, significant residues were only found in the top 7.5 cm of soil. The studies were carried out according to USEPA guideline 164-1 and under GLP. The soil properties at each location varied, with soil types ranging from clay to sand and pH values ranging from 4.9 to 7.8.

The results were re-analysed for the review (see Table B.8.1.3.17). Generally, captan and THPI degraded rapidly under field conditions. DT_{50} values for captan were calculated starting from the residues measured from the last application of captan. For THPI, however, calculations started from the maximum residue value for THPI (which varied from 0 days following the last application of captan to 28 days after the last application). This is likely to result in an over estimate for the THPI DT_{50} value. Best-fit values were obtained by applying a first-order decay optimised for both initial concentration (C_0) and the rate constant against the square of the residual using EXCEL SOLVER.

The DT_{50} values for captan ranged from 0.33 to 7.04 days and for THPI ranged from 2.63 to 33.94 days. There was no correlation between the DT_{50} values and the pH of the soils. Captan degraded readily in soils of all pH's.

Table B.8.1.3.17: Summary of USA field dissipation studies, associated re-calculated DT_{50} values, goodness of fit coefficients and examples of climatically similar locations in the EU

Location (*study*)	Soil pH	Soil organic carbon (%)	Soil texture	Treated crop	Application details (first application)	Köppen classification	Similar EU locations	Captan DT_{50} days (r^2 coef.)	THPI DT_{50} days (r^2 coef.)
Lakeland, Florida (*7.1.1.2.2/07*)	4.9	1.2	Sand	Tomato	4 x 4.48 kg a.s./ha (11 April)	Am	None	3.28 (**0.99**)	7.41 (**0.89**)
Waterloo, New York (*7.1.1.2.2/02*)	5.5	1.2	Loamy sand	Apples	8 x 4.48 kg a.s./ha (14 April)	Dfb	Helsinki (Finland)	7.04 (**0.91**)	2.63 (**0.98**)
Hillsboro, Oregon (*7.1.1.2.2/04*)	5.6	2.2	Silt loam	Grapes	6 x 2.24 kg a.s./ha (3 June)	Csb	Porto (Portugal), La Coruna (Spain)	3.38 (**0.94**)	33.94 (**0.91**)
Gilroy, California (*7.1.1.2.2/06*)	6.9	0.9	Loam	Tomato	4 x 4.48 kg a.s./ha (21 July)	Csb	Porto (Portugal), La Coruna (Spain)	4.21 (**0.91**)	16.70 (**0.87**)
Fresno, California (*7.1.1.2.2/03*)	7.1	0.3	Loamy sand	Strawberry	8 x 3.36 kg a.s./ha (14 May)	Csa	Granada (Spain), Badajoz (Spain), Palermo (Italy), Toulon (France)	4.12 (**0.98**)	4.62 (**0.97**)
Center Point, Texas (*7.1.1.2.2/05*)	7.8	1.4	Clay	Canteloupe	7 x 2.24 kg a.s./ha (23 June)	Cfa	Toulouse (France), Milano (Italy)	0.33 (**1.00**)	3.44 (**1.00**)

An analysis was also carried out to determine the relevance of each field study location in the USA to possible locations in the EU. The characterisation of regional climate for the purposes of the assessment relied upon well-established classification techniques. Most geographers today recognize five major climatic groups, based mainly on the work of the German meteorologist Wladimir Köppen (1923). Its categories are based on the annual and monthly averages of temperature and precipitation. The Köppen system recognizes five major climatic types; each type is designated by a capital letter:

A: Tropical Moist Climates: all months have average temperatures above 18 degrees Celsius;
B: Dry Climates: with deficient precipitation during most of the year;
C: Moist Mid-latitude Climates with Mild Winters;
D: Moist Mid-Latitude Climates with Cold Winters;
E: Polar Climates: with extremely cold winters and summers.

Each of these major regions are also broadly sub-divided according to seasons into a total of 24 sub-categories. An example is provided below for 'C Class', the most significant climatic class for southern Europe:

The 'C Class'generally has warm and humid summers with mild winters. Its extent is from 30 to 50 degrees of latitude mainly on the eastern and western borders of most continents. During

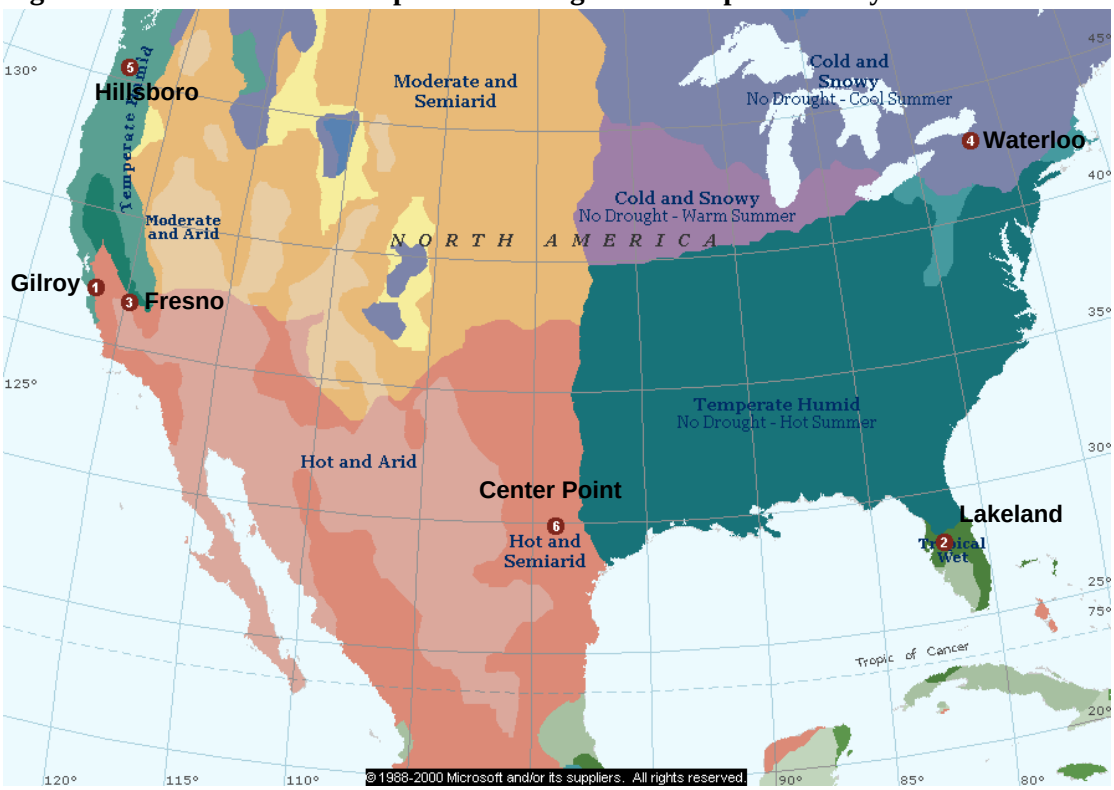
the winter the main weather feature is the mid-latitude cyclone. Convective thunderstorms dominate summer months. Three minor types exist:

- Cfa - humid subtropical;
- Cs – Mediterranean;
- Cfb - marine.

The humid subtropical climate (Cfa) has hot muggy summers and mainly thunderstorms. Winters are mild and precipitation during this season comes from mid-latitude cyclones. Examples of Cfa climate can be found in the southeastern USA. Cfb, marine, climates are found on the western coasts of continents. They have a humid climate with short dry summer. Heavy precipitation occurs during the mild winters because of continuous presence of mid-latitude cyclones. Mediterranean climates (Cs) receive rain primarily during winter season from the mid-latitude cyclone. Extreme summer aridity is caused by the sinking air of the subtropical highs and may exist for up to 5 months. Locations in North America are from Portland, Oregon to all of California.

Figure B.8.1.3.1 shows an approximation of the Köppen scheme classifications for North America. Study sites Hillsboro (5) is located in a temperate humid region and is representative of the Csb Köppen climatic region, which is characterised by long, mild and dry summers. Study sites Gilroy (1), Fresno (3) are located within a hot, semi-arid area typical of the Csb and Csa climatic regions, respectively, as identified by the Köppen classification. Center Point (6) is also located within a hot semi-arid area typical of the Cfa climatic region identified by the Köppen classification. The Lakeland site (2) is located within a wet tropical area typical of Köppen climatic region Am. The Waterloo site (4) is located within a cold and snowy area typical of Köppen climatic region Dfb. It must, however, be noted that the map shown in Figure 3 is rather generalised and gives only an indication of the climatic type experienced at a particular site and not the exact Köppen designation.

Figure: B.8.1.3.1 - Climatic Map Summarising Field Dissipation Study Locations



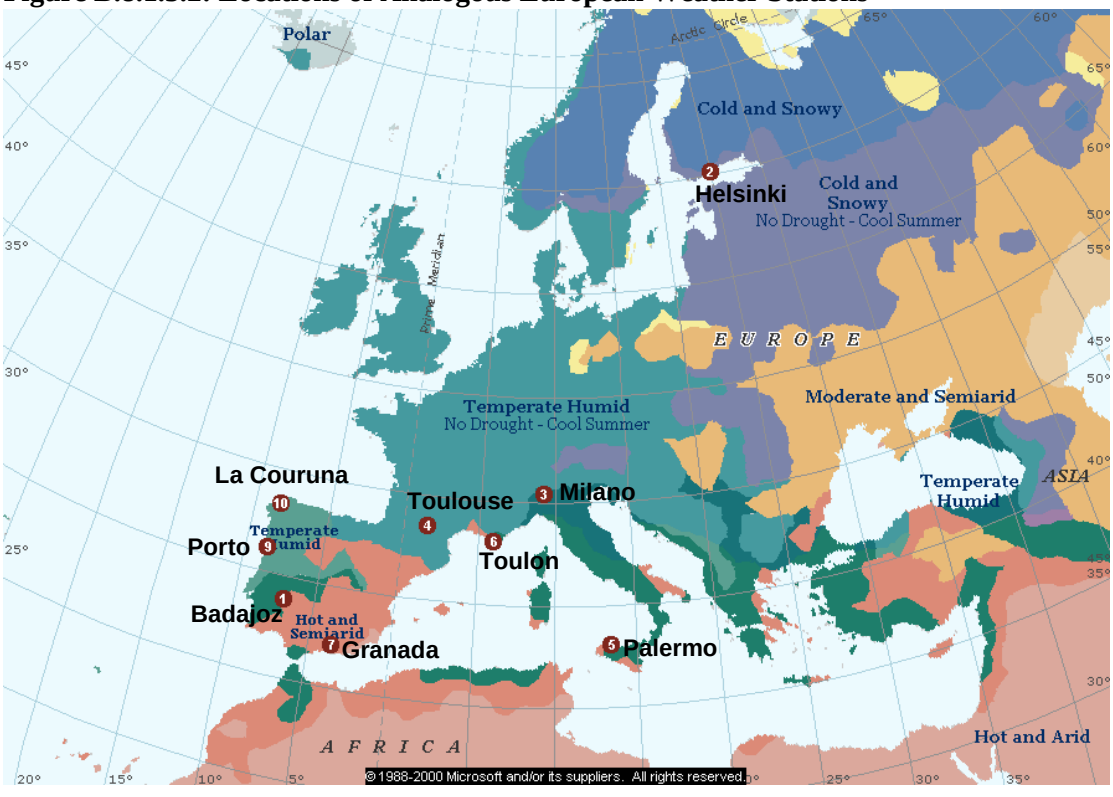
The next stage in the assessment involved evaluating the extent to which the non-European field studies could be extrapolated to European conditions. This was carried out in three stages as follows:

1) Characterisation of climate zones within Europe;
2) Identification of regions in Europe that are characterised by the same climatic classification as non-European field studies;
3) Identification of European sites characterised by similar long-term climate profiles to non-European field study sites.

From Figure B.8.1.3.2 it can be seen that much of northern and western Europe has a temperate humid climate which is characterised by cool summers (climatic region Cfb). Within Southern Europe there are three main climate types. Much of South Eastern Spain (including a large proportion of the regions of Andalucia, Murcia, Castilla La Mancha, Valenciana and Aragon) experiences a hot and semi arid climate that typifies the Csa region identified in the Köppen classification. Smaller areas of this climate also occur in the Puglia region of Italy, Sicily, Sardinia, and the Thessalonika, Sterea Ellada and Macedonia regions of Greece. A temperate humid climate that equates to the Csb climatic zone identified by Köppen occurs throughout much of Italy, Greece and parts of Spain. This climate is characterised by mild, rainy winters and is affected by the subtropical high pressure cell in the summer, resulting in long, arid periods. A significant proportion of Northern Italy falls within a zone of temperate humid climate characterised by long, hot, but humid summers and short, cool and humid winter seasons. This is consistent with the Csb climatic region identified in the Köppen classification scheme.

Comparison of the study site characteristics with climatic information for Southern Europe indicated that there was no European climatic analogy for the Lakeland site. This site experiences wet, tropical conditions typical of Köppen region Am. Such conditions are not present within Europe. However, it appears that the hot, semi-arid (Köppen classifications Csa and Cfa) climate experienced at the Fresno study site and the Texas Study site are potentially replicated by a number of regions within southern Europe. The Csa and Cfa climates occur throughout large areas of Spain as well as regions of Greece and Italy. In addition, the area of Csb climate found in Northern Italy correlates very well with the generally temperate humid conditions experienced at the study sites in Hillsboro and Gilroy.

Figure B.8.1.3.2: Locations of Analogous European Weather Stations



The climatic classification of the USA field site locations, together with corresponding representative locations in the EU are summarised in Table B.8.1.3.18:

Table B.8.1.3.18: Summary of climatic relevance of USA field locations to locations in the EU

US Location	Köppen classification	Representative EU location
Center Point (Texas)	Cfa	Toulouse (France) Milano (Italy)
Fresno (California)	Csa	Granada (Spain) Badajoz (Spain) Palermo (Italy) Toulon (France)
Hillsboro (Oregon) Gilroy (California)	Csb	Porto (Portugal) La Coruna (Spain)
Lakeland (Florida)	Am	None
Waterloo (New York)	Dfb	Helsinki (Finland)

Four of the field studies were conducted at locations corresponding to climates similar to various locations in Southern Europe, but one (conducted at Waterloo, New York) had a climate corresponding to Helsinki, Finland. This also had the longest field DT_{50} for captan (7.04 days).

RMS comment: The Notifier points out that according to the DT_{50} values obtained in the laboratory for captan, THPI and THPAM (all <60 days) field investigations were not actually triggered. However, the field dissipation data has been useful to establish that soil degradation was not dependent on soil pH. The field DT_{50} values have been re-calculated using modern tools and r^2 values also derived. The climatic analysis established that five of the six field locations in the USA did correspond to locations in the EU. The longest field DT_{50} value for captan (7.04 days) was found at Waterloo, New York, which corresponded to conditions in Helsinki, Finland. As such, it can be regarded as a realistic worst case value for the purposes of calculating PEC_{soil} values.

B.8.2 Adsorption, desorption and mobility in soil (Annex IIA 7.1.2 and 7.1.3; Annex IIIA 9.1.2)

B.8.2.1 Adsorption and desorption

Data requirement 4.6	Literature data and references to support Captan Koc must be provided and assessed.

Captan

In the Reporting Table, three comments are stated with respect to the adsorption and desorption of captan to soil. Responses addressing these are provided by the RMS below.

Comment 4(41), 4(44) SI & EFSA: more information on the source and derivation of the 'mean' K_{OC} value of 200 mL/g for captan should be provided.

The authors of the published report from which the mean K_{OC} for captan was derived (Wauchope R.D., Buttler T.M., Hornsby A.G., Augustijn-Beckers P.W.M., Burt J.P. 'The SCS/ARS/CES Pesticide Properties Database for Environmental Decision-Making' Reviews of Environmental Contamination and Toxicology, (1992)) gathered data from the literature and selected representative values for various parameters. The captan K_{OC} values and the literature references are listed in Table B.8.2.1.6. The authors selected a captan K_{OC} of 200 mL/g.

Table B.8.2.1.6: Captan K_{OC} values reported in Wauchope R.D., Buttler T.M., Hornsby A.G., Augustijn-Beckers P.W.M., Burt J.P. 'The SCS/ARS/CES Pesticide Properties Database for Environmental Decision-Making' Reviews of Environmental Contamination and Toxicology, (1992)

Reported captan K_{OC} value (mL/g)	Reference
33	Jury W.A., Focht D.C., Farmer W.J. (1987) Evaluation of pesticide groundwater pollution potential from standard indices of soil chemical adsorption and degradation. *J. Environ. Qual.*, **16**, 422-428; Rao P.S.C., Hornsby A.G., Jessup R.E. (1985) Indices for ranking the potential for pesticide contamination of groundwater. *Soil Crop Sci. Fl. Proc.*, **44**, 1-8.
67, 29	Briggs G.G. (1981) Theoretical and experimental relationships between soil adsorption, octanol-water partition coefficient, water solubilities, bioconcentration factors and the parachor. *J. Agric. Food Chem.*, **29**, 1050-1059.
198	Davies F.M., Leonard R.A., Knisel W.G. (1990) GLEAMS user manual version 1.8.55. USDA-ARS Southeast Watershed Research Laboratory, Tifton, GA, 39p; Green R.E., Karickhoff S.W. (1990) Estimating pesticide sorption coefficients for soils and sediments. In: DeCoursey D.G. (ed) Small watershed model (SWAM) for water, sediment and chemical movement: supporting documentation. USDA-ARS Publ ARS-80, USDA-ARS, Washington, DC, pp 1-18.
140 (TLC)	Pionke H.B., Deangelis R.J., Nash R.G. (1980) Chapters 17 and 18. In: Knisel W.G. (ed) CREAMS: A field scale model for chemicals, runoff, and erosion from agricultural management systems. USDA Rep. No. 26, USDA, Washington, DC, pp 560-643.
115	Gerstl Z., Helling C.S. (1987) Evaluation of molecular connectivity as a predictive method for the adsorption of pesticides by soils. *J. Environ. Sci. Hlth (Part B) Pestic. Food Contam. Agric. Wastes*, **22**, 55-69.
100-600 (based on soil TLC)	Travis K.Z. (1990) Personal Communication, ICI Agrichemicals, Berkshire, England.
3	Fuller M. (1988) Personal Communication, Florida Department of Agriculture and Consumer Services, Tallahassee Florida, Original data from US Fish and Wildlife Service.

Comment 4(43) FR :a typographical error appears in Tables B.8.2.1.4 and B.8.2.1.5; the pH of 'East Anglia' soil was erroneously stated as 3.1 instead of 8.1.

The relevant corrected portions of these two tables are presented here:

Table B.8.2.1.4 Summary of adsorption/desorption values for THPI in soils [amended section]

Soil and principal characterisitcs	Nominal rate applied aqueous phase (mg/L)	Adsorption						Desorption		
		K_d	K_{OC}	K'	K'_{OC}	Freundlich 1/n	Freundlich r^2	K_d	K_{OC}	% increase in K_d adsorption to desorption
East Anglia	0.04	0.19	10	0.14	7.6	0.92	1.0	0.46	25	140
Organic matter = 3.2 %	0.1	0.18	9.6					0.56	30	220
pH 8.1	0.2	0.14	7.8					0.31	17	110
Clay = 13 %	1.0	0.17	9.0					0.37	20	120
	5.0	0.12	6.3					0.27	14	130
Average values		0.16	8.6					0.39	21	140

Table B.8.2.1.5 Summary of adsorption/desorption values for THPAM in soils [amended section]

Soil and principal characterisitcs	Nominal rate applied aqueous phase (mg/L)	Adsorption						Desorption		
		K_d	K_{OC}	K'	K'_{OC}	Freundlich 1/n	Freundlich r^2	K_d	K_{OC}	% increase in K_d adsorption to desorption
East Anglia	0.04	0.02	1.1	0.14	7.6	1.26	0.97	0.12	6.6	530
Organic matter = 3.2 %	0.1	0.11	5.8					0.64	35	500
pH 8.1	0.2	0.07	3.7					0.28	15	300
Clay = 13 %	1.0	0.20	11					1.0	54	390
	5.0	0.12	6.4					0.63	34	430
Average values		0.10	5.6					0.53	29	430

Comment 4(45) SI: the K_{OC} value derived from the Lilly Field soil for THPI is unreliable as the Freundlich coefficient was only 0.37. This value should be excluded from the risk assessment process.

The section detailing the adsorption and desorption of THPI in the original DAR has been amended to reflect the non-inclusion of the K_{OC} data for THPI generated in Lilly Field soil:

The measured K_d, K', K_{OC}, and K'$_{OC}$ values for the adsorption and desorption stages of THPI are shown in Table B.8.2.1.4, together with Freundlich 1/n and r^2 coefficients for adsorption. THPI was weakly adsorbed to soil, with average Kd values ranging from 0.13 in the lowish organic matter 'Salmonds Bridge' soil to 0.23 in the higher organic matter 'Kenny Hill' soil (K_{OC} ranging from 7.6-13.0 mL/g). K_d values decreased with increasing rate of application, indicating that some adsorption sites were becoming saturated as the rate of application increased, although the adsorption isotherms suggested that adsorption had not ceased at the highest rate of application. The 1/n values of 0.83 to 1.00 showed that the isotherms were nearly linear, and the values of r^2 were close to 1, indicating a good fit of data to the linear regression for five of the soils (data for 'Lilly Field' soil has been excluded on the basis of the unreliability of the data, given that the Freundlich coefficient was only 0.37).

Plots of adsorption K_d values against organic matter indicated a correlation ($r^2 = 0.81$) between this soil property and the adsorption of THPI on soils. No correlations were observed with pH, clay content or cation exchange capacity.

Average desorption K_d values ranged from 0.28 to 0.47, with generally between a 2 and 3 fold increase in average K_d values between adsorption and desorption steps. These data suggest that the adsorption of THPI to soil is not entirely reversible, reducing the potential mobility of the compound.

B.8.2.2 Column leaching and lysimeter studies

B.8.2.2.1 Column leaching

In the Reporting Table, two comments were made regarding column leaching studies. Responses to these comments have been provided by the Notifier (ref: Terry, A. 2005. Responses to questions raised in the Reporting Table on fate and behaviour of captan):

Comment 4(42) ES: given that the K_{OC} of captan could not be estimated due to its rapid degradation, a leaching column study should be performed according to 95/35/CEE

Given the very fast hydrolysis of captan at all pH values it would not be possible to conduct a meaningful column leaching study with captan. It was evident from the aged column leaching study (*7.1.3.2/01)* that captan present in the aged soil added to the top of the column degraded very rapidly. Performing a leaching column study with captan would serve no useful purpose.

The RMS agrees with the above statement.

Open point 4.10:
RMS to consider relevance of leaching studies with respect to soil degradation. Also to consider if a reliable K_{OC} may be obtained from column leaching studies.

Comment 4(46) EFSA: captan seems to be considerably more stable in the soils used in the aged column leaching study than any of those used in the soil degradation studies. These results should be taken into consideration when revising the degradation rate of captan. Also, it seems that, under some circumstances, captan is stable enough to obtain reliable adsorption/desorption parameters.

A new evaluation of the hydrolysis, soil degradation and field dissipation studies for captan and its major soil metabolites has been conducted and is reported in *Terry, A. and Price, O. (2005). Fate of captan in soil under aerobic conditions: A Review. (CEA, unpublished report January 2005)*. This has been summarised and evaluated above in B.8.1.1. The fate and behaviour of captan in soil has been derived from studies designed to investigate the fate in soil of captan, including the generation of representative DT_{50} values. The aged column leaching study was designed to investigate the leaching potential of captan degradation products rather than the rate of degradation of captan; and the incubation of captan in soil would have been carried out in a way that would have allowed the best opportunity to arrive at a mixture of all captan soil metabolites so that their leaching characteristics could be examined. Given the results of the other studies designed to measure captan degradation it is more reasonable to assume that the DT_{50} derived from the aged column leaching study is atypical. It would not be appropriate to include any DT_{50} values derived from an aged leaching study for risk assessment purposes.

It is clear that as soon as the aged soil was added onto the column and leaching started that the captan present in the soil degraded very rapidly. It is therefore very unlikely that a column leaching study with captan would allow any conclusions to be drawn with respect to captan's intrinsic adsorption/desorption to soil.

The RMS agrees with the above statements.

B.8.2.2.2 Lysimeter studies

Open point 4.16:
The request of a lysimeter study to be discussed in an expert meeting.

Comment 4(92) DE: A lysimeter study was waived with the argument that dissipation of parent and metabolites is rapid. However, the results of FOCUS PELMO modelling would indicate that lysimeter studies are appropriate to compare groundwater leaching on neutral/alkaline and acidic soils. It is suggested to request a lysimeter study.

Statement provided by the Notifier (ref: Terry, A. 2005. Responses to questions raised in the Reporting Table on fate and behaviour of captan):

A new FOCUS PELMO modelling exercise (see B.8.6) has been conducted taking into account the pH variability of K_{OC} for THPAM (there is no pH sensitivity for captan and THPI K_{OC} values). This demonstrates that significant 'safe usage' for captan is predicted to exist in the EU (i.e. there are scenarios with PECgw values <0.1 µg/L), although there are scenarios where PECgw for THPI and THPAM is predicted to exceed 0.1 µg/L. As such, it is unreasonable to require a lysimeter study for annex 1 listing, in this case.

The RMS agrees with the above statement.

B.8.2.3 Summary and assessment

Open point 4.12:
RMS to clarify which DT_{50} values are relevant for the risk assessment of metabolite THPI.

RMS comment: The following Summary and Assessment replaces the one provided in the DAR. This takes account of the expert review of fate in soil, and other responses provided by the Notifier:

Several studies have been performed under laboratory and field conditions to assess the behaviour of captan in soil. Laboratory studies indicated that the soil degradation of captan is very rapid under both aerobic conditions, with a DT_{50} of less than or equal to about 1 day. Both the tetrahydrophthalimide ring and the trichloromethyl side chain moieties of captan are eventually mineralised to carbon dioxide. Degradation of captan was observed under sterile conditions, indicating the importance of abiotic hydrolysis. Photolysis of captan was shown to be a minor degradation route of captan in soil. Given the proposed GAP for captan containing products and the very rapid degradation of captan and its soil metabolites degradation under anaerobic conditions was not considered relevant for the risk assessment process.

The principal initial degradate is THPI which undergoes cleavage of the imide ring to give THPAM. Other metabolites are generally at levels below 5% of the applied dose. THPAM is further degraded to CO_2, which is incorporated into natural constituents of the soil.

THPI and THPAM were found not to accumulate in soil, laboratory studies indicating that the DT_{50} values were less than 7 days. Recalculations using first order kinetics gave maximum estimated values of DT_{50} of 14.4 days for THPI and 11.1 days for THPAM. The soil degradation DT_{50} values were also normalised to 20°C and pF2 to allow selection of parameters for the use in the calculation of PEC groundwater values. For captan, a normalised value of 1.10 days was derived and for THPI and THPAM values of 9.05 and 7.80 days, respectively.

Stability studies on captan in soil/water mixtures indicated that adsorption/desorption batch equilibrium studies would not obtain meaningful adsorption/desorption coefficients, because of the instability of captan. Adsorption/desorption batch equilibrium studies on THPI (K_{OC} values ranging from 7.6-13.0) and THPAM (pH dependent adsorption with higher K_{OC} values at lower pH; 3.8-110 mL/g) indicated that these degradates may be weakly adsorbed to soil, and aged column leaching studies with captan indicated that THPAM and THPI appeared in the leachate, although no captan was found below 5 cm in the soil column nor in the leachate.

Although the laboratory degradation studies did not trigger field dissipation studies (DT_{50} values for captan, THPI and THPAM <60 days), six field dissipation studies, analysing for captan and THPI were performed in the USA. These were conducted under varying conditions of pH, soil textures, soil temperatures and precipitation levels, using application rates comparable to the proposed GAP with short sampling intervals following applications. The applicability of these trials to a Northern European situation has been assessed, with five of the six USA locations found to correspond to climatic conditions found in EU locations. Recalculations using first order kinetics demonstrated that captan was rapidly degraded with DT_{50} values of 0.33 – 7.04 days (r^2 values of 0.91-1.00). Recalculations using first order kinetics using the field dissipation results indicated a DT_{50} for THPI of 2.63-33.94 days (r^2 values of 0.87-1.00).

In these studies, neither captan nor THPI were found below 15 cm in four of the trials, and in the other two trials either captan or THPI, but not both, were found at low levels (max. 0.05 mg/kg) in the 15 – 30 cm layer horizon, but not below 30 cm.

B.8.3 Predicted environmental concentrations in soil (PECS) (Annex IIIA 9.1.3)

Data requirement 4.8	New PEC soil with worst case field DT_{50} should be calculated in the lack of more reliable data (see data requirements 4.1, 4.2 and 4.3 (in comment 4(16) of the reporting table).

RMS comment: Following the re-calculation of soil DT_{50} values for captan, THPI and THPAM it is necessary for amended PEC_{soil} values to be calculated (4(55), 4(56), 4(57) and 4(58) in the reporting table). It has also been noted (4(56)) that PEC_{soil} values for THPI and THPAM were not presented in the original DAR. The Notifier has submitted a new report in which appropriate PEC_{soil} values have been calculated according to the revised DT_{50} values. This report is summarised here and the original Table B.8.3.1 in the DAR is replaced by Tables B.8.3.3 to B.8.3.14:

Report: *Terry, A. (2005). Predicted environmental concentrations of captan and its major degradation products in soil in the European Union. CEA, unpublished report February 2005.*

PEC_{soil} values have been calculated for the EU GAPs for captan products using standard assumptions with respect to soil density (1.5 g/cm^3), depth of incorporation (5 cm) and crop interception factors (as recommended by FOCUS, 2000). PEC_{soil} values were also calculated for tetrahydrophthalimide (THPI) and tetrahydrophthamic acid (THPAM), the two major soil metabolites of captan. For the purposes of the simulations it was assumed that each metabolite was immediately generated at the maximum percentage at which it formed in the laboratory soil degradation study for each successive captan application. Both instantaneous PEC_{soil} values and Time Weighted Average (TWA) PEC_{soil} values were calculated.

Captan is subject to degradation under aerobic conditions as summarised in the proposed degradation scheme illustrated in Figure 1. Captan is hydrolysed to form the major soil metabolites THPI and THPAM. This is then followed by mineralisation to CO_2 via at least one minor metabolite (THPAI). THPI reached a maximum level of 66% of applied captan whereas THPAM reached 16.8%.

The degradation of captan under aerobic conditions has been recently reviewed (*Terry, A. and Price, O. (2005). Fate of captan in soil under aerobic conditions: A Review*). Captan degraded very rapidly under both laboratory and field conditions (field studies were conducted in the USA) with the worst case field DT_{50} (7.04 days) being obtained under conditions equivalent to those in Helsinki (Finland). Although used in the PEC_{soil} calculations this value should be considered as very much a worst case value.

The degradation of the two major soil metabolites was investigated in the laboratory. In addition, the degradation in the field of THPI was also monitored during the field studies conducted with captan. However, these studies were not ideal for this purpose, mainly because

multiple applications of captan were made which resulted in a more chaotic set of decline data for THPI than was obtained for captan. As such, the worst case laboratory DT_{50} values have been selected for THPI (14.37 days) and THPAM (11.07 days) for use in the calculation of PEC_{soil} values. An adjustment was made to these values to convert them to what would be expected at 15°C, rather than the 20°C at which they were obtained. This was achieved using the Arrhenius equation assuming an activation energy of 54 KJ/mol (FOCUS, 2000) and yielded a value of 21.1 days for THPI and 16.3 days for THPAM. A temperature of 15°C was chosen as a realistic worst case to represent average temperatures in the EU during summer.

Table B.8.3.2 summarises the selection of soil DT_{50} values for the three substances.

Table B.8.3.2: Summary of DT_{50} values Selected for use in the PEC_{soil} calculations

Substance	Selected soil DT_{50} value (days)	Source of Data
Captan	7.04	Worst case field DT_{50} value
THPI	21.1	Worst case laboratory DT_{50} value adjusted for temperature (20 to 15ºC)
THPAM	16.3	Worst case laboratory DT_{50} value adjusted for temperature (20 to 15ºC)

PEC_{soil} values were calculated for pome fruit (both Northern Europe and Southern Europe), for Nectarine/Peaches and Tomatoes. The initial applications are all within the BBCH ranges of 53 (bud burst) – 69 (end of flowering) which has been taken to correspond to at least 'foliage development' as given in the FOCUS guidance table for crop interception (FOCUS, 2000) giving a minimum crop interception value of 70%. This value has been used in the calculation of PEC_{soil} values for all three crop scenarios.

The concentration of captan in soil following an application was calculated by assuming that the crop intercepted 70% of the applied captan, which was then distributed uniformly in the top 5 cm of soil (with a density of 1.5 g/cm^3). The decline of captan was simulated in an EXCEL spreadsheet according to first order exponential decay with a DT_{50} value of 7.04 days. In all cases the GAP calls for multiple applications with an application interval of 7 days. This was simulated in the EXCEL spreadsheet by adding each additional application as a soil concentration to that remaining from the previous application(s) and then allowing the new concentration to decay as previously described. These values constituted the instantaneous PEC_{soil} value at any given time following the first or last application.

The TWA PEC_{soil} values were calculated by first calculating average soil concentrations for each day of the simulation and then averaging the required number of days' averages with a sliding window to arrive at a maximum TWA PEC_{soil} for the use.

For the purpose of calculating THPI PEC_{soil} values, an unrealistic worst case assumption was made that immediately following each captan application 66% of the applied captan was converted into THPI. This allowed the PEC_{soil} calculation for THPI to be carried out according to the method outlined above for captan, with a first order exponential decay DT_{50} of 21.1 days being used. The concentration of THPI was calculated ensuring an adjustment for molecular weight difference was made (THPI molecular weight 151.165 g/mol, captan molecular weight 300.593 g/mol).

For the purpose of calculating THPAM PEC_{soil} values, an unrealistic worst case assumption was made that immediately following each captan application 16.8% of the applied captan was

converted into THPAM. This allowed the PEC_{soil} calculation for THPAM to be carried out according to the method outlined above for captan and THPI, with a first order exponential decay DT_{50} of 16.3 days being used. The concentration of THPAM was calculated ensuring an adjustment for molecular weight difference was made (THPAM molecular weight 169.180 g/mol, captan molecular weight 300.593 g/mol).

The calculated PEC_{soil} values are presented in Tables B.8.1.3.3 to B.8.1.3.14.

Table B.8.2.3.3: Simulated PEC_{soil} values for captan following use on Pome Fruit in Northern Europe (10 x 1.25 kg a.s./ha)

Time (days)	Instantaneous PEC (mg/kg)	Maximum TWA PEC (mg/kg)	Day interval for TWA PEC calculation
app 1 (0)	0.500		
app 2 (7)	0.751		
app 3 (14)	0.877		
app 4 (21)	0.940		
app 5 (28)	0.972		
app 6 (35)	0.988		
app 7 (42)	0.996		
app 8 (49)	1.000		
app 9 (56)	1.002		
app 10 (63)	1.003		
1 (64)	0.909	0.956	(63)
2 (65)	0.824	0.911	(63-64)
3 (66)	0.746	0.869	(63-65)
4 (67)	0.676	0.830	(63-66)
7 (70)	0.503	0.725	(63-69)
14 (77)	0.253	0.725	(56-69)
21 (84)	0.127	0.724	(49-69)
28 (91)	0.064	0.723	(42-69)
50 (113)	0.007	0.708	(21-70)
100 (163)	0.000	0.505	(0-99)

Numbers in parentheses are days after first application

Table B.8.2.3.4: Simulated PEC_{soil} values for THPI following use on Pome Fruit in Northern Europe (10 x 1.25 kg a.s./ha)

Time (days)	Instantaneous PEC (mg/kg)	Maximum TWA PEC (mg/kg)	Day interval for TWA PEC calculation
app 1 (0)	0.166		
app 2 (7)	0.298		
app 3 (14)	0.403		
app 4 (21)	0.486		
app 5 (28)	0.552		
app 6 (35)	0.605		
app 7 (42)	0.646		
app 8 (49)	0.679		
app 9 (56)	0.706		
app 10 (63)	0.727		
1 (64)	0.703	0.715	(63)
2 (65)	0.681	0.704	(63-64)
3 (66)	0.659	0.692	(63-65)
4 (67)	0.637	0.681	(63-66)
7 (70)	0.577	0.649	(63-69)
14 (77)	0.459	0.640	(56-69)
21 (84)	0.365	0.629	(49-69)
28 (91)	0.290	0.616	(42-69)
50 (113)	0.141	0.571	(28-77)
100 (163)	0.027	0.442	(7-106)

Numbers in parentheses are days after first application

Table B.8.2.3.5: Simulated PEC_{soil} values for THPAM following use on Pome Fruit in Northern Europe (10 x 1.25 kg a.s./ha)

Time (days)	Instantaneous PEC (mg/kg)	Maximum TWA PEC (mg/kg)	Day interval for TWA PEC calculation
app 1 (0)	0.047		
app 2 (7)	0.082		
app 3 (14)	0.108		
app 4 (21)	0.128		
app 5 (28)	0.142		
app 6 (35)	0.153		
app 7 (42)	0.161		
app 8 (49)	0.167		
app 9 (56)	0.171		
app 10 (63)	0.174		
1 (64)	0.167	0.171	(63)
2 (65)	0.160	0.167	(63-64)
3 (66)	0.153	0.164	(63-65)
4 (67)	0.147	0.160	(63-66)
7 (70)	0.129	0.151	(63-69)
14 (77)	0.096	0.149	(56-69)
21 (84)	0.071	0.147	(49-69)
28 (91)	0.053	0.145	(42-69)
50 (113)	0.021	0.135	(21-70)
100 (163)	0.002	0.103	(0-99)

Numbers in parentheses are days after first application

Table B.8.2.3.6: Simulated PEC_{soil} values for captan following use on Pome Fruit in Southern Europe (9 x 1.25 kg a.s./ha + 3 x 2.4 kg a.s./ha)

Time (days)	Instantaneous PEC (mg/kg)	Maximum TWA PEC (mg/kg)	Day interval for TWA PEC calculation
app 1 (0)	0.500		
app 2 (7)	0.751		
app 3 (14)	0.877		
app 4 (21)	0.940		
app 5 (28)	0.972		
app 6 (35)	0.988		
app 7 (42)	0.996		
app 8 (49)	1.000		
app 9 (56)	1.002		
app 10 (63)	1.463		
app 11 (70)	1.694		
app 12 (77)	1.811		
1 (78)	1.641	1.726	(77)
2 (79)	1.487	1.645	(77-78)
3 (80)	1.347	1.569	(77-79)
4 (81)	1.221	1.498	(77-80)
7 (84)	0.909	1.309	(77-83)
14 (91)	0.456	1.270	(70-83)
21 (98)	0.229	1.200	(64-83)
28 (105)	0.115	1.081	(56-83)
50 (127)	0.013	0.925	(35-84)
100 (177)	0.000	0.731	(0-99)

Numbers in parentheses are days after first application

Table B.8.2.3.7: Simulated PEC_{soil} values for THPI following use on Pome Fruit in Southern Europe (9 x 1.25 kg a.s./ha + 3 x 2.4 kg a.s./ha)

Time (days)	Instantaneous PEC (mg/kg)	Maximum TWA PEC (mg/kg)	Day interval for TWA PEC calculation
app 1 (0)	0.166		
app 2 (7)	0.298		
app 3 (14)	0.403		
app 4 (21)	0.486		
app 5 (28)	0.552		
app 6 (35)	0.605		
app 7 (42)	0.646		
app 8 (49)	0.679		
app 9 (56)	0.706		
app 10 (63)	0.879		
app 11 (70)	1.017		
app 12 (77)	1.127		
1 (78)	1.091	1.109	(77)
2 (79)	1.055	1.091	(77-78)
3 (80)	1.021	1.073	(77-79)
4 (81)	0.988	1.056	(77-80)
7 (84)	0.896	1.007	(77-83)
14 (91)	0.712	0.958	(70-83)
21 (98)	0.565	0.905	(70-90)
28 (105)	0.449	0.875	(63-90)
50 (127)	0.218	0.764	(49-98)
100 (177)	0.042	0.615	(14-113)

Numbers in parentheses are days after first application

Table B.8.2.3.8: Simulated PEC_{soil} values for THPAM following use on Pome Fruit in Southern Europe (9 x 1.25 kg a.s./ha + 3 x 2.4 kg a.s./ha)

Time (days)	Instantaneous PEC (mg/kg)	Maximum TWA PEC (mg/kg)	Day interval for TWA PEC calculation
app 1 (0)	0.047		
app 2 (7)	0.082		
app 3 (14)	0.108		
app 4 (21)	0.128		
app 5 (28)	0.142		
app 6 (35)	0.153		
app 7 (42)	0.161		
app 8 (49)	0.167		
app 9 (56)	0.171		
app 10 (63)	0.218		
app 11 (70)	0.252		
app 12 (77)	0.278		
1 (78)	0.267	0.272	(77)
2 (79)	0.256	0.267	(77-78)
3 (80)	0.245	0.261	(77-79)
4 (81)	0.235	0.256	(77-80)
7 (84)	0.207	0.241	(77-83)
14 (91)	0.153	0.229	(70-83)
21 (98)	0.114	0.216	(64-83)
28 (105)	0.085	0.206	(63-90)
50 (127)	0.033	0.179	(42-91)
100 (177)	0.004	0.143	(7-106)

Numbers in parentheses are days after first application

Table B.8.2.3.9: Simulated PEC_{soil} values for captan following use on Nectarines/Peaches in Southern Europe (4 x 2.5 kg a.s./ha)

Time (days)	Instantaneous PEC (mg/kg)	Maximum TWA PEC (mg/kg)	Day interval for TWA PEC calculation
app 1 (0)	1.000		
app 2 (7)	1.502		
app 3 (14)	1.754		
app 4 (21)	1.880		
1 (22)	1.704	1.792	(21)
2 (23)	1.544	1.708	(21-22)
3 (24)	1.400	1.629	(21-23)
4 (25)	1.268	1.556	(21-24)
7 (28)	0.944	1.360	(21-27)
14 (35)	0.474	1.317	(14-27)
21 (42)	0.238	1.241	(7-27)
28 (49)	0.119	1.111	(0-27)
50 (71)	0.014	0.792	(0-49)
100 (121)	0.000	0.407	(0-99)

Numbers in parentheses are days after first application

Table B.8.2.3.10: Simulated PEC_{soil} values for THPI following use on Nectarines/Peaches in Southern Europe (4 x 2.5 kg a.s./ha)

Time (days)	Instantaneous PEC (mg/kg)	Maximum TWA PEC (mg/kg)	Day interval for TWA PEC calculation
app 1 (0)	0.332		
app 2 (7)	0.596		
app 3 (14)	0.805		
app 4 (21)	0.972		
1 (22)	0.940	0.956	(21)
2 (23)	0.910	0.941	(21-22)
3 (24)	0.880	0.925	(21-23)
4 (25)	0.852	0.911	(21-24)
7 (28)	0.772	0.868	(21-27)
14 (35)	0.613	0.794	(14-27)
21 (42)	0.487	0.759	(14-34)
28 (49)	0.387	0.706	(14-41)
50 (71)	0.188	0.585	(7-56)
100 (121)	0.036	0.382	(0-99)

Numbers in parentheses are days after first application

Table B.8.2.3.11: Simulated PEC_{soil} values for THPAM following use on Nectarines/Peaches in Southern Europe (4 x 2.5 kg a.s./ha)

Time (days)	Instantaneous PEC (mg/kg)	Maximum TWA PEC (mg/kg)	Day interval for TWA PEC calculation
app 1 (0)	0.095		
app 2 (7)	0.165		
app 3 (14)	0.217		
app 4 (21)	0.256		
1 (22)	0.245	0.250	(21)
2 (23)	0.235	0.245	(21-22)
3 (24)	0.225	0.240	(21-23)
4 (25)	0.216	0.235	(21-24)
7 (28)	0.190	0.221	(21-27)
14 (35)	0.141	0.204	(14-27)
21 (42)	0.105	0.191	(14-34)
28 (49)	0.078	0.179	(7-34)
50 (71)	0.030	0.143	(0-49)
100 (121)	0.004	0.087	(0-99)

Numbers in parentheses are days after first application

Table B.8.2.3.12: Simulated PEC_{soil} values for captan following use on Tomatoes (4 x 1.8 kg a.s./ha)

Time (days)	Instantaneous PEC (mg/kg)	Maximum TWA PEC (mg/kg)	Day interval for TWA PEC calculation
app 1 (0)	0.720		
app 2 (7)	1.081		
app 3 (14)	1.263		
app 4 (21)	1.354		
1 (22)	1.227	1.290	(21)
2 (23)	1.112	1.230	(21-22)
3 (24)	1.008	1.173	(21-23)
4 (25)	0.913	1.120	(21-24)
7 (28)	0.680	0.979	(21-27)
14 (35)	0.341	0.947	(14-27)
21 (42)	0.171	0.892	(14-34)
28 (49)	0.086	0.799	(7-34)
50 (71)	0.010	0.570	(0-49)
100 (121)	0.000	0.293	(0-99)

Numbers in parentheses are days after first application

Table B.8.2.3.13: Simulated PEC_{soil} values for THPI following use on Tomatoes (4 x 1.8 kg a.s./ha)

Time (days)	Instantaneous PEC (mg/kg)	Maximum TWA PEC (mg/kg)	Day interval for TWA PEC calculation
app 1 (0)	0.239		
app 2 (7)	0.429		
app 3 (14)	0.580		
app 4 (21)	0.700		
1 (22)	0.677	0.688	(21)
2 (23)	0.655	0.677	(21-22)
3 (24)	0.634	0.666	(21-23)
4 (25)	0.613	0.656	(21-24)
7 (28)	0.556	0.625	(21-27)
14 (35)	0.442	0.571	(14-27)
21 (42)	0.351	0.546	(14-34)
28 (49)	0.279	0.508	(14-41)
50 (71)	0.135	0.421	(7-56)
100 (121)	0.026	0.275	(0-99)

Numbers in parentheses are days after first application

Table B.8.2.3.14: Simulated PEC_{soil} values for THPAM following use on Tomatoes (4 x 1.8 kg a.s./ha)

Time (days)	Instantaneous PEC (mg/kg)	Maximum TWA PEC (mg/kg)	Day interval for TWA PEC calculation
app 1 (0)	0.068		
app 2 (7)	0.119		
app 3 (14)	0.156		
app 4 (21)	0.184		
1 (22)	0.176	0.180	(21)
2 (23)	0.169	0.176	(21-22)
3 (24)	0.162	0.173	(21-23)
4 (25)	0.155	0.169	(21-24)
7 (28)	0.137	0.159	(21-27)
14 (35)	0.101	0.147	(14-27)
21 (42)	0.075	0.137	(14-34)
28 (49)	0.056	0.129	(14-41)
50 (71)	0.022	0.103	(7-56)
100 (121)	0.003	0.063	(0-99)

Numbers in parentheses are days after first application

B.8.4 Fate and behaviour in water (Annex IIA 7.2.1; Annex IIIA 9.2.1, 9.2.3)

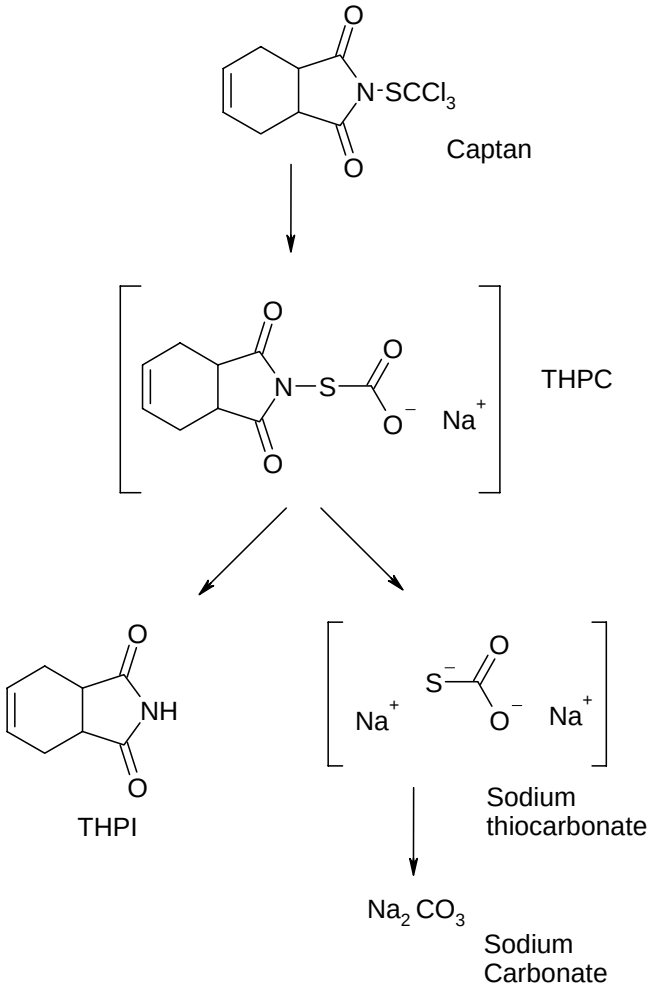
B.8.4.1 Aqueous hydrolysis

Data requirement 4.11	Hydrolysis of metabolites THPI, THPC and THPAM should be provided according to EEC guidelines. Metabolites should be reported.

Comment 4(61) and 4(65) EFSA & SI: The proposed route of degradation of captan by hydrolysis should include metabolite THPC.

The scheme presented in the DAR as B.8.4.1.1 came from one of the earlier hydrolysis studies before the route was fully clear. It is agreed that the scheme presented in report *7.2.1.1/03* (Lee, K.S. *[ring-1-^{14}C] Captan – Hydrolysis at 25°C*) is more appropriate and is given here:

Figure B.8.4.1.2: Proposed pathway of captan hydrolysis



Comment 4(62) EFSA: the hydrolysis rates calculated from the degradation of the ring labelled captan should be calculated and provided.

The requested values were, in fact, reported in the study but, by oversight, were not included in the DAR. The calculated hydrolysis DT_{50} values were determined to be 11.7 hours, 4.7 hours and 8.1 minutes at pH values of 5, 7 and 9 respectively.

Comment 4(63) NL: Study e is with THPAM. However, the text about dosage and the tables mention THPI.

RMS comment: Agreed. The affected text/tables have been reproduced below with corrected text.

e) *Hydrolysis determination of THPAM at different pH values. (Tognucci, A 2002b; IIA, 7.2.1.1/05)* The hydrolysis of non-radiolabelled THPAM was investigated in sterile aqueous buffer solutions at pH values of 4.0, 7.0 and 9.0.

The study met the essential criteria of OECD 111 and EEC 92/69, C.7. It was conducted according to Good Laboratory Practice.

Initially buffer solutions were prepared with THPI concentrations of 47.4, 55.0 and 45.1 µg/mL at pH values of 4, 7 and 9 and incubated at a temperature of 50°C.
Further test were conducted at temperatures of 60 and 70°C with buffer solutions at pH values of 7 and 9.
Initial investigations conducted at 50°C are summarised in Table B.8.4.1.12.

Table B.8.4.1.12: Hydrolysis of THPAM at a temperature of 50°C

Buffer pH value	Incubation period						
	0 hours	2.4 hours		24 hours		5 days	
	Initial concentration (µg/mL)	THPAM (µg/mL)	Hydrolysis reaction (%)	THPAM (µg/mL)	Hydrolysis reaction (%)	THPAM (µg/mL)	Hydrolysis reaction (%)
pH 4.0	50.36	30.28	40	<1.7	n.a	<1.7	n.a
	49.78	30.36	39	<1.7	n.a	<1.7	n.a
pH 7.0	54.04	52.79	2	51.28	5	43.39	20
	52.98	52.85	0	50.52	5	43.64	18
ph 9.0	51.87	51.74	0	50.96	2	52.64	-1
	51.77	52.05	-1	52.13	-1	48.80	6

At a pH value of 9.0 no significant degradation (i.e. < 10%) was observed after 5 days, corresponding to an estimated half-life of greater than 1 year under environmental conditions (i.e. 25°C). At pH values of 4.0 and 7.0 significant degradation had occurred (i.e. > 10%) after 5 days, however as the level of degradation observed after 2.4 hours was < 50% further testing was conducted. In addition as the degradation of THPAM at pH values of 4.0 and 7.0 followed pseudo-first order kinetics the degradation was investigated at two additional temperatures (60 and 70°C) as summarised in Table B.8.4.1.13 and Table B.8.4.1.14.

Table B.8.4.1.13: Hydrolysis of THPAM in sterile aqueous buffer at pH value 4.0 at various temperatures

Temperature 29°C		Temperature 39°C		Temperature 50°C	
Time (hours)	**THPAM (µg/mL)**	**Time (hours)**	**THPAM (µg/mL)**	**Time (hours)**	**THPAM (µg/mL)**
0.0	45.7	0.0	41.0	0.0	54.5
4.0	44.8	6.0	29.5	1.3	42.0
6.5	43.2	7.5	26.2	1.8	38.4
24.0	33.5	8.5	25.2	2.3	33.6
31.0	30.2	9.5	23.2	2.8	30.6
48.5	23.5	11.0	21.4	3.3	27.8
53.5	22.3	13.5	18.1	4.0	23.8
57.3	22.3	14.5	17.5	4.5	20.1
72.3	17.4	--	--	5.0	18.9
77.5	16.6	--	--	5.5	17.2
Rate constant, k ($hours^{-1}$) = 0.01314 $T_{1/2}$ (hours) = 53		Rate constant, k ($hours^{-1}$) = 0.06143 $T_{1/2}$ (hours) = 11.5		Rate constant, k ($hours^{-1}$) = 0.21505 $T_{1/2}$ (hours) = 3	

Table B.8.4.1.14: Hydrolysis of THPAM in sterile aqueous buffer at pH value 7.0 at various temperatures

Temperature 50°C		Temperature 60°C		Temperature 70°C	
Time (hours)	**THPAM (µg/mL)**	**Time (hours)**	**THPAM (µg/mL)**	**Time (hours)**	**THPAM (µg/mL)**
0.0	57.1	0.0	53.5	0.0	56.2
124.5	46.3	67.5	35.6	22.0	38.5
172.0	42.9	95.5	31.2	30.0	36.0
260.0	38.3	115.0	28.2	46.0	29.0
333.0	34.5	139.5	27.7	54.0	26.8
436.0	29.7	235.8	18.1	70.0	21.7
484.0	28.4	238.0	18.0	78.0	21.0
604.5	23.7	--	--	94.0	20.0
675.5	21.4	--	--	--	--
Rate constant, k ($hours^{-1}$) = 0.00137 $T_{1/2}$ (hours) = 507		Rate constant, k ($hours^{-1}$) = 0.00393 $T_{1/2}$ (hours) = 177		Rate constant, k ($hours^{-1}$) = 0.00992 $T_{1/2}$ (hours) = 70	

Hydrolysis was more rapid at pH 4 with half-lives ranging from 3 to 53 hours at temperatures of 50 and 29°C, respectively. At pH 7 the hydrolysis rate ranged from 70to 507 hours at a temperature of 70 and 50°C respectively.

The rate constants determined at the various temperatures were used to calculate the equivalent rate constant at a temperature of 25°C.

Table B.8.4.1.15: Calculation of rate constants for hydrolysis at 25°C

Temperature	Rate constant, k (hours^{-1})	Activation energy, E (kJ/mol)	Rate constant, k at 25°C (hours^{-1})	Half-life, $T_{1/2}$ at 25°C (days)
pH 4.0				
29°C	0.01314	108	7.8×10^{-3}	4
39°C	0.06143			
50°C	0.21505			
pH 7.0				
50°C	0.00137	91.2	8.03×10^{-5}	360
60°C	0.00393			
70°C	0.00992			

Using this method the activation energy was determined to be 108 and 91.2 kJ/mol at pH values of 4 and 7 respectively. Using the Arrhenius equation the half-live at 25°C was calculated for pH 4 and 7.

The metabolite THPAM was stable to hydrolysis at pH 9 in sterile aqueous buffer solutions at 25°C. At pH values of 4 and 7 hydrolysis proceeded with pseudo-first order half lives of 4 and 360 days respectively.

Comment 4(64) EFSA: accumulation of THPI and THPC is observed in the study c. According to 95/35/CEE information with regard to the hydrolysis metabolites above 10% should be reported. On the other hand the studies in for THPI and THPAM cannot be considered valid since they were carried out at temperatures of 50, 60 and 70°C and no identification of the metabolites was made. Finally no information with regarding THPC is given.

Statement from Notifier (ref: Terry, A. 2005. Responses to questions raised in the Reporting Table on fate and behaviour of captan):

The hydrolysis studies conducted with THPI and THPAM were reasonable and sufficient to derive the rate of hydrolysis of these two metabolites at 25°C, as the rate constants for the hydrolyses had been determined at three temperatures. This allowed the Arrhenius equation to be used to derive activation energies for the hydrolysis reactions from which the rate of hydrolysis at any temperature can be derived. Only THPI, THPAM and THPC were detected above 10% in the parent hydrolysis study. Therefore, although it is agreed that the rate of degradation of these metabolites should be provided, it is not considered necessary that the nature of their transformation products be determined. It is not believed that additional studies are required.

The RMS agrees with the above statement.

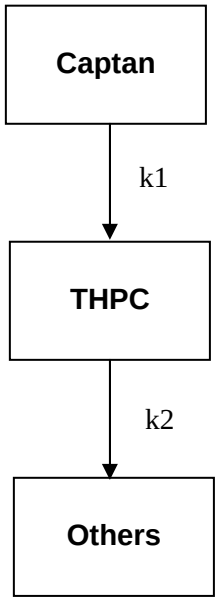
The rate of transformation of THPC can be calculated from the parent study using a multicompartment modelling package. This has been carried out and reported in a new report which has been provided by the Notifier:

Report: *Terry, A. (2005). Kinetic analysis of the degradation of THPC generated in hydrolysis studies on captan at pH9. CEA, unpublished report January 2005.*

The hydrolysis of captan has been investigated and reported in two studies (Lee, K.S. 1989a; Lee, K.S. 1989b) where the transformation product S-(tetrahydrophthalimido)thiocarbonate

(THPC) was also detected and quantified. This metabolite was only detected in significant quantities at pH7 and 9 (and not at pH5) where it reached a maximum of 28% of applied captan at pH7 and 46.6% at pH9. THPC was evidently most stable at pH9. Therefore, the three separate hydrolysis runs conducted in these two studies at pH9 have been analysed to derive a maximum rate of degradation for THPC at pH9 using the multi-compartmental model ModelMaker4. The model given in Figure B.8.4.1.3 was used to find best-fit degradation parameters for THPC in the three runs. All transformations were modelled with first-order kinetics.

Figure B.8.4.1.3: Multi-compartmental model used to derive kinetic parameters for formation and degradation of THPC



The results of these investigations are summarised in Table B.8.4.16.

Table B.8.4.16 Summary of results of kinetic analyses of captan hydrolysis runs conducted at pH9

Rate constant k2	THPC DT_{50} (minutes)	Goodness of fit (r^2)	Data source
0.0441	15.73	0.95	**run 1 from *Lee, K.S. 1989a***
0.0953	7.27	1.00	**run 1 from *Lee, K.S. 1989b***
0.0557	12.43	0.98	**run 2 from *Lee, K.S. 1989b***

Kinetic analysis of captan hydrolysis studies allowed DT_{50} values for the degradation of the captan hydrolysis product THPC to be derived at pH9 (conditions under which THPC is most stable). The analysis revealed that THPC was a very transient species with a maximum DT_{50} of 15.7 minutes.

RMS comment: The results obtained from the hydrolysis studies carried out with THPI and THPAM allow the degradation rates at 25°C to be derived. The transient nature of THPC has also been demonstrated, indicating that it is not a relevant metabolite in the aqueous phase.

B.8.4.3 Ready biodegradation

Data requirement 4.12	Notifier to provide readily biodegradability test.

Comment 4(66), 4(67) EFSA, ES: ready biodegradability should be assessed with available information or test required.

Statement provided by Notifier (ref: Terry, A. 2005. Responses to questions raised in the Reporting Table on fate and behaviour of captan):

Captan is extremely rapidly degraded in water and in water/soil mixtures. This strongly implies that it would also be degraded very rapidly in a readily biodegradability test. As such, captan should be regarded as being readily biodegradable and further studies are not necessary.

The RMS agrees with the above statement.

B.8.4.4 Water sediment studies

Data requirement 4.13	Notifier to provide calculation of DT_{50} value of the metabolite THPI in the water sediment system.

Comment 4(69) NL the DT_{50} value of the metabolite THPI can be determined accurately in one of both systems.

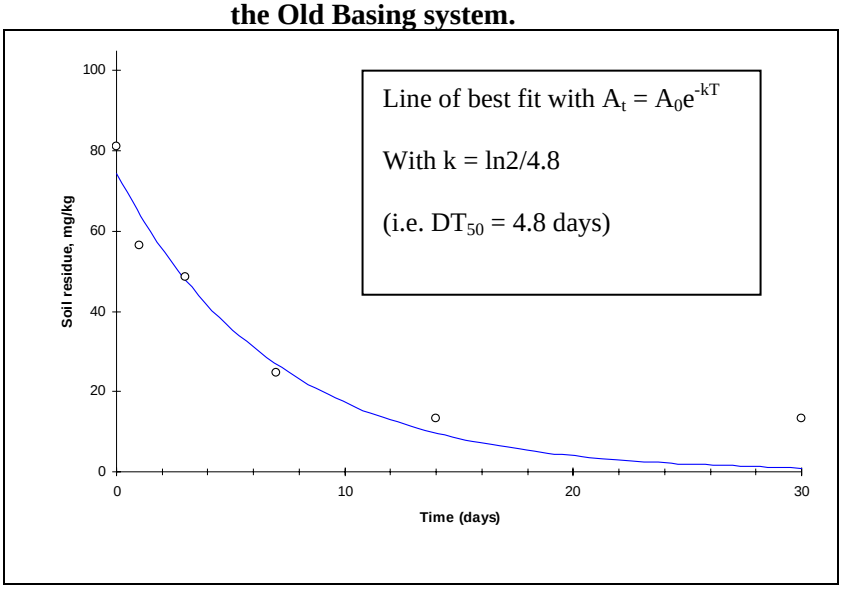
Statement provided by the Notifier (ref: Terry, A. 2005. Responses to questions raised in the Reporting Table on fate and behaviour of captan):

The degradation of captan in sediment/water systems was investigated in the laboratory in two contrasting sediment/water systems at 20°C, using [cyclohexene 1,2-^{14}C]-captan (Travis, 1993). Captan was found to degrade extremely rapidly. In the water phase, THPI and THPAM were found to be major metabolites with THPI reaching a maximum of 50.7% of applied captan in the Virginia Water system and THPAM reaching a maximum of 25.6% of applied in the Old Basing system. In sediment, THPI was the only major metabolite reaching a maximum of 41.2% of applied captan in the Old Basing system.

In the new report: *Predicted Environmental Concentrations of THPI and THPAM in surface water and sediment arising from spray drift, in the European Union, CEA, unpublished report January 2005*, it is reported that it was possible to analyse the decline of THPI according to simple first order decay kinetics for total residues in the Old Basing system, which yielded 4.8 days as the overall system DT_{50} for THPI (see Figure B.8.4.4.2). However, the pattern of decline of THPI in the Virginia Water system could not be analysed with a simple approach. Nor could the pattern of residues for THPAM in either system.

The RMS agrees with the above statement.

Figure B.8.4.4.2: The degradation profile, along with the determined line of best fit for the Old Basing system.



Open point 4.12:
Due to the lack of water sediment study at alkaline pH, a worst case assessment may be performed for alkaline conditions using results of hydrolysis study to make the risk assessment for surface water contamination by metabolite THPC.

Comment 4(70) ES, It seems as if THPC had not been monitored (in the sediment/water studies)

Statement from Notifier (ref: Terry, A. 2005. Responses to questions raised in the Reporting Table on fate and behaviour of captan):

It is not surprising that THPC does not feature in the water/sediment studies because it was a very transient intermediate (calculated DT_{50} maximum of 15.7 minutes at pH9; see B.8.4.1 above) under sterile conditions at a pH value where it was most stable. Therefore, THPC is not relevant for the risk assessment process.

RMS agrees with above statement.

Comment 4(86) FR, PECsed should be calculated for THPI (max. 41% in sediment on day 0) and THPAI (max. 11.3% in sediment after 30 d).

Statement from Notifier (ref: Terry, A. 2005. Responses to questions raised in the Reporting Table on fate and behaviour of captan):

THPAI was detected in sediment in two sediment/water systems over time (*Travis, J.S. and Simmons, N.D. 1993; IIA, 7.2.1.3.2./01;* see Table B.8.4.4.6). It reached a maximum of 7.3% in sediment in the Old Basing system (12.5% organic carbon) and 11.3% in the Virginia Water system (3.1% organic carbon). This latter was the only time when THPAI exceeded 10% of applied in the sediment of either system. In addition, it was reported in the study that most of the THPAI detected in sediment was extracted in a second of two sediment extractions which was found (upon further investigation) to result in breakdown of THPAM to THPAI. As such, it is very likely that some of the THPAI recorded as in the sediment was probably originally THPAM and that the one detect above 10% was probably an artefact of the extraction procedure. Therefore, it appears unnecessary to designate THPAI as a sediment metabolite and PEC_{sed} values are not required.

Table B.8.4.4.6: Residues of THPAI detected in sediment in two sediment/water systems

Days after application	THPAI in Virginia Water sediment (% of applied captan)	THPAI in Old Basing sediment (% of applied captan)
0	<0.1	<0.1
1	1.5	2.5
3	1.5	<0.1
7	3.1	3.6
14	1.9	7.3
30	11.3	3.0
59	<0.1	<0.1

RMS agrees with the above statements.

B.8.6 Predicted environmental concentrations in surface water and in ground water (PEC_{SW}, PEC_{GW}) (Annex IIIA 9.2.1, 9.2.3)

Groundwater

Data requirement 4.15	Notifier to provide new PEC GW modelling consistent with GAPs and reliable input parameters. Metabolites should be assessed according SANCO/221/2000-rev 10.

Open point 4.13:
RMS to assess relevance of ground water metabolite THPAM if enough data available or identify data gaps.

Open point 4.14:
RMS to prepare new addendum with new information of potential groundwater contamination.

In the Reporting Table, requests were made for new FOCUS PEC_{GW} calculations to be carried out according to updated GAPs and fully justified parameters (comments 4(74) and 4(80)). The Notifier has submitted a new report detailing appropriate PEC_{GW} calculations:

Report: *Terry, A. and Price, O. (2005). Predicted Environmental Concentrations of captan and its major degradation products in groundwater in the European Union using the FOCUS groundwater scenarios. CEA, unpublished report January 2005.*

Ground water modelling of captan has been undertaken with the FOCUS groundwater scenarios using the PELMO (v3.3.2) model. Simulations were conducted with applications to peaches/nectarines based on an application rate of 4 x 2.5 kg a.s./ha in southern EU. In addition, simulations were conducted with applications to tomatoes based on an application of 4 x 1.8 kg a.s./ha. Simulations were also carried out for southern EU pome fruit (apples) usages at 9 x 1.25 plus 3 x 2.4 a.s./ha (however, PELMO could not accommodate 12 applications each year. Therefore the last five applications were combined into three). Simulations were also carried out for northern EU pome fruit (apples) usages at 10 x 1.25 a.s./ha. These scenarios represent a clear worst-case. Simulations included the evaluation of two major soil degradation products, tetrahydrophthalimide (THPI) and tetrahydrophthamic acid (THPAM). A conservative crop interception of 70% was implemented for all the scenarios.

The molecular weights of captan, THPI and THPAM are 300.59, 151.17 and 169.18 g/mol, respectively.

Captan hydrolyses rapidly in soil solutions at both pH 5 and pH 7 ($t_{½}$ <5 hours), although hydrolysis is slower at pH 5. Because of the steady decomposition of captan, a true equilibrium of captan is never reached, and therefore a reliable Freundlich adsorption constant cannot be determined. Hence batch equilibrium studies cannot be used to investigate the adsorption/desorption characteristics of the captan parent molecule. A number of estimates of the soil adsorption coefficient (K_{OC}) for captan have been made in the literature and these range from 33 to 600 mL/g. From these estimates an average value of 200 mL/g was selected. A default coefficient defining the Freundlich sorption isotherm was employed (1/n = 0.90), consistent with the guidance provided by the FOCUS Groundwater Work Group.

The adsorption and desorption properties of THPI and THPAM, the major aerobic soil degradation products of captan, were studied in six European soils. The soils were representative of a wide a range of texture and pH.

There was no evidence of pH dependant sorption for THPI. In one of the soils tested (Lilly Field) there was evidence of a significant deviation from a linear sorption isotherm (1/n = 0.37). Therefore, simulations were based upon a mean sorption coefficient and Freundlich exponent (1/n) taking all of the data into account with the exception of the assessment conducted on the Lilly Field soil. The mean K_{OC} value was 9.34 cm^3/g. The mean Freundlich exponent (1/n) defining the Freundlich isotherm was 0.91.

In the case of THPAM, the use of mean K_{OC} values was not appropriate due to the pH-dependency of sorption. Therefore, a different strategy needed to be developed in order to refine the simulations. The refinement strategy is discussed in detail below.

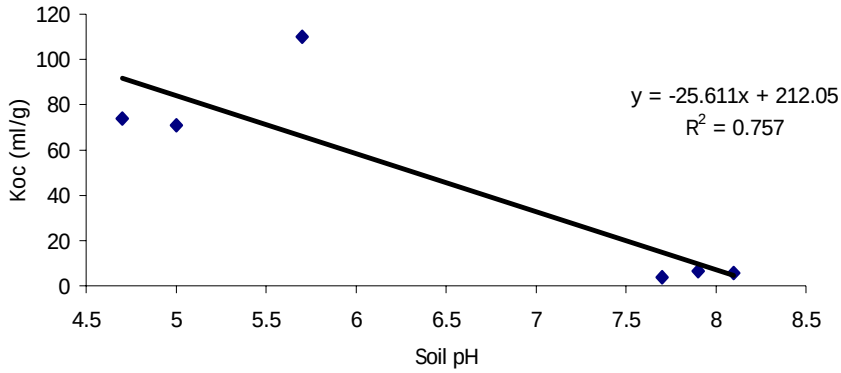
A summary of the topsoil pH conditions in each of the scenarios is summarised in Table B.8.6.15.

Table B.8.6.15: Topsoil pH conditions in FOCUS scenarios

Site	pH (H_20)	Textural class
Châteaudun	8.0	silty clay loam
Hamburg	6.4	sandy loam
Jokioinen	6.2	loamy sand
Kremsmünster	7.7	loam/silt
Okehampton	5.8	Loam
Piacenza	7.0	Loam
Porto	4.9	Loam
Sevilla	7.3	silt loam
Thiva	7.7	Loam

There is significant variation in the sorption results for THPAM. The laboratory assessments focussed upon evaluating sorption at relatively low and relatively high pH conditions with no measurements available between pH 6.0 and 7.5. Therefore, rather than match individual scenarios to individual K_{OC} values and soils a different strategy has been employed. Instead, the adsorption coefficients were plotted against pH. This correlation was then used to interpolate adsorption coefficients using the individual pH of each FOCUS scenario. The results of this strategy are summarised in Figure B.8.6.6.

Figure B.8.6.6. Relationship between adsorption coefficient of THPAM and soil pH



The Freundlich exponents for THPAM are pH dependant (Table B.8.6.16). Soils with a pH below 6 had a mean Freundlich exponent value of 0.99. Those soil samples with a pH >7.5 had a mean Freundlich exponent of 1.19. The average Freundlich exponent for the complete data set was 1.09. Therefore, where the scenario soil pH was <6 a Freundlich exponent of 0.99 was selected; when pH >6 but <7.5 a Freundlich exponent of 1.09 was selected; and when pH >7.5 a Freundlich exponent of 1.19 was selected.

Table B.8.6.16: K_{OC} and Freundlich exponents for THPAM

	pH	K_{OC}	1/n
Salmonds Bridge	4.7	74	1.00
Nebo	5	71	0.99
Lilly Field	5.7	110	0.99
Kenny Hill	7.7	3.8	1.14
Gayton	7.9	6.5	1.16
East Anglia	8.1	5.6	1.26
	Average:		1.09

The data in Table B.8.6.17 show the interpolated K_{OC} value for each FOCUS scenario and the 1/n value selected for use in the modelling simulations.

Table B.8.6.17. Derived K_{OC} and 1/n values for individual FOCUS scenarios

Site	pH	K_{OC} (K_{OC}= (-25.611*pH)+212.05	1/n
Châteaudun	8.0	7.16	1.19
Hamburg	6.4	48.14	1.09
Jokioinen	6.2	53.26	1.09
Kremsmünster	7.7	14.85	1.19
Okehampton	5.8	63.51	0.99
Piacenza	7.0	32.77	1.09
Porto	4.9	86.56	0.99
Sevilla	7.3	25.09	1.09
Thiva	7.7	14.85	1.19

Captan's vapour pressure was taken as 4.2×10^{-6} Pa at 20°C an its water solubility as 5.2 mg/L.

Captan is subject to degradation under aerobic conditions. Captan is hydrolysed to form THPI followed by degradation to THPAM. This is then followed by mineralisation to CO_2. The degradation of captan under aerobic conditions has recently been comprehensively reviewed and normalised DT_{50} values were derived and justified for use in standard FOCUS modelling (*Terry, A. and Price, O. (2005). Fate of captan in soil under aerobic conditions: A Review. See summary above under point B.8.1.1*). The kinetic fraction for the transformation of captan to THPI was also derived (1.0) and from THPI to THPAM (0.502). These data (which were selected for use in this modelling) are presented in Table B.8.6.18.

Table B.8.6.18. Soil degradation parameters for use in FOCUS groundwater modelling

Compound	Normalised soil DT_{50} (days)	Degradation Rate Constant ($days^{-1}$)	Kinetic Fraction (corresponding rate constant)
Captan	1.10	0.6301338	To THPI 1.0 (0.6301338)
THPI	9.05	0.0765908	To THPAM 0.502 (0.0384486) To CO_2 etc. 0.498 (0.0381422)
THPAM	7.80	0.0888650	NR

NR: not relevant

As captan has partitioning characteristics suggesting moderate to high potential for transpiration uptake (derived using PETE version 3.0), a value of 0.5 was used as a default 'worst-case' value in line with the FOCUS guidance. The same value was used for the major soil metabolites THPI and THPAM.

A set of simulations was carried out employing the FOCUS PELMO model (version 3.3.2) and the parameters outlined above. In all simulations, and for all scenarios captan was <0.000 µg/L at 1 m depth. Concentrations of THPI and THPAM at 1 m depth are summarised below for the different simulations and scenarios (Tables B.8.6.19-22).

Table B.8.6.19: Predicted 80th percentile annual average concentrations in groundwater following use of captan in pome fruit (apples) in Northern Europe

Scenario	Concentration of THPI at 1 m Depth (µg/L)	Concentration of THPAM at 1 m Depth (µg/L)
Châteaudun	2.294	5.566
Hamburg	1.260	1.461
Jokioinen	1.745	1.914
Kremsmünster	2.088	4.396
Okehampton	1.641	0.901

Tables B.8.6.20: Predicted 80th percentile annual average concentrations in groundwater following use of captan in pomefruit (southern EU)

Scenario	Concentration of THPI at 1 m Depth (µg/L)	Concentration of THPAM at 1 m Depth (µg/L)
Piacenza	2.081	2.645
Porto	0.022	0.002
Sevilla	0.036	0.109
Thiva	0.064	0.227

Table B.8.6.21: Predicted 80th percentile annual average concentrations in groundwater following use of captan in peaches/nectarines

Scenario	Concentration of THPI at 1 m Depth (µg/L)	Concentration of THPAM at 1 m Depth (µg/L)
Piacenza	0.963	1.246
Porto	0.010	0.001
Sevilla	0.015	0.048
Thiva	0.012	0.049

Table B.8.6.22: Predicted 80th percentile annual average concentrations in groundwater following use of captan in tomatoes

Scenario	Concentration of THPI at 1 m Depth (µg/L)	Concentration of THPAM at 1 m Depth (µg/L)
Châteaudun	0.165	0.690
Piacenza	0.459	0.721
Porto	0.001	0.000
Sevilla	0.000	0.000
Thiva	0.000	0.003

Captan did not exceed 0.000 µg/L in any simulation.

Tomatoes: PEC_{GW} values for THPI and THPAM were <0.1 µg/L in 3 of 5 scenarios.

Peaches/Nectarines: PEC_{GW} values for THPI and THPAM were <0.1 µg/L in 3 of 4 scenarios.

Pome fruit (North EU): PEC_{GW} values for THPI and THPAM were >0.1 µg/L, but <10 µg/L for all scenarios.

Pome fruit (South EU): PEC_{GW} values for THPI were <0.1 µg/L in 3 of 4 scenarios. PEC_{GW} values for THPAM were <0.1 µg/L in 1 of 4 scenarios.

Hence, 'safe use' scenarios have been identified for all the above uses, except Pome Fruit (apples) in Northern Europe, in the context of listing in Annex 1 of Directive 91/414 EEC.

The framework of modelling established by FOCUS for simulating PEC values in groundwater may exaggerate the mobility potential of active substances and their degradation products. This is due to simplistic regular annual scheduling of applications. It is expected that a more realistic scheduling of applications relative to rainfall events would decrease apparent mobility – particularly where applications are frequent and there is evidence of rapid degradation and relatively low sorption (as in the case of THPI and THPAM).

RMS comment: The results indicate that there are significant 'safe use' scenarios for captan products in the EU. This is sufficient to allow Annex 1 listing. No scenarios were identified

for use in pome fruit in Northern Europe with metabolites PECgw <0.1 µg/l, although the predicted 80th-percentile concentrations for THPI and THPAM were all <10 µg/L. The Notifier has submitted a study on the pesticidal (fungicidal) activity of THPI and THPAM. In this respect they were demonstrated to be 'non-relevant' in the context of the EU guidance document on relevance of metabolites (see Addendum to DAR on ecotoxicology for summary of this study).

Surface Water

Data requirement 4.9	New initial PEC sw, taking into account multiple applications must be provided for metabolites THPI and THPAM.
Data requirement 4.14	PEC sed for metabolites THPI and THPAI must be provided.
Data requirement 4.16	PEC FOCUS sw taking into account run off and drainage must be provided. Input parameters should be clearly justified.

Comment 4(82) EFSA, it should be clarified where the DT50 (2.6 h at 25°C) employed for captan PEC SW calculation comes from.

The DT_{50} value of 2.6 hours used for calculation of PEC_{SW} was the hydrolysis rate observed in the study by Pack, (1987) at neutral pH 7. This value was used as it was not possible to determine a degradation rate for captan in the water/sediment study due to extremely rapid degradation under non-sterile conditions.

In the Reporting Table, requests were made for PEC_{SW} and PEC_{sed} calculations to be carried out for THPI and THPAM to particularly address multiple applications (comments 4(74) and 4(80)). It was suggested that these PEC values be calculated using the FOCUS SW modelling package. However, the Notifier maintains that as FOCUS SW was not required when the dossier was submitted a decision on annex1 listing can be made without FOCUS SW. The Notifier has submitted a new report detailing PEC_{SW} and PEC_{sed} calculations for THPI and THPAM following multiple applications:

Report: *Terry, A. (2005). Predicted Environmental Concentrations of THPI and THPAM in surface water and sediment arising from spray drift, in the European Union. CEA, unpublished report January 2005.*

PEC_{SW} and PEC_{sed} values have been calculated for two of the EU GAPs for captan products using standard assumptions with respect to water depth (30 cm), mixing depth in sediment (5 cm), sediment density (1.5 g/cm^3) and spray drift factors (Rautmann, 2001). PEC_{SW} and PEC_{sed} values were calculated for THPI, whilst only PEC_{SW} values were calculated for THPAM, simulating multiple applications of captan with resulting multiple drift into a water body.

From an application point of view, the nectarines/peaches usage is a more worst case version of the tomatoes usage and pome fruit in Southern Europe is a more worst case version of pome fruit in Northern Europe. Therefore, PEC_{SW} and PEC_{sed} values were calculated for pome fruit

Southern Europe and for nectarine/peaches. The initial applications are all within the BBCH ranges of 53 (bud burst) – 69 (end of flowering) which has been taken to correspond to late applications to fruit crops, with respect to the Rautmann, 2001 spray drift tables.

The degradation of captan in sediment/water systems was investigated in the laboratory in two contrasting sediment/water systems (see Table 4) at 20°C, using [cyclohexene 1,2-^{14}C]-captan (Travis, 1993).

Captan was found to degrade extremely rapidly. In the water phase, THPI and THPAM were found to be major metabolites with THPI reaching a maximum of 50.7% of applied captan in the Virginia Water system and THPAM reaching a maximum of 25.6% of applied in the Old Basing system. In sediment, THPI was the only major metabolite reaching a maximum of 41.2% of applied captan in the Old Basing system.

An analysis of the formation and decline of THPI and THPAM in the two sediment/water systems was undertaken to arrive at DT_{50} values for use in the calculation of PEC values, but not a full kinetic analysis of the data. As such, it was not possible to derive specific DT_{50} values for the separate water and sediment compartments. Given the very rapid degradation of captan it was possible to analyse the decline of THPI according to simple first order decay kinetics for total residues in the Old Basing system, which yielded 4.8 days as the overall system DT_{50} for THPI (see above, point B.8.4.4). However, the pattern of decline of THPI in the Virginia Water system could not be analysed with a simple approach. Nor could the pattern of residues for THPAM in either system.

However, it was noted that for both systems all degradation products had declined to the point of being non-detectable in either sediment or water phases by 59 days of incubation. By taking the 59 days value as representing a worst case first order DT_{90} value for degradation products, it was possible to calculate a worst case DT_{50} value for the total systems of 17.8 days (DT_{50} =(ln(2)*DT_{90})/ln(10). These derived values are summarised in Table B.8.6.23.

Table B.8.6.23: Summary of derived DT_{50} values for THPI and THPAM in two sediment/water systems

Substance	Total System DT_{50} (days)	
	Old Basing System	Virginia Water System
THPI	4.8	17.8
THPAM	17.8	17.8

THPI was found to be a major captan degradation product in both the water and sediment phases. However, THPI reached only 9.9% in the sediment phase in the Virginia Water system whilst reaching 41.2% in the Old Basing system. As such, THPI was a major sediment metabolite in the Old Basing system only. Given that in the Old Basing system the overall system DT_{50} value for THPI was calculated to be 4.8 days, it was decided to use this value as the degradation rate for THPI in sediment in the calculation of PEC_{sed} values. The general conservative system DT_{50} of 17.8 days was selected as the DT_{50} for THPI in the calculation of PEC_{SW} values.

THPAM was a major captan degradation product in the water phase only. The general conservative system DT_{50} of 17.8 days was selected as the DT_{50} for THPAM in the calculation of PEC_{SW} values.

The calculation of PEC values was carried out according to the assumption that a percentage of the applied captan drifts into a 30 cm deep water body with a 5 cm layer of sediment (with a density of 1.5 g/cm^3). The spray drift rate was taken from the Rautmann (2001) tables of values, using the value for late applications to fruit crops from a distance of 3 m. In addition, the drift value for three or more applications (77th percentiles) was selected (11.01%) and used for each of the multiple applications simulated. Following calculation of the initial concentration of captan in the water phase following each application it was assumed that THPI and THPAM were formed instantaneously in both water and sediment phases at the maximum percentage found in the sediment/water systems, with initial PEC values accounting for the molecular weight differences between parent and metabolite.

The decline of each metabolite was simulated in an EXCEL spreadsheet according to first order exponential decay with the appropriate DT_{50} value (see Table B.8.6.24 for a summary of the parameters selected for calculations of the PEC values). In all cases the GAP calls for multiple applications with a minimum application interval of 7 days. This was simulated in the EXCEL spreadsheet by adding each additional application as a concentration to that remaining from the previous application(s) and then allowing the new concentration to decay as previously described. These values constituted the instantaneous PEC value at any given time following the first or last application.

The sediment TWA PEC values were calculated by first calculating average concentrations for each day of the simulation and then averaging the required number of days' averages with a sliding window to arrive at a maximum TWA PEC for the use.

Table B.8.6.24: Summary of Parameters Selected for Use in the Calculation of PEC_{SW} values for THPI and THPAM and PEC_{sed} values for THPI

Compound:	Captan	THPI	THPAM
Molecular Weight (g/mol)	300.59	151.17	169.18
%-drift into water body	11.01	NR	NR
Water depth (cm)	30	30	30
Sediment depth (cm)	NR	5	5
Sediment density (g/cm^3)	NR	1.5	1.5
Maximum % formed in water phase	NR	50.7	25.6
Maximum % formed in sediment phase	NR	41.2	NR
DT_{50} in water phase (days)	NR	17.8	17.8
DT_{50} in sediment phase (days)	NR	4.8	NR

NR: not relevant for these calculations

The calculated PEC_{SW} and PEC_{sed} values are presented in Tables B.8.6.25-B.8.6.30.

Table B.8.6.25: Simulated PEC_{SW} values for THPI following use on pome fruit in Southern Europe (9 x 1.25 kg a.s./ha + 3 x 2.4 kg a.s./ha)

Time (days)	Instantaneous PEC (µg/L)
app 1 (0)	11.70
app 2 (7)	20.60
app 3 (14)	27.38
app 4 (21)	32.55
app 5 (28)	36.48
app 6 (35)	39.47
app 7 (42)	41.75
app 8 (49)	43.49
app 9 (56)	44.81
app 10 (63)	56.57
app 11 (70)	65.53
app 12 (77)	72.35
1 (78)	69.59
2 (79)	66.93
4 (81)	61.92
7 (84)	55.09
14 (91)	41.95
21 (98)	31.94
28 (105)	24.32
42 (127)	14.10
100 (177)	1.47

Numbers in parentheses are days after first application

Table B.8.6.26: Simulated PEC_{SW} values for THPAM following use on pome fruit in Southern Europe (9 x 1.25 kg a.s./ha + 3 x 2.4 kg a.s./ha)

Time (days)	Instantaneous PEC (ug/L)
app 1 (0)	6.61
app 2 (7)	11.64
app 3 (14)	15.47
app 4 (21)	18.39
app 5 (28)	20.61
app 6 (35)	22.31
app 7 (42)	23.59
app 8 (49)	24.57
app 9 (56)	25.32
app 10 (63)	31.97
app 11 (70)	37.03
app 12 (77)	40.89
1 (78)	39.33
2 (79)	37.82
4 (81)	34.99
7 (84)	31.13
14 (91)	23.70
21 (98)	18.05
28 (105)	13.74
42 (127)	7.97
100 (177)	0.83

Numbers in parentheses are days after first application

Table B.8.6.27: Simulated PEC_{SW} values for THPI following use on nectarines/peaches in Southern Europe (4 x 2.5 kg a.s./ha)

Time (days)	Instantaneous PEC (ug/L)
app 1 (0)	23.39
app 2 (7)	41.20
app 3 (14)	54.77
app 4 (21)	65.09
1 (22)	62.61
2 (23)	60.22
4 (25)	55.70
7 (28)	49.56
14 (35)	37.74
21 (42)	28.73
28 (49)	21.88
42 (71)	12.68
100 (121)	1.33

Numbers in parentheses are days after first application

Table B.8.6.28: Simulated PEC_{SW} values for THPAM following use on nectarines/peaches in Southern Europe (4 x 2.5 kg a.s./ha)

Time (days)	Instantaneous PEC (ug/L)
app 1 (0)	13.22
app 2 (7)	23.29
app 3 (14)	30.95
app 4 (21)	36.78
1 (22)	35.38
2 (23)	34.03
4 (25)	31.48
7 (28)	28.01
14 (35)	21.33
21 (42)	16.24
28 (49)	12.36
42 (71)	7.17
100 (121)	0.75

Numbers in parentheses are days after first application

Table B.8.6.29: Simulated PEC_{sed} for THPI following use on pome fruit in Southern Europe (9 x 1.25 kg a.s./ha + 3 x 2.4 kg a.s./ha)

Time (days)	Instantaneous PEC (ug/kg)	Maximum TWA PEC (ug/kg)	Day interval for TWA PEC calculation
app 1 (0)	38.02		
app 2 (7)	51.86		
app 3 (14)	56.89		
app 4 (21)	58.72		
app 5 (28)	59.39		
app 6 (35)	59.63		
app 7 (42)	59.72		
app 8 (49)	59.75		
app 9 (56)	59.76		
app 10 (63)	94.75		
app 11 (70)	65.53		
app 12 (77)	112.11		
1 (78)	97.03	104.57	(77)
2 (79)	83.99	97.54	(77-78)
4 (81)	62.92	85.31	(77-80)
7 (84)	40.80	70.67	(77-83)
14 (91)	14.85	69.21	(70-83)
21 (98)	5.40	66.05	(63-83)
28 (105)	1.97	58.95	(56-83)
42 (127)	0.26	51.85	(42-83)
100 (177)	0.00	38.65	(0-99)

Numbers in parentheses are days after first application

Table B.8.6.30: Simulated PEC_{sed} values for THPI following use on nectarines/peaches in Southern Europe (4 x 2.5 kg a.s./ha)

Time (days)	Instantaneous PEC (ug/kg)	Maximum TWA PEC (ug/kg)	day interval for TWA PEC calculation
app 1 (0)	76.04		
app 2 (7)	103.71		
app 3 (14)	113.78		
app 4 (21)	117.45		
1 (22)	101.65	109.55	(21)
2 (23)	87.98	102.18	(21-22)
4 (25)	65.91	89.37	(21-24)
7 (28)	42.74	74.03	(21-27)
14 (35)	15.55	72.88	(14-27)
21 (42)	5.66	70.38	(7-27)
28 (49)	2.06	64.77	(0-27)
42 (71)	0.27	49.30	(0-41)
100 (121)	0.00	21.10	(0-99)

Numbers in parentheses are days after first application

B.8.7 Fate and behaviour in air (Annex IIA 7.2.2; Annex IIIA 9.3)

Data requirement 4.17	Relevance of depleted thiophosgen in air should be assessed. An analytical method for monitoring thiophosgene may be needed if it is finally included in the residue definition in air.

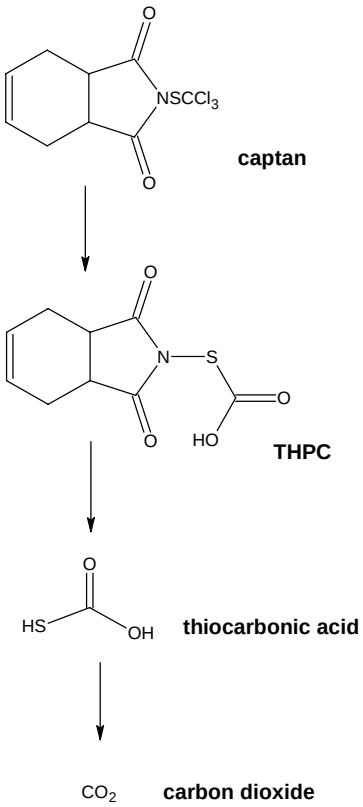
Comment 4(87) EFSA, Soil metabolite thiophosgene should be considered to be relevant to the air compartment. Higher apparent volatility of trichloromethyl^{14}C-Captan (in Pack, D.E. 1987c) could be due to depletion of this toxic metabolite.

Statement from Notifier (ref: Terry, A. 2005. Responses to questions raised in the Reporting Table on fate and behaviour of captan):

The amount of trichloromethyl –^{14}C captan volatilised from the soil surface amounted to 0.4% per day averaged over the 9 day study. As a worst-case, on the first day the amount volatilised comprised < 1%. This would lead to negligible concentrations of thiophosgene in air, even if all the trapped material had been thiophosgene. However, it is known that trichloromethyl^{14}C-captan degrades very rapidly to ^{14}C-carbon dioxide in soil and that hydrolysis at pH7 (the pH of the soil used in the soil volatility study) proceeds *via* THPC. That is, the first step in the degradation of captan under aerobic conditions appears to be oxidation of the trichloromethyl group where the chlorine atoms are replaced by oxygens. This yields firstly THPC and then the release of thiocarbonic acid (rather than thiophosgene), which in turn degrades into carbon dioxide (see Figure B.8.7.1). It is possible that the radioactivity in the methanol trapping solutions consisted of thiocarbonic acid and its derivatives.

Therefore, it is not believed that thiophosgene is relevant for the air compartment.

Figure B.8.7.1: Proposed fate of trichloromethyl side-chain



RMS agrees with above statement.

B.8.7 Rate of degradation in air

Data requirement 4.18	Rate of degradation in air must be provided.

The Notifier has submitted an estimation of the rate of degradation of captan in air according to the Atkinson model:

Report: *Curl, M.G. (2004).The Estimation of Photochemical Oxidative Degradation of Captan. TSGE, unpublished report November 2004.*

The rate constant for the atmospheric, gas phase reaction between photochemically produced hydroxyl radicals (and ozone) and organic chemicals has been estimated using the Atmospheric Oxidation Program v 1.90 (AOPWIN) produced by Syracruse Research Corporation. The rate constants estimated by the program have been used to calculate atmospheric half-lives for captan based on average atmospheric concentrations of hydroxyl radicals and ozone.

The half-life for captan corresponding to reaction with hydroxyl radicals was calculated to be 1.465 hours (12 hour day). The half-life for captan corresponding to reaction with ozone was

calculated to be 1.375 hours (12 hour day). Therefore, the photochemical oxidative half-life of captan in air was predicted to be < 1.5 hours.

B.8.9 Definition of the residue (Annex IIA 7.3)

Open point 4.15: RMS to revise the residue definition in ground water.

Comment 4(81) SE, a definition of the residue in groundwater is missing. We suggest that it include both metabolites THPI and THPAM.

Comment from RMS: The PEC_{GW} calculations (see B.8.6) indicate that there are many use scenarios where captan, THPI and THPAM do not exceed 0.1 µg/L. In those scenarios where THPI and THPAM do exceed 0.1 µg/L, the concentrations are not predicted to reach 10 µg/L. The Notifier has submitted a study which demonstrates that THPI and THPAM are non-relevant in terms of pesticidal (fungicidal) activity. As such, it is proposed that the residue in groundwater should be considered to be captan only (although based on the modelling captan would not occur in groundwater).

B.8.10 Monitoring data

Data requirement 4.19	Report with the monitoring data should be provided and assessed in an addendum by RMS.

Comment 4(90) EFSA: Report quoted is not found in the dossier.

Both the original report (in Dutch) and an English translation of the report text has now been provided by the Notifier:

Report: *Brouwer, P.A.M . (1998) Meetnet Fruitteelt, tusserapportage na 2 jaar, Zulveringschap Hollandse Eilanden en Waarden (Meetnet Fruitteelt, interim report after two years).*

This report summarises the first two years of a monitoring programme set up to measure the exposure to surface water of products used in fruit farming areas in a region of the Netherlands for which the Hollandse Eilanden and Waarden Waste Water Treatment Board has responsibility for. The monitoring programme was set up in 1996 to monitor surface water at locations representative of 1670 ha of fruit growing area in the Dutch regions of Vijfheerenlanden, Alblasserwaard and Hoekse Waard. Actual sampling locations were chosen based on intensively farmed areas (apple and pear production) and such that ditches with immediately adjacent fruit trees (9 locations), ditches with adjacent windbreak tree lines (6 locations) and ditches with no trees within 3 m (3 locations) were represented.

Water samples were collected each month from each sampling location during the spray season (June-December 1996 and March-December 1997). A total of 336 water samples were collected (including a small number of control samples). Analysis was conducted for a large number of pesticides and herbicides known to have been in use in the fruit growing areas, including captan (detection limit of 0.05 µg/L). Although many of the pesticides and herbicides were frequently detected at levels higher than the permitted concentrations, captan was

detected only once (on 16 December 1996, at one site in Vijfheerenlanden), at a level of 0.08 µg/L, below the permitted level (0.3 µg/L). The report went on to recommend that captan be removed as an analytical target from the ongoing monitoring programme.

RMS comment: the report demonstrates that captan contamination of surface water, following use in intensive fruit growing regions in the Netherlands in 1996 and 1997, was negligible. This finding is of limited use with respect to the risk assessment process.

B.8.11 References relied on

B.8.11.1Active ingredient

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
	Terry, A	2005	Responses to questions raised in the Reporting Table on fate and behaviour of captan	Y	Makhteshim/ Calliope
IIA, 7.1.1/04	Terry, A., Price, O.	2005	Fate of captan in soil under aerobic conditions: A Review CEA report CEA.046 Not GLP, Unpublished	Y	Makhteshim/ Calliope
IIA, 7.1.2/03	Wauchope R.D., Buttler T.M., Hornsby A.G., Augustijn-Beckers P.W.M., Burt J.P.	1992	'The SCS/ARS/CES Pesticide Properties Database for Environmental Decision-Making' Reviews of Environmental Contamination and Toxicology, Not GLP, Published	N	-
IIA, 7.2.1.1/06	Terry, A., Price, O.	2005	Kinetic analysis of the degradation of THPC generated in hydrolysis studies on captan at pH9 CEA report CEA.050 Not GLP, Unpublished	Y	Makhteshim/ Calliope
IIA, 7.2.2/02	Curl, M.G.	2004	The estimation of photochemical oxidative degradation of captan. TSGE report 13-3-15/20-2-05 Not GLP, Unpublished.	Y	Makhteshim/ Tomen
IIA, 7.4/01	Brouwer, P. A. M	1998	Meetnet Fruiteelt tussenrapportage na 2 jaar, Zulveringschap Hollandse Eilanden en Waarden. Not GLP, Unpublished.	N	-

B.8.11.2 Formulation

Merpan 80 WDG/ Malvin WG

IIIA 9.1.3/01	Terry, A.	2005	Predicted environmental concentrations of captan and its major degradation products in soil in the European Union. CEA report CEA.045 Not GLP, Unpublished	Y	Makhteshim/ Calliope
IIIA, 9.2.1/02	Terry, A., Price, O.	2005	Predicted Environmental Concentrations of captan and its major degradation products in groundwater in the European Union using the FOCUS groundwater scenarios. CEA report CEA.048 Not GLP, Unpublished	Y	Makhteshim/ Calliope
IIIA, 9.2.3/01	Terry, A.	2005	Predicted Environmental Concentrations of THPI and THPAM in surface water and sediment arising from spray drift, in the European Union CEA report CEA.049 Not GLP, Unpublished	Y	Makhteshim/ Calliope

Captan

Addendum to Draft Assessment Report:

Ecotoxicology

Rapporteur Member State: Italy

EU review under Directive 91/414 EEC

Relating to Annex B (Volume 3) of the DAR

January 2005

Table of Contents

B.9 Ecotoxicology

Introduction

This document is an Addendum to the Draft Assessment Report (DAR) for the EU review of **captan**. The aim of this Addendum is to address comments, 'Open points' and 'Data requirements' as raised in the official Reporting Table (dated 17.01.05) and Evaluation Table (dated 19.01.05) in the area of **Ecotoxicology**.

This Addendum includes summarisation and evaluation of new studies and risk assessments submitted by Makhteshim Chemical Works Ltd and *Calliope (*formerly, Tomen France S.A.S.).

Section numbering in this Addendum is in line with Annex B (Volume 3) of the DAR.

The Good Agricultural Practice (GAP) uses proposed by the Notifier for consideration under the review are specified in Table 1.

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Table 1: Critical Good Agricultural Practice for captan in the EU review

Crop	Member state or country	Product name	F, G or I	Pests or group of pests controlled	Formulation		Application			Application rate per treatment			PHI (days)	Remarks:
					Type	Conc. of a.s.	method kind	growth stage/ timing	number[b] (max.)	kg a.s./hL (max.)	water L/ha	kg a.s./ha (max.)		
Pome fruit	North EU	'Merpan' 80 WDG / 'Malvin' WDG	F[a]	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 53 / April	9 - 10	0.125	1000	1.25	14	
	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69 / April	9 + 3 [c]	0.125 0.24	1000 1000	1.25 2.4	14	
Tomatoes	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Foliar spray; down-wards	From BBCH 60 to 87	4	0.15	1200	1.8	14	
Peaches/ nectarines	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69: petal fall	4	0.25	1000	2.5	7	

[a] F = field.
[b] Applications at a minimum of 7 days for all crops.
[c] Nine applications at 1.25 kg a.s./ha (scab control) followed by three applications at 2.4 kg a.s/ha (*Nectria* control).

B.9.1 Effects on birds (Annex IIA 8.1; Annex IIIA 10.1)
B.9.3 Effects on other terrestrial vertebrates (Annex IIIA 10.3)

As the issues are closely linked, and to avoid duplication, the risk to birds and mammals is evaluated together in this Addendum.

Open Point 5.6:
RMS is proposed to prepare an addendum with a revised risk assessment for birds and mammals according to SANCO/4145/2000. (see reporting table 5(10))

In response to the above, the Notifier has submitted a risk assessment for birds and mammals according to the Guidance document on risk assessment for birds and mammals (SANCO/4145/2000). This is summarised below.

Report: *Norman, S. and Wyness, L. (2003). Captan. Response to Rapporteur Member State request for a revised avian and mammalian risk assessment in accordance with EU guidance document on risk assessment for birds and mammals (SANCO/4145/2000. Makhteshim Agan and TSGE, unpublished report September 2003.*

Guidance: Guidance Document on Risk Assessment for Birds and Mammals under Council Directive 91/414/EEC' (SANCO/4145/2000; 25 September 2002.

Results of toxicity studies on birds and mammals are summarised below in Tables 2 and 5. Overall, captan is of low toxicity.

In accordance with the guidance document on birds and mammals, toxicity:exposure ratios (TER) are based on intake in terms of daily dose (mg/kg body weight/day). Therefore, Tables 3 and 4 present the conversions for bird studies from dietary concentrations to daily doses.

Table 2: Captan: Endpoints from toxicity studies on birds

Study	Species	Endpoint	Result
Acute single oral	Bobwhite quail	LD_{50}	> 2000 mg/kg bw
	Mallard duck	LD_{50}	> 2000 mg/kg bw
Short-term dietary	Bobwhite quail	LC_{50}	> 5200 ppm in diet
	Mallard duck	LC_{50}	> 5200 ppm in diet
One generation reproduction	Bobwhite quail	NOEC (reproductive effects)	1000 ppm in diet *
		NOEC (adults)	1000 ppm in diet *
	Mallard duck	NOEC (reproductive effects)	1000 ppm in diet *
		NOEC (adults)	1000 ppm in diet *

* Highest concentration tested. No treatment-related effects on adults or reproductive parameters at any test level.

Table 3. Conversion of short-term dietary endpoints to daily doses

Species	LC_{50} (ppm in diet)	Mean food intake (g/bird/day)[a]	Mean bodyweight (g/bird)[a]	Mean daily dose (mg/kg bw/day)
Bobwhite	> 5200[b]	3.0	19.5	> 800
Mallard	> 5200[b]	21	105	> 1040

[a] Averaged over the 5 day exposure period.
[b] The highest dietary concentration tested. Food intake was reduced at this treatment level compared with the control, suggesting a possible avoidance reaction. Daily doses are calculated based on mean bodyweight and food intake at this treatment level during the 5 day exposure period.

Table 4: Conversion of long-term dietary endpoints to daily captan dose equivalents

Species	NOEC (ppm in diet)	Mean food intake (g/bird/day)[a,b]	Mean bodyweight (g/bird)[a,c]	Mean daily dose (mg/kg bw/day)
Bobwhite	1000	15.3	204.3	74.9
Mallard	1000	88.2	1186	74.4

[a] Birds of the NOEC treatment group.
[b] Based on 10 weekly values.
[c] Based on 6 weekly values.

For the avian risk assessment the following endpoints are selected:

Acute risk: > 2000 mg captan/kg bw (limit value from two studies)**;**
Short-term risk: > 800 mg captan/kg bw/day (lowest daily dose between two species)**;**
Long-term risk: 74.4 mg captan/kg bw/day (lowest daily dose between two species).

Endpoints from mammalian toxicity studies are summarised in Table 5. The justification for the choice of no observed adverse effect level (NOAEL) from the reproduction studies is contained in the text after the table.

Table 5. Summary of mammalian toxicity studies with captan, Malvin WG and Merpan 80 WDG

Study	Test substance	Species	Endpoint	Result
Acute oral	captan	rat	LD_{50}	> 2000 mg/kg[a]
		rat	LD_{50}	> 5000 mg/kg[a]
		rat	LD_{50}	7000 mg/kg (male) 6170 mg/kg (female)
		mouse	LD_{50}	2110
	'Malvin' WG	rat	LD_{50}	> 5000 mg/kg[a]
	'Merpan' 80 WDG	rat	LD_{50}	> 2000 mg/kg[a]
Acute dermal	'Malvin' WG	rat	LD_{50}	> 2000 mg/kg[a]
	'Merpan' 80 WDG	rat	LD_{50}	> 5000 mg/kg[a]
Oral toxicity, 4 weeks	captan	dog	0, 30, 100, 300, 600, 1000 mg/kg bw/day	100 mg/kg bw/day
Oral toxicity, one-year	captan	dog	0, 12.5, 60, 300 mg/kg bw/day	300 mg/kg bw/day
Inhalation, 90-day (nose only)	captan	rat	0.13, 0.60, 5.06, 12.98 µg/L	0.60 µg/L
Dermal, 3 weeks	captan	rabbit	0, 12.5, 110, 1000 mg/kgbw	local: < 12.5 mg/kg bw, systemic: 110 mg/kg bw
Three- generation reproduction	captan	rat	NOAEL[b]	250 mg/kg bw/day
One-generation reproduction[c]	captan	rat	NOAEL	25 mg/kg bw/day (highest dose tested)

[a] Results for males and females were the same.
[b] No observed adverse effect level for use in ecological risk assessment (see text which follows the table).
[c] One–generation study was a follow-up to the three-generation study, but with testing at lower doses.

Mammalian multigeneration studies are conducted for the purpose of determining hazard and risk to humans. Therefore, the study designs (endpoints, selection of treatment levels) are usually inappropriate for ecological risk assessments. However, from such studies, ecologically meaningful information has to be gained in order to quantify long-term risk to mammals. As stated in the EU guidance document '*The usual approach is based on the consideration that effects on populations will not occur if the survival rate, reproduction rate and development of individuals are not affected. Therefore, in principle, only endpoints in toxicity tests which are related to these key factors of population dynamics are ecotoxicologically relevant.*'

An appropriate endpoint for long-term risk in mammals should be related to the survival of a mammalian population at risk in the field. Such parameters may be reduced survival rate, reproduction rate or development of individuals (as stated above). The three- and one-generation reproduction studies in the rat have been evaluated on this basis in order to derive and appropriate endpoint for use in the long-term risk assessment.

Three-generation reproduction study in the rat:

Captan was administered in the diet to give doses of 25, 100, 250 and 500 mg/kg bw/day. There were no treatment-related effects on general behaviour or appearance of parental rats or pups at any treatment level. Survival of parental rats was unaffected at all treatment levels.

Parental food consumption: There were reductions in parental food consumption, which were correlated with exposure concentration. Reduction in mean F_0 parental food consumption was 5% at 25, 5-6% at 100, 15% at 250, and 19-24% at 500 mg/kg bw/day. The reduction in food consumption was broadly similar in the F_1 and F_2 parents. However, there was less effect in F_2 females at 25, 100 and 250 mg/kg bw/day where differences from the control were 0%, +4.5%, and –3.8%, respectively.

Parental body weight: For the F_0 generation, the combined parental male and female weight reductions compared with the control, where there were statistically significant differences recorded, ranged from 1 - 6% at 25, 4 - 8% at 100, 6 - 13% at 250 and 12 - 18% at 500 mg/kg bw/day. The statistically significant body weight differences were recorded only on two (week 14 and 34) out of 35 weeks of data. For the F_1 parents, the body weight reductions compared with the control were similar at the lower doses, but were slightly increased at 250 mg/kg bw (14 to 16%) and at 500 mg/kg bw (22 to 28%). The body weight reductions compared with the control for F_2 parents were similar to those of the F_1 parents.

The reduction in food consumption corresponded very closely with the reduction in body weight at each dose compared to the control treatment. The body weight reductions are therefore likely to be a result of the reduced consumption of diet containing captan. In turn, the reduced consumption is likely to be related to reduced palatability of diet due to the presence of captan.

Litter size: F_{1a} and F_{1b} mean litter size was reduced compared with the control, although only at 500 mg/kg bw/day in the F_{1b} litter was the reduction statistically significant. The F_{1a} and F_{1b} reductions ranged from 16 to 24% (compared with the control) at 25 mg/kg bw/day to 23 - 45% at 500 mg/kg bw/day. The reduction at 250 mg/kg bw was 15% to 34%. The F_2 mean litter size was reduced only at 250 mg/kg bw/day (F_{2b} only: by 11% compared with control) and at 500 mg/kg bw/day (10 to 24% compared with the control). The F_3 mean litter sizes were reduced only at 500 mg/kg bw/day (by 13% in F_{3a} only). Mean litter size is likely to have been affected by the reduced food consumption of the F_0 females. The effect on litter size was greatest at 500 mg/kg (- 45%) which also showed the highest reduction in food consumption in F_0 females (-23.7%). Reduced food consumption was greatest in the F_0 females and the effect

decreased by the F_2 generation where food consumption by F_2 females was only affected at 500 mg/kg bw/day. This coincided with a lack of effect on the size of F_{3a} and F_{3b} litters at 25 to 250 mg/kg, and a 13% reduction in litter size at 500 mg/kg (F_{3a} only). Overall, reductions in litter size were probably caused by reduced food consumption (as discussed in previous paragraphs), and should not be regarded as a direct effect on reproductive processes. In any case, the slight effects at 250 mg/kg (34% and 15% for F_{1a} and F_{1b}, 0% and 11% in F_{2a} and F_{2b}, and no effect in F_{3a} and F_{3b}) should not be regarded as ecologically significant.

Pup survival: Pup survival (from birth to 4 days) at 25-250 mg/kg day was 95-100% for all litters, and was only 0-4% different from the control. At 500 mg/kg bw pup survival from birth to 4 days was 85-97% (2-14% difference from the control). The slight effect at 500 mg/kg bw/day may be related to reduced food consumption of parental rats.

Teratogenic effects: There were no teratological effects at any dose level during the study.

Pup body weight: Pup body weight at lactation day 21 was slightly lower than the controls at 25 and 100 mg/kg bw/day. Reductions at 25 mg/kg bw/day compared with the control ranged from 1 to 6%, and were 6 to 13% at 100 mg/kg bw/day. At 250 mg/kg bw/day negative differences from the control ranged from 17 to 30% (mean 22%), and were 31 to 44% at 500 mg/kg bw/day. The effect at 250 and 500 mg/kg bw/day is probably related to reduced parental food consumption, and resulting reduced milk production.

Overall: Effects on parental and pup body weights, and litter size, at 250 and 500 mg/kg bw/day can be attributed to reduced parental food consumption. This was probably related to the reduced palatability of the test diet due to the presence of captan, and the lack of an alternative food source. There were no direct effects on reproduction or any cumulative effects of captan, on subsequent generations, in the diet up to 500 mg/kg bw/day. However, at 500 mg/kg bw/day, a slight effect on pup survival was observed (possibly related to reduced parental food consumption). For the purposes of ecological risk assessment, 250 mg/kg bw/day is considered a relevant NOAEL.

One-generation reproduction study in the rat:

As a follow-up study to the three-generation study, captan was administered in the diet at doses up to 25 mg/kg bw/day. There were no effects on parents or reproduction at any dose level. Mean pup bodyweight on lactation days 4, 7 and 14 was slightly lower (5 - 6%) than the controls at 25 mg/kg bw/day, but was then within 1% on lactation day 21. These minor differences from the control are not relevant to the ecological risk assessment. Hence, the NOAEL from the three-generation study should be used in the risk assessment.

Conclusion on long-term endpoint for mammals:

At 250 mg/kg bw/day: Parental food consumption was marginally reduced compared with the control (maximum 15%, as observed in the F_0 generation). This is likely to have been caused by the reduced palatability of the test diet due to the presence of captan, and the lack of an alternative food source. This reduced food consumption probably resulted in the corresponding marginal effect on parental body weight (6 - 16%) and pup weight (22%) at this treatment level. F_1 (a and b) and F_2 (a only) litter sizes were slightly reduced, again correlated with reduced food consumption. Where there was no effect on food consumption in F_2 parental females, there was no effect on litter size (supporting the link between food consumption and litter size). To achieve a dose of 250 mg/kg bw/day dietary concentrations ranged from 1860 to 4480 mg a.s./kg food (increasing during the exposure period) with an overall mean of 3075 mg a.s./kg food. This high concentration is likely to have had a negative influence on the palatability of the test diet. The concentration in the test diet is much higher than could be

carried by sprayed insects or foliage in the field. Hence, the marginally reduced food consumption (and consequent effect on bodyweight and litter size) at 250 mg/kg bw/day is an artefact of the high treatment concentration and would not occur in the field.

Overall, a reasonable NOAEL for ecological risk assessment purposes is 250 mg/kg bw/day. It should be noted that this is based on continuous dosing over a prolonged period (102 days), and therefore is worst case.

An NOEL of 250 mg/kg bw/day is supported by the results from 'short-term' toxicity studies in the dog. Following a one year oral dosing regimen the NOEL was 300 mg/kg bw. A higher incidence of emesis and soft/mucoid stool was sporadically noted in 300 mg/kg bw/day animals compared to the control, although these were also noted in other groups including controls. This was probably a treatment-related effect but was not considered as a toxicological effect. There were no significant differences in group mean body weight at any interval. Food consumption values for females administered test substance appeared lower than control females. However, food consumption in the control group females was considered higher than normal and therefore no toxicological significance is attached to the relatively low food consumption in the 60 and 300 mg/kg bw/day animals. No treatment-related ophthalmological abnormalities were detected. Physical examination findings revealed no significant findings.

In summary a long-term mammalian NOAEL of 250 mg/kg bw/day is supported by a one-year toxicity study with the dog, in which the NOEL was 300 mg/kg bw/day following daily oral dosing of captan in gelatin capsules.

For the mammalian risk assessment the following endpoints are selected:

Acute risk: > 2000 mg captan/kg bw/day (lowest limit value available)**;**
Long-term risk: 250 mg captan/kg bw/day (from the multi-generation reproduction studies and short term toxicity studies discussed above)**.**

Tier 1 Exposure Scenarios

The estimated theoretical exposure (ETE) is based on the following:

ETE = (FIR/bw) x C x AV x PT x PD (mg/kg bw/d)

where:

FIR: Food intake rate of selected indicator species (g fresh wt. food/day);
bw: body weight (g);
C: concentration of captan in fresh diet (mg captan/kg);
AV: avoidance factor (1 = no avoidance);
PT: fraction of diet obtained from treated area (assume 1 for first tier evaluation);
PD: fraction of food type in diet (assume 1 for first tier evaluation).

C_0 is a function of the application rate (kg captan/ha), the residue per unit dose (RUD), and multiple application factor (MAF), taking into account crop interception, where appropriate.

For multiple application products, the concentration C, is expressed as $C = C_0 \times MAF \times f_{twa}$

where:

C_0: initial concentration in food after a single application;
MAF: multiple application factor;
f_{twa}: time-weighted average factor.

Table 6. Tier 1 acute exposure scenarios for birds and mammals

Crop (scenario)	Crop stage	Indicator species	FIR/bw[a]	Food
Pome fruit, peaches, nectarines ('Orchard / vine / hops')	Early/late	Small herbivorous mammal	1.39	Short grass
		Insectivorous bird	1.04	Small insects
Tomatoes ('Leafy crops')	Early/late	Medium herbivorous mammal	0.28	Leafy crops
		Medium herbivorous bird	0.76	Leafy crops
		Insectivorous bird	1.04	Small insects

[a] Food intake rate based on food type, energy contents of foods, assimilation efficiencies and moisture contents.

Short grasses beneath pome fruit and nectarine/peach trees will be exposed to a fraction of the applied spray deposit as a result of crop interception. For orchard crops including peaches and nectarines, interception factors as stated in the EU guidance document are 70% during foliar development and 80% at full foliage. Given that captan is applied during these periods, an average of 75% interception of the spray deposit is assumed in the exposure calculations below. Acute ETE values are presented in Table 7.

Table 7. Captan acute ETE values for birds and mammals

Crop (scenario)	Indicator species	App. rate (kg captan/ha)	RUD (90%)[a]	Crop interception	MAF[b]	C (mg captan/kg diet)[c]	ETE (mg captan/kg bw/day)[e]
Pome fruit North EU. ('Orchard / vine / hops')	Small herbivorous mammal	1.25	142	75% (deposition 0.25)	2.0	88.8	123.4
	Insectivorous bird	1.25	52	n/a	n/a	65.0	67.6
Pome fruit South EU. ('Orchard / vine / hops')	Small herbivorous mammal	2.4	142	75% (deposition 0.25)	1.7[d]	144.8	201.3
	Insectivorous bird	2.4	52	n/a	n/a	124.8	129.8
Peaches/ nectarines ('Orchard / vine / hops')	Small herbivorous mammal	2.5	142	75% (deposition 0.25)	1.8	159.8	222.1
	Insectivorous bird	2.5	52	n/a	n/a	130.0	135.2
Tomatoes ('Leafy crops')	Medium herbivorous mammal	1.8	87	n/a	1.8	281.9	78.9
	Medium herbivorous bird	1.8	87	n/a	1.8	281.9	214.2
	Insectivorous bird	1.8	52	n/a	n/a	93.6	97.3

[a] Residue per unit dose (90th percentile).
[b] MAF based on number of applications and spray interval.
[c] Concentration of captan in fresh diet (application rate x RUD x deposition x MAF); no interception or MAF applicable to insects as a food source.
[d] Number of applications taken to be three, since the previous 9 applications are represented by the uses in North EU.
[e] ETE = C x FIR/bw.

Short term exposure scenarios for birds are stated in Table 8.

Table 8. Tier 1 short-term exposure scenarios for birds

Crop (scenario)	Crop stage	Indicator species	FIR/bw[a]	Food
Pome fruit, peaches, nectarines ('Orchard / vine / hops')	Early/late	Insectivorous bird	1.04	Small insects
Tomatoes ('Leafy crops')	Early/late	Medium herbivorous bird	0.76	Leafy crops
		Insectivorous bird	1.04	Small insects

[a] Food intake rate based on food type, energy contents of foods, assimilation efficiencies and moisture contents.

Short term ETE values for the above scenarios are presented in Table 9.

Table 9. Captan short-term ETE values for birds and mammals

Crop (scenario)	Indicator species	App. rate (kg captan/ha)	RUD mean[a]	Crop interception	MAF[b]	C (mg captan/kg diet)[c]	ETE (mg captan/kg bw/day)
Pome fruit North EU ('Orchard / vine / hops')	Insectivorous bird	1.25	29	n/a	n/a	36.3	37.7
Pome fruit South EU ('Orchard / vine / hops')	Insectivorous bird	2.4	29	n/a	n/a	69.6	72.4
Peaches/ nectarines ('Orchard / vine / hops')	Insectivorous bird	2.5	29	n/a	n/a	72.5	75.4
Tomatoes ('Leafy crops')	Medium herbivorous bird	1.8	40	n/a	2.2	158.4	120.4
	Insectivorous bird	1.8	29	n/a	n/a	52.2	54.3

[a] Residue per unit dose (90th percentile).
[b] MAF based on number of applications and spray interval.
[c] Concentration of captan in fresh diet (application rate x RUD x deposition x MAF); no interception or MAF applicable to insects as a food source.

Long-term exposure scenarios for birds and mammals are stated in Table 10.

Table 10: Tier 1 long-term exposure scenarios for birds and mammals

Crop (scenario)	Crop stage	Indicator species	FIR/bw[a]	Food
Pome fruit, peaches, nectarines ('Orchard / vine / hops')	Early/late	Small herbivorous mammal	1.39	Short grass
		Insectivorous bird	1.04	Small insects
Tomatoes ('Leafy crops')	Early/late	Medium herbivorous mammal	0.28	Leafy crops
		Medium herbivorous bird	0.76	Leafy crops
		Insectivorous bird	1.04	Small insects

[a] Food intake rate based on food type, energy contents of foods, assimilation efficiencies and moisture contents.

Long term ETE values are presented in Table 11, including the use of the standard time-weighted average factor of 0.53 for foliar residues.

Table 11: Captan long-term ETE values for birds and mammals

Crop	Indicator species	App. rate (kg captan/ha)	RUD mean[a]	Crop interception	MAF[b]	C (mg captan/kg diet)[c,e]	ETE (mg captan/kg bw/day)
Pome fruit North EU ('Orchard / vine / hops')	Small herbivorous mammal	1.25	76	75% (deposition 0.25)	2.5	31.5	43.7
	Insectivorous bird	1.25	29	n/a	n/a	36.3	37.7
Pome fruit South EU ('Orchard / vine / hops')	Small herbivorous mammal	2.4	76	75% (deposition 0.25)	2.0[d]	48.4	67.2
	Insectivorous bird	2.4	29	n/a	n/a	69.6	72.4
Peaches/ nectarines ('Orchard / vine / hops')	Small herbivorous mammal	2.5	76	75% (deposition 0.25)	2.2	55.4	77.0
	Insectivorous bird	2.5	29	n/a	n/a	72.5	75.4
Tomatoes ('Leafy crops')	Medium herbivorous mammal	1.8	40	n/a	2.2	84.0	23.5
	Medium herbivorous bird	1.8	40	n/a	2.2	84.0	63.8
	Insectivorous bird	1.8	29	n/a	n/a	52.2	54.3

[a] Residue per unit dose (mean).
[b] MAF based on number of applications and spray interval.
[c] Concentration of captan in fresh diet (application rate x RUD x deposition x MAF); no interception or MAF applicable to insects as a food source.
[d] Number of applications taken to be three, since the previous 9 applications are represented by the uses in North EU.
[e] Including standard time-weighted average factor of 0.53 for foliar residues.

Risk Assessment for Birds and Mammals

Tier 1 Toxicity exposure ratios (TERs) are presented in Tables 12, 13 and 14.

Tier 1 Acute risk assessment

Table 12: Tier 1 acute TER values for birds and mammals

Crop	Indicator species	ETE (mg captan/kg bw/day)	LD_{50} (mg captan/kg bw)	TER_a
Pome fruit (North EU)	Small herbivorous mammal	123.3	> 2000	>16.2
	Insectivorous bird	67.6	> 2000	>29.6
Pome fruit (South EU)	Small herbivorous mammal	201.3	> 2000	>9.9
	Insectivorous bird	129.8	> 2000	>15.4
Peaches/ nectarines	Small herbivorous mammal	222.1	> 2000	>9.0
	Insectivorous bird	135.2	> 2000	>14.8
Tomatoes	Medium herbivorous mammal	78.9	> 2000	>25.3
	Medium herbivorous bird	214.2	> 2000	>9.3
	Insectivorous bird	97.3	> 2000	>20.6

Captan has a low acute toxicity to birds and mammals with LD50s of >2000 mg/kg bw (generally the highest dose which is tested in acute toxicity studies). Hence, all TERs are also '*greater than*' values. Three of these values in Table 12 are slightly below the Annex VI trigger of 10 (>9.0, >9.3, >9.9). However, it is clear that if the tested dose was marginally above 2000 mg/kg bw, then these TERs would be greater than the trigger. In any case, the foliage of tomato plants is not an attractive food source for birds, so the TER for medium herbivorous birds is not relevant to the risk assessment. All other TERs are greater than the Annex VI trigger of 10 indicating a low risk. Overall, there is a low acute risk to birds and mammals.

Tier 1 Short-term risk assessment

Table 13: Tier 1 short-term TER values for birds

Crop	Indicator species	ETE (mg captan/kg bw/day)	LD_{50} (mg captan/kg bw)	TER_{st}
Pome fruit (North EU)	Insectivorous bird	37.7	> 800	>21.2
Pome fruit (South EU)	Insectivorous bird	72.4	> 800	>11.0
Peaches/nectarines	Insectivorous bird	75.4	> 800	>10.6
Tomatoes	Medium herbivorous bird	120.4	> 800	>6.6
	Insectivorous bird	54.3	> 800	>14.7

The TER for medium herbivorous birds in tomatoes is less than the trigger of 10 (although it is a 'greater than' value). However, the foliage of tomato plants is not an attractive food source for birds. Hence, the risk is low. All other short term TERs in Table 13 are greater than the Annex VI trigger of 10, indicating a low risk.

Tier 1 Long-term risk assessment

Table 14: Tier 1 long-term TER values for birds and mammals

Crop	Indicator species	ETE (mg captan/kg bw/day)	NOEC (mg captan/kg bw)	TER_{lt}
Pome fruit (North EU)	Small herbivorous mammal	43.7	250	5.7
	Insectivorous bird	37.7	74.4	2.0
Pome fruit (South EU)	Small herbivorous mammal	67.2	250	3.7
	Insectivorous bird	72.4	74.4	1.0
Peaches/ nectarines	Small herbivorous mammal	77.0	250	3.2
	Insectivorous bird	75.4	74.4	1.0
Tomatoes	Medium herbivorous mammal	23.5	250	10.6
	Medium herbivorous bird	63.8	74.4	1.2
	Insectivorous bird	54.3	74.4	1.4

The long-term TER for small mammals in pome fruit in North EU is greater than the Annex VI long-term trigger of 5. Hence, there is a low risk. Similarly the TER for medium herbivorous mammals in tomatoes is >5, indicating a low risk (in any case tomato foliage is unlikely to be grazed). The long-term TER values for small herbivorous mammals in South EU pome fruit and peaches/nectarines, and insectivorous birds for all uses, are less than 5.0. Hence, further assessment is required. A refined risk assessment is described below.

Refined assessment of long term risk

General:

The Tier 1 scenarios as presented in the EU guidance document on risk assessment for birds and mammals have a tendency to combine worst case elements (exposure concentration; extent and duration of exposure; daily food consumption) leading to high predicted intakes, but with a low probability of occurrence. Together with the long-term TER trigger of 5, the scenarios provide a very conservative first tier screen to identify low risk situations (TER>5), and indicate where refinement is needed (TER <5).

Captan undergoes rapid hydrolysis, with a DT_{50} of 2.6 hours at pH 7 and 25 °C in sterile water (Ref: Pack, 1987). In the presence of moisture on leaf surfaces (dew and rain), this property would limit the potential duration and magnitude of exposure of grazing birds and mammals.

Birds:

Low toxicity: Captan caused no treatment-related effects on adults or reproductive processes in birds at 1000 ppm in the diet (the highest concentration tested) in bobwhite quail and mallard. It is common to set the highest treatment level in avian reproduction studies at 1000 ppm. Having no effects at this high concentration indicates an inherent low long-term toxicity.

Concentrations on insects ('C'): Exposure predictions in the Tier 1 risk assessment for insects are based on the published paper by Hoerger and Kenaga (1972), and are extrapolated from generic measurements of residues on small seeds (residue per unit dose, i.e. RUD, of 29). The EU guidance document clearly states that this residue estimate for small insects 'appears unsatisfactory…'. In Tier 1, it is also assumed that birds feed constantly (and exclusively) on insects carrying initial concentrations. The EU guidance document on risk assessment for birds and mammals (Appendix 2) provides a comprehensive review of available data on

residues on food items, including data on insects. For long-term exposure it is suggested that an arithmetic mean residue value is used. For foliar insects, this value is stated to be 5.1 mg/kg (normalised for an application rate of 1 kg a.s./ha), and is derived from the generic database collected by Fischer and Bowers (1997). It was commented by the Scientific Committee on Plants (SCP) that these data should be used for large insects only, due to a bias in the sampling methods. However, in comparison with a Tier 1 extrapolation based on small *seeds*, these data for measured levels on *insects* provide a useful basis for refining the risk assessment. Hence, an RUD of 5.1 mg/kg has been used for refined exposure estimates. No generic estimates of dissipation of residues on insects are currently available. Hence, at present, assessments have to be based on initial residues. In any case, this fully addresses the exposure from the proposed multiple applications. An RUD of 5.1 mg/kg has been used in the refined TERs for insectivorous birds stated in Table 15.

Proportion of diet obtained from the treated area ('PT'): Research by the Central Science Laboratory in the UK has studied the behaviour of insectivorous birds in orchards. The results of this research are quoted (on p31) in the EU guidance document. The data indicate that for blue tits (a common example of a small insectivore, and one of two species used in the standard scenario) 95% of the local population spent less than 61% of potential foraging time among orchard trees. Hence, as a conservative (95^{th} percentile) refinement option PT may be adjusted to 0.61 for applications in orchards (there is also the potential to use lower percentiles for long term assessments). As this PT value is based on the 95^{th} percentile, it is also proposed to extrapolate to nectarine and peach orchards, to provide a general indication of how PT can be refined. Hence, a PT of 0.61 has been used to derive the refined TERs stated in Table 15 for insectivorous birds in orchards.

Attractiveness of tomato foliage as a food source: It is generally recognised that the foliage of tomato plants is not an attractive food source for birds. Hence, there is minimal potential for consumption of foliage treated with captan. Hence, the TER of 1.2 for a medium herbivorous bird (in Table 14) is not relevant for the risk assessment. Therefore, the risk to herbivorous birds from the use in tomatoes will be low.

Mammals:

Low toxicity: Ecologically relevant endpoints should be selected from multigeneration studies. Multigeneration studies on the rat for captan have shown no ecologically significant effects on individuals or reproductive success at 250 mg/kg bw. Such an endpoint indicates an inherent low long term toxicity.

Proportion of diet obtained from the treated area ('PT'): The tier 1 standard scenarios are based on the assumption of long term feeding exclusively on contaminated foliage. The tier 1 scenario is based on the worst case of a field vole. The field vole occurs typically in ungrazed grassland or in the early stages of forestry plantations but may also live in woodland, hedgerows, dunes, scree or moorland, wherever grass is available (ref: website of The Mammal Society). The grass under trees in a commercial orchard is likely to be managed in some way, and in any case its growth will be restricted by shading from the trees. It is unlikely that a field vole would obtain its entire diet of grass from the treated area over an extended period. It is more likely that feeding in field margins and ungrazed grassland would make up a significant portion of the diet. A more reasonable generic assumption (still worst case) would be that 50% of the diet is obtained from the treated area over the long term. A PT value of 50% has been used in the derivation of refined TER values which are stated in Table 15. It should also be noted that the growth of contaminated grass will serve to dilute the residue, and further mitigate potential magnitude and duration of exposure.

Food intake: It should be noted that the assumption of 139% daily food consumption compared with bodyweight makes the Tier 1 scenario particularly worst case. Larger herbivores would tend to have a lower consumption relative to bodyweight, and hence, have a lesser potential for exposure.

Refined TERs for birds and mammals are presented in Table 15.

Table 15: Refined long-term ETE and TER values for birds and mammals

Crop	Indicator species	Standard ETE (mg a.s./kg bw/day)	Refined ETE (mg a.s./kg bw/day)	NOEC (mg a.s./kg bw)	Refined TER_{lt}
Pome fruit North EU	Insectivorous bird	37.7	37.7 x 5.1/29 x 0.61 = 4.0	74.4	18.6
Pome fruit South EU	Small herbivorous mammal	67.2	67.2 x 0.5 = 33.6	250	7.4
	Insectivorous bird	72.4	72.4 x 5.1/29 x 0.61 = 7.8	74.4	9.5
Peaches/ nectarines	Small herbivorous mammal	77.0	77.0 x 0.5 = 38.5	250	6.5
	Insectivorous bird	75.4	75.4 x 5.1/29 x 0.61 = 8.1	74.4	9.2
Tomatoes	Insectivorous bird	54.3	54.3 x 5.1/29 = 9.5	74.4	7.8

All the refined TERs are greater than the Annex VI trigger of 5, indicating a low risk.

Conclusions: Overall, there is a low risk to birds and mammals.

Comments from RMS on birds and mammals risk assessment submitted by the Notifier:

Captan is of relatively low toxicity to birds and mammals. Where TER values are low, this is a result of the relatively high application rates and number of applications, rather than inherent toxicity. The RMS supports the risk assessment submitted by the Notifier. One query would be whether an RUD of 5.1 covers the worst case of the consumption of *small* insects by birds. However, it is recognised that this value is used in the *long*-term assessment and over this period the diet of an insectivorous bird is likely to consist of a mixture of small and large insects. In addition, the long term endpoints for birds are derived from the highest treatment levels in the reproduction studies, with no indications of reproductive effects in the studies. The long term risk to insectivorous birds is considered to be acceptable.

The assessment as presented above is considered to have addressed the following comments as presented in the Reporting Table: 5(10), 5(12), 5(15), 5(16), 5(17), 5(18), 5(19)(partially, with remainder of question addressed below), 5(20), 5(33), 5(34)(partially, with remainder of question addressed below), 5(35) and the additional two comments received from Germany (in letter dated 29.10.04).

Additional responses to address comments in Reporting Table on birds and mammals assessments:

Comment 5(19) (UK):

Suggestion to use 7 day twa for foliar residues (as this is minimum interval between treatments).

Statement from Notifier (Ref: Norman, 2005): Using the formula on p 27 of the EU guidance document on birds and mammals, based on the default foliar DT50 of 10 days, the time weighted average factor (ftwa) can be calculated for a 7 day period (instead of default 21 d) as follows:

ftwa = $(1-e^{-kt})/kt$ k = ln2/DT50 t = averaging time

k = 0.6931471/10 = 0.0693147 t = 7

ftwa = $(1 - e^{-0.485203})/0.485203$ = (1 – 0.6155722)/0.485203 = **0.792303**

With reference to Table 15, for herbivorous small mammals in south EU pome fruit (feeding on 'short grass' under the trees) this ftwa can be used to adjust the TER of 7.4 to give a TER of (0.53/0.79) x 7.4 = 5.0. This TER is equal to the trigger of 5, indicating low risk.

For peaches (using the assumptions in Table 15), using an ftwa of 0.79 the mean time-weighted residue for the three 7 day periods following the final 3 applications can be calculated as follows (for feeding of small mammals on 'short grass' under the trees). This effectively provides a 21 d twa residue for the period of the final 3 applications:

Estimated residue (mg/kg) = appln rate x deposition rate x RUD x MAF x PT x ftwa

for 2 applications, residue = 2.5 x 0.25 x 76 x 1.6 x 0.79 x 0.5 = 30.02 mg/kg
for 3 applications, residue = 2.5 x 0.25 x 76 x 2.0 x 0.79 x 0.5 = 37.525 mg/kg
for 4 applications, residue = 2.5 x 0.25 x 76 x 2.2 x 0.79 x 0.5 = 41.2775 mg/kg
mean = 36.27 mg/kg

ETE for small herbivorous mammal = 36.27 x 1.39 (FIR) = 50.41 mg/kg bw/day
TER = 250 / 50.41 = 4.96

The TER is approximately equal to the trigger of 5, indicating low risk. It is not necessary to repeat this calculation for tomatoes, as the foliage of these plants (member of Solanceae) is unlikely to be consumed by birds or mammals.

The RMS agrees with the above statement.

Comment 5 (34) (FR):

'NOEC of 12.5 mg/kg/day [from Benson, 1982b] is proposed to cover toxic effects on pups. Toxic effects on pups should be considered in the risk assessment.':

Statement from Notifier (Ref: Norman, 2005): The above comment relates to the one generation study in the rat. The 'effect' at the next highest dose level of 25 mg/kg bw (the highest treatment level in the study) was a 5-6% reduction in pup weight. This is not considered to be ecologically significant. It is considered that the risk assessment should be

based on observations which are relevant for reproductive performance in the field (e.g. marked effects on litter size and pup weight which are a direct effect of the test material). Hence, the treatment level of 250 mg/kg bw from the three generation study is considered a relevant endpoint for the risk assessment.

The RMS agrees with the above statement.

For other comments in the Reporting Table on the bird and mammal assessments, responses from the RMS are provided in the Reporting Table itself. These are: 5(11)(=Open Point 5.7, in the Evaluation Table), 5(14).

Overall conclusion of the RMS:

It is concluded that there is a low risk to birds and mammals from the proposed uses.

B.9.2 Effects on aquatic organisms (Annex IIA 8.2; Annex IIIA 10.2)

Relevant Open Points and Data requirement from the Evaluation Table are listed below:

Open point 5.8: Pending on the outcome of the discussion on the PECsw and water sediment study in the section on Fate and behaviour, a revision of the aquatic risk assessment may be necessary. (see reporting table 5(21))
Open point 5.9: MS to discuss the aquatic risk assessment in an expert meeting taking into account the written comments from DE (29-10-2004). (see reporting table 5(22))
Open point 5.10: RMS to prepare an addendum with a revised risk assessment to fish (based on the LC_{50} of 98 µg/L). (see reporting table 5(24))
Open point 5.11: RMS to prepare an addendum to revise the endpoints for aquatic organisms (based on measured concentrations if appropriate) and revise the aquatic risk assessment if necessary. (see reporting table 5(29))
Open point 5.12: RMS to prepare an addendum regarding the risk of the metabolite THPAI to sediment dwelling organisms (THPAI was not tested on aquatic invertebrates) to be discussed in an expert meeting. (see reporting table 5(32))
Data requirement 5.1: Notifier to submit the composition of the tested formulations to proof their comparability to the lead formulations. (see reporting table 5(31))

Data on the toxicity of captan and metabolites to aquatic organisms have been fully summarised in Section B.9.2 Annex B/Volume 3 of the DAR. Following comments and Open Points recorded in the Reporting Table and Evaluation Table, and additional comments from Germany (in letter dated 29.10.04) the risk assessment section (B.9.2.6) has been amended and presented in full below. This replaces the version of this section (B.9.2.6) in the DAR.

Change in the Ecologically Acceptable Concentration (EAC):

In response to **Open Point 5.10**, the risk assessment has been amended to change the EAC so that it is now based on the static acute LC50 for the most sensitive fish species tested (brown trout: LC50 98 µg a.s./l), together with an uncertainty factor (TER trigger) of 10. Hence, the **EAC** is **9.8 µg a.s./l**. This approach was supported in the following comments:

5(24)(**NL**)(fully supported);
5(25)(**DK**, although states 'The appropriate safety factor should be discussed');
5(26)(**FR**, although states 'We are not convinced that a safety factor of 10 is sufficient as assessment remains based on acute effects');
5(27)(**UK**)(fully supported).

Validity of toxicity studies on fish (**Open Point 5.9**):

One of the comments from Germany (in letter dated 29.10.04; **Open Point 5.9**) stated that: 'The acute and chronic toxicity studies with fish presented for captan in the DAR are predominantly not valid since the chemical analysis was only performed in the stock solutions but not in the test media.'.

In response to the above comment, the Notifier has supplied two new static acute

toxicity studies (on rainbow trout, and stickleback) which include analysis of the test media. These studies are a repeat of two previously submitted studies (which were in a series of studies on six fish species). They were conducted according to the same study design, using the same test concentrations, and at the same laboratory as the previous studies. The purpose of these studies is to justify that the previous studies on six fish species included exposure at close to the nominal concentrations. This can be achieved by comparing the LC50 values in terms of measured initial concentrations, with those derived in the previous studies (on rainbow trout and stickleback) which were based on nominal concentrations.

The RMS considers the above to be a reasonable approach. In the interests of minimising vertebrate testing it is considered acceptable that two studies have been repeated, rather than all six in the series. The new studies are summarised below:

i) *Captan: acute toxicity to rainbow trout (Jenkins, C. A. 2004a)*

Repeat of a previous study ref: Jenkins C.A, 2002a, which is summarised on p 172 of Annex B of the DAR. The new study includes analysis of test media for captan.

The 96-hour acute toxicity of captan technical (purity 95.4% w/w) to rainbow trout (*Oncorhynchus mykiss*, mean wet weight 1.9 g, mean fork length 5.3 cm) was determined in a static test system without replacement of the test medium. Groups of seven fish in glass aquaria containing 35 L of test medium (12 to 15°C, 16:8 hour light/dark regime) were exposed to nominal concentrations of captan technical (dissolved in dimethylformamide) at 30.1, 66.1, 145, 320 and 704 µg/L in comparison with a dilution water control treatment (dechlorinated, softened tap water, total hardness approximately 180 mg $CaCO_3$/L) and a solvent control treatment (100 µL dimethylformamide/L) for four days. The fish were not fed during exposure.

Samples of test media were taken at 0 and 48 hours, and were analysed using a gas chromatograph fitted with an electron capture detector (GC-ECD). The 0 hour samples were taken at the same time the fish were added. Measurements of pH, dissolved oxygen and temperature were taken daily in all test vessels and hardness was measured at the start of the test. Temperature was monitored continuously in the control medium. Mortality and behaviour were recorded at 2, 4, 24, 48, 72 and 96 hours after the start of exposure.

The study met the essential criteria of OECD 203 and EC Methods Part C 1. It was conducted according to Good Laboratory Practice.

Measured concentrations in the test media at 0 hours ranged between 79 and 91% of nominal, giving initial mean measured concentrations of 24.2, 58.2, 124, 279 and 623 µg captan technical/L. At 48 hours, no captan was detected in the test media. Full analytical results are presented in Table 16

Table 16: Results of analysis of test media in acute toxicity study on rainbow trout

Nominal concentrations (µg/L)		Measured captan concentrations (µg/L)				
captan technical	captan	0 hours		mean	48 hours	
control	-	nd	nd	-	nd	nd
solvent control	-	nd	nd	-	nd	nd
30.1	28.7	22.7 (79)	23.4 (82)	23.1	nd	nd
66.1	63.1	57.7 (91)	53.3 (84)	55.5	nd	nd
145	139	117.5 (85)	119.3 (86)	118	nd	nd
320	305	275.6 (90)	257.0 (84)	266	nd	nd
704	672	579.6 (86)	609.4 (91)	595	nd	nd

nd: none detected.

( ): measured concentration expressed as a percentage of the nominal concentration.

Note: The concentrations of captan technical, calculated from the initial mean measured levels of captan and a purity of 95.4%, were 24.2, 58.2, 124, 279 and 623 µg/L.

Results for cumulative mortality of fish are presented in Table 17. A summary of observations of sublethal effects is contained in Table 18.

Table 17: Cumulative mortality in an acute toxicity study on rainbow trout

Exposure conc. (µg/L)		Cumulative mortality (initial population = 7 fish/concentration)						
captan technical[#]	captan*	2h	4h	24h	48h	72h	96h	%
Control	nd	0	0	0	0	0	0	-
Solvent control	nd	0	0	0	0	0	0	-
24.2	23.1	0	0	0	0	0	0	-
58.2	55.5	0	0	0	0	0	0	-
124	118	0	0	0	0	0	0	-
279	266	0	1	7	7	7	7	100
623	595	1	7	7	7	7	7	100

nd: none detected. * : initial mean measured levels.

[#]: calculated levels, based on initial mean measured levels of captan .

Table 18: Sub-lethal effects in an acute toxicity study on rainbow trout

Exposure conc. (µg/L)		Abnormalities	Initial population = 7 fish / concentration					
captan technical[#]	captan*		2h	4h	24h	48h	72h	96h
Control	nd	Hyperventilation	-	2/7	-	2/7	1/7	-
Solvent control	nd	None exhibited	All fish appeared normal					
24.2	23.1	Darkened pigmentation	1/7	17	1/7	1/7	1/7	1/7
58.2	55.5	Hyperventilation	1/7	1/7	-	-	-	-
124	118	Hyperventilation	5/7	7/7	7/7	-	6/7	2/7
		Darkened pigmentation	-	-	1/7	2/7	2/7	2/7
		Lethargy	-	-	-	-	-	2/7
279	266	Hyperventilation	7/7	6/6	All dead			
		Darkened pigmentation	2/7	1/6				
		Bleeding (fin)	-	1/6				
623	595	Loss of co-ordination	2/6	All dead				
		Hyperventilation	6/6					

nd : none detected. *: initial mean measured levels.
[#] : levels, based on initial mean measured levels of captan .
x/y : number of fish affected / number of fish surviving. - : not applicable.

LC50 values were calculated using the results in Table 18. These values are based on **mean measured initial concentrations**. Values are expressed in terms of concentration of captan technical. The 24, 72 and **96 hour LC50 was 186 µg a.s./L** (95% C.I: 124-279 µg/L).

(ii) *Captan: acute toxicity to 3-spined stickleback (Jenkins, C. A. 2004b)*

Repeat of a previous study ref: Jenkins C.A, 2002d, which is summarised on p 176-177 of Annex B of the DAR. The new study includes analysis of test media for captan.

The 96-hour acute toxicity of captan technical (purity 95.4% w/w) to the 3-spined stickleback (*Gasterosteus aculeatus*, mean wet weight 0.57 g, mean fork length 3.58 cm) was determined in a static test system without replacement of the test medium. Groups of seven fish in glass aquaria containing 10 L of test medium (12 to 15°C, 16:8 hour light/dark regime) were exposed to nominal concentrations of captan technical (dissolved in dimethylformamide) at 23.3, 51.2, 113, 248, 545 and 1,200 µg/L in comparison with a dilution water control treatment (dechlorinated, softened tap water, total hardness approximately 180 mg $CaCO_3$/L) and a solvent control treatment (100 µL dimethylformamide/L) for four days. The fish were not fed during exposure.

Samples of test media were taken at 0 and 48 hours, and were analysed using a gas chromatograph fitted with an electron capture detector (GC-ECD). Measurements of pH, dissolved oxygen and temperature were taken daily in all test vessels and hardness was measured at the start of the test. Temperature was monitored continuously in the control medium. Mortality and behaviour were recorded at 2, 4, 24, 48, 72 and 96 hours after the start of exposure.

The study met the essential criteria of OECD 203 and EC Methods Part C1. It was conducted according to Good Laboratory Practice.

Measured concentrations in the test media at 0 hours ranged between 64 and 91% of nominal, giving initial mean measured concentrations in terms of captan technical of 15.3, 39.9, 95.3, 180, 399 and 1088 µg/l. At 48 hours, no captan was detected in the test media. Full analytical results are presented in Table 19.

Table 19: Results of analysis of test media in acute toxicity study on 3-spined stickleback

Nominal concentrations (µg/L)		Measured captan concentrations (µg/L)				
Captan Technical	captan	0 hours		mean	48 hours	
control	-	nd	nd	-	nd	nd
solvent control	-	nd	nd	-	nd	nd
23.3	22.2	14.2 (64)	15.0 (68)	14.6	nd	nd
51.2	48.8	36.5 (75)	39.7 (81)	38.1	nd	nd
113	108	87.5 (81)	94.3 (87)	90.9	nd	nd
248	237	162.8 (69)	180.7 (76)	172	nd	nd
545	520	362.9 (70)	399.3 (77)	381	nd	nd
1200	1145	1030.4 (90)	1044.7 (91)	1038	nd	nd

nd: none detected.

( ): measured concentration expressed as a percentage of the nominal concentration.

Note: The concentrations of captan technical, calculated from the initial mean measured levels of captan and purity of 95.4%, were 15.3, 39.9, 95.3, 180, 399 and 1088 µg/L.

Results for cumulative mortality of fish are presented in Table 20. A summary of observations of sublethal effects is contained in Table 21.

Table 20: Cumulative mortality in an acute toxicity study on 3-spined stickleback

Exposure conc. (µg/L)		Cumulative mortality (initial population = 7 fish/concentration)						
captan technical[#]	captan*	2h	4h	24h	48h	72h	96h	%
Control	nd	0	0	0	0	0	0	-
Solvent control	nd	0	0	0	0	0	1	14
15.3	14.6	0	0	0	0	0	0	-
39.9	38.1	0	0	0	0	0	0	-
95.3	90.9	0	0	0	0	0	0	-
180	172	0	0	0	0	0	0	-
399	381	0	1	2	4	4	4	57
1088	1038	0	5	7	7	7	7	100

nd: none detected. [#] : calculated levels, based on initial mean measured levels of captan.

* : initial mean measured levels.

Table 21: Sub-lethal effects in an acute toxicity study on 3-spined stickleback

Exposure conc. (µg/L) captan technical[#]	captan*	Abnormalities	Initial population = 7 fish / concentration 2h	4h	24h	48h	72h	96h
Control	nd	None exhibited	All fish appeared normal					
Solvent control	nd	None exhibited	All fish appeared normal					
15.3	14.6	Aggression	1/7	-	1/7	1/7	1/7	1/7
39.9	38.1	None exhibited	All fish appeared normal					
95.3	90.9	Hyperventilation	-	-	1/7	1/7	-	-
180	172	Hyperventilation	3/7	3/7	3/7	2/7	-	-
		Lethargy	3/7	2/7	3/7	2/7	-	-
399	381	Loss of co-ordination	1/7	-	-	-	-	-
		Hyperventilation	4/7	6/6	5/5	3/3	1/3	-
1088	1038	Hyperventilation	7/7	2/2	All dead			
		Darkened pigmentation	-	1/2				
		Loss of co-ordination	-	1/2				

nd: none detected. *: initial mean measured levels.
[#]: calculated levels, based on initial mean measured levels of captan.
x/y : number of fish affected / number of fish surviving. - : not applicable

LC50 values were calculated using the results in Table 18. These values are based on **mean measured initial concentrations**. Values are expressed in terms of concentration of captan technical. The 24 hour LC50 was 509 µg a.s./L. The 48, 72 and **96 hour LC50 was 370 µg a.s./L** (95% C.I: 285-532 µg/L).

Comparison of results of the two new acute toxicity studies on fish with the previous corresponding studies on rainbow trout and stickleback:

The results (LC50 values) are compared in Table 22:

Table 22: Comparison of results between new and previous static acute studies on rainbow trout and 3-spined stickleback

Species		**Previous study (Jenkins, 2002a) µg a.s./L***	**New study (Jenkins, 2004a) µg a.s./L****
rainbow trout	24 h LC50	215	186
	48 h LC50	215	186
	72 h LC50	215	186
	96 h LC50	215	186
		Previous study (Jenkins, 2002d) µg a.s./L *	New study (Jenkins, 2004b) µg a.s./L**
Stickleback	24 h LC50	367	509
	48 h LC50	275	370
	72 h LC50	275	370
	96 h LC50	275	370

*Results based on **nominal** concentrations, supported by analysis of applied stock solutions.
Results based on mean initial **measured concentrations in the test medium.

Comparing the results of the new studies with the previous studies (Table 22) it can be seen that the results are similar. The 96 h LC50 in the previous rainbow trout study is slightly higher (13%) than for the new study. The 96 h LC50 in the previous

stickleback study is lower (35%) than for the new study. It is concluded by the RMS that the new studies demonstrate that the previous studies on rainbow trout and 3-spined stickleback are valid, and that this conclusion can be extended to the studies on the other 4 species (bream, roach, brown trout, and carp) which used the same methodology. Hence, in this respect the existing risk assessment does not require amendment.

The other fish study which is used in the risk assessment is the 28 day semi-static study on rainbow trout using Merpan 83 WP (Schanne, 1999). This study included analysis of the applied stock solutions, rather than the test media. Stock solutions were analysed to be 89.5 to 114.99% of the intended concentration. The analyses were for freshly prepared stocks which were made on the day of each media exchange, which took place 3 times per week. Although the test medium itself was not analysed, the analysis of the stocks can be taken as a reasonable indication that test systems received the correct loading of test material, and that exposure was close to nominal. The study is considered valid by the RMS. In the risk assessment, this study is used to address potential for accumulation of acute effects following multiple applications. Actual long term exposure to captan would not occur in the field due to rapid hydrolysis.

B.9.2.6 Risk to aquatic organisms

The following replaces the risk assessment at B.9.2.6 of the DAR.. The Ecologically Acceptable Concentration (EAC) has been amended and is now based on the LC50 for brown trout (Open Point 5.10), and a TER trigger of 10. The RMS considers this to be a reasonable approach. In addition, to promote a logical progression through the risk assessment, the RMS proposes that the Tier 1 TER values for fish should be based on the LC50 for the standard species, rainbow trout (from a static study). Table and paragraph numbering is as stated in the original assessment. Where a change has been made to the assessment, this is indicated by an explanatory note in italics..

Captan is not a herbicide and so a test on aquatic plants has not been conducted.

The proposed critical GAPs are summarised in Table B.9.2.6.1.

Table B.9.2.6.1: GAPs for the use of captan, as an 80% WG formulation

Crop	Application method	Timing	Max. no. of applications	Max. individual dose kg a.s./ha	Spray interval
Pome fruit (S)	airblast sprayer	From April	9*	1.25	7 days
			+ 3*	2.4	
Pome fruit (N)			9 – 10	1.25	
Peaches, nectarines (S)		From petal fall	4	2.5	
Tomatoes (S)	boom sprayer	-	4	1.8	

* Nine applications at 1.25 kg a.s./ha (scab control) followed by three applications at 2.4 kg a.s/ha (*Nectria* control).
N: North EU, S: South EU.
Uses are in the field.

The degradation of captan in water has been investigated in a number of laboratory hydrolysis, photolysis and water sediment studies. Captan undergoes rapid hydrolysis, with a DT_{50} of 2.6 hours at 25°C in the sterile hydrolysis study. Using the Arhenius

equation, the DT_{50} at 20°C was estimated to be 3.84 hours. Due to this rapid hydrolysis the whole-system DT_{90} in water/sediment systems is less than 1 day.

The main potential route of contamination of surface water is through spray drift. On reaching surface water captan will be rapidly hydrolysed. Initial Predicted Environmental Concentrations (PEC_i) for spray drift onto a 30 cm deep static water body, for a range of distances are presented in Tables B.9.2.6.2 and B.9.2.6.3. The individual 90th percentile values for spray drift from the Guidance Document on Aquatic Ecotoxicology (Dated 1.10.01)[1] have been used. Given that the DT_{90} is < 1 day and the minimum spray interval is 7 days, there will be no accumulation of residues from one application to the next. Hence, initial PEC values for a single application should be used as the basis for the acute risk assessment.

Exposure to aquatic organisms via runoff is considered to be negligible as a result of the very rapid degradation of captan in soil. There is no potential for acute or chronic exposure via run-off (*this paragraph has been amended compared with previous version*).

Table B.9.2.6.2: PEC_i for applications in orchards (using late season spray drift data)

Dist. (m)	Late season Drift (%)	Pome fruit		Peaches, nectarines
		1.25 kg a.s./ha PEC_i (µg a.s./L)	2.4 kg a.s./ha PEC_i (µg a.s./L)	2.5 kg a.s./ha PEC_i (µg a.s./L)
3	15.73	65.54	125.84	131.08
5	8.41	35.04	67.28	70.08
10	3.60	15.00	28.80	30.00
15	1.81	7.54	14.48	15.08
20	1.09	4.54	8.72	9.08
30	0.54	2.25	4.32	4.50
40	0.32	1.33	2.56	2.67
50	0.22	0.92	1.76	1.83

Table B.9.2.6.3: PEC_i for spray drift from application to tomatoes

Distance (m)	Drift (%)	Tomatoes 1.8 kg a.s./ha
		PEC_i (µg a.s./L)
1	2.77	16.62
5	0.57	3.42
10	0.29	1.74
15	0.20	1.20
20	0.15	0.90
30	0.10	0.60
40	0.07	0.42
50	0.06	0.36

Given the rapid hydrolysis of captan, any exposure of aquatic organisms will be to a short pulse of captan for no more than a few hours. Hence, there is no potential for chronic exposure (in either the water column or in sediment). There is a possibility of repeat acute exposures of aquatic systems as a result of multiple applications.

[1] Working Document: Guidance Document on Aquatic Ecotoxicology. Sanco/3268/2001, 1 October 2001.

The degradation of captan in water leads to two major metabolites which are THPI and THPAM. The concentrations of these metabolites can be estimated on the basis that, in terms of percentage applied radioactivity (%AR), 50.7% of the parent molecule is transformed into THPI and 25.6 % to THPAM. These levels of conversion are based on peak concentrations (%AR) in the water phase in a water sediment study (Annex II, Section 5, Point IIA 7.2.1.3.2). The molecular weight conversion factors for THPI and THPAM (molecular weight of captan = 300.59, THPI = 151.17, THPAM = 169.18) are 0.50 and 0.56, respectively. Based on the highest PEC_i for captan (in Table 11.2-2) of 131.08 µg/L, using %AR and taking account of molecular weight differences, this would give peak PEC values of 33.23 µg THPI/L and 18.79 µg THPAM/L. The PECsw values for THPI and THPAM following *multiple* applications (spray drift inputs) of captan have also been derived (see Addendum on fate and behaviour). For the worst case GAP on South EU pome fruit the maximum PEC following 12 applications is 72.35 µg/l for THPI and 40.89 µg/l for THPAM. This is based on worst case assumption that all applications are separated by the minimum interval of 7 days. (*The last three sentences of this paragraph have been added compared with previous version.*)

Exposure in surface water to THPI and THPAM from runoff may occur. A maximum theoretical estimate of exposure is 710 µg/l for either metabolite. This very worst- case estimate is based on the assumption that the conversion from parent is 100% and that there is no dissipation or degradation of the metabolite. This estimate also assumes an additive contribution for each spray application.

Toxicity of captan to aquatic organisms

Data on the toxicity of captan technical and an 80% WG formulation ('Merpan' 80 WDG) to aquatic organisms are presented in Table B.9.2.6.4. Relevant data on the formulation 'Merpan' 83 WP (containing 830 g captan/kg) have also been included. The endpoints selected for use in the risk assessment have been highlighted in **bold**. An explanation of the choices is given later in the assessment.

Table B.2.6.4 has been amended compared with previous version to include data on 'Malvin' WP and WG which had been summarised in the text of the DAR, but were missing from this Table. In addition, the endpoint for use in the acute assessment for fish has been amended to a more standard approach.

Table B.9.2.6.4: Data on the toxicity of captan technical and 'Merpan' 80 WDG to aquatic organisms (and relevant endpoints for 'Merpan' 83 WP)

Test organism (Test Substance)	Exposure period	Endpoint	Result (µg a.s./L)	Reference
Fish:				
Rainbow trout (captan technical)	96 hours Flowthrough	LC_{50}	50	Sankey, 1991a Ref: R-6414
		NOEC	18	
Mirror carp (captan technical)	96 hours Flowthrough	LC_{50}	240	Sankey, 1991b Ref: R-6419
		NOEC	180	
Rainbow trout[e] (captan technical)	96 hours Static	LC_{50}	215	Jenkins (2002a) Ref: R-12335
		NOLC*	145	
Rainbow trout (captan technical)	96 hours Static	**LC_{50}**	**186**	Jenkins (2004a)
		NOLC*	124	
Rainbow trout (Merpan 80 WDG)	96 hours Flowthrough	24 h LC_{50} 48 h LC_{50} 72 h LC_{50} 96 h LC_{50}	154 a.s. 192 pr 141 a.s. 176 pr 134 a.s. 167 pr 122 a.s. 153 pr	Naudin (1998) Ref: R-10155
		NOEC	40 a.s. 50 pr	
Rainbow trout (Malvin 80 WG)	96 hours Static	96 h LC_{50}	470 a.s. 620 pr	Drottar (1999)
		NOEC	370 a.s. 480 pr	
Rainbow trout (Merpan 83 WP)	96 hours Flowthrough	24 h LC_{50} 48 h LC_{50} 72 h LC_{50} 96 h LC_{50}	116 a.s. 142 pr 99 a.s. 121 pr 88 a.s. 108 pr 85 a.s. 104 pr	Naudin (1998) Ref: R-10009
		NOEC	60 a.s. 74 pr	
Rainbow trout[d] (Malvin 83 WP)	96 hours Flowthrough	96 h LC_{50}	161 a.s. 190 pr	Kent (1993b)[d]
		NOEC	85 a.s. 100 pr	
Rainbow trout (captan technical)	21 days Flowthrough	LC_{50}	75	Sankey (1991c) R-6413
		NOEC	56	
Rainbow trout (Merpan 83 WP)	28 days Semi-static[a]	LC_{50}	>199.2 a.s. >240 pr	Schanne, 1999 R-10519
		NOEC	199.2 a.s. 240 pr	
Invertebrates :				
Daphnia magna (captan technical)	48 hours Static	EC_{50}	> 3250	Rapley and Hamer (1993)
		NOEC	1100	
Daphnia magna (captan technical)	48 hours Static	EC_{50}	> 7100	Boudreau *et al*. (1980) R-6341
		NOEC	7100	
Daphnia magna (Merpan 80 WDG)	48 hours Semi-static[b]	**24h EC_{50}** 48h EC_{50}	**5200 a.s 6500 pr** 3400 a.s. 4300 pr	Knoch (1996) R-8854
		NOEC	248 a.s. 310 pr	
Daphnia magna (Malvin 83 WP)	48 hours static	24h EC_{50}	3400 a.s. 4100 pr	Kent (1993b)
		48 h EC50	2800 a.s. 3300 pr	
		NOEC	460 a.s. 560 pr	
Daphnia magna (captan technical)	21 days Semi-static[c]	EC_{50}	> 1000	Stewart *et al* (1991) R-6412
		NOEC	560	

[a] Test solutions replaced every 2 or 3 days (three times per week; total of 12 replacements)
[b] Test solutions replaced after 24 hours.
[c] Test solutions replaced every 2 or 3 days.
[d] Measured concentrations in stocks solutions were only 47-65% of nominal. Hence, study should not be used in the risk assessment.
[e] This study on rainbow trout is one of six static acute studies on fish on a range of 6 species. The endpoints from the six studies (on rainbow trout, brown trout, bream, roach, stickleback and carp) are summarised in Table B.9.2.6.16, later in this section.
a.s.: active substance, pr: product, * No observed lethality concentration.

Annotations 'd' and 'e' above have been added compared with the previous version.

Table B.9.2.6.4 continued

Test organism (Test Substance)	Exposure period	Endpoint	Result (µg a.s./L)	Reference
Algae:				
Selenastrum capricornutum (captan technical)	96 hours Static	**E_bC_{50}**	**1600**	Smyth *et al.* (1991) R-6342
		NOEC	200	
		E_rC_{50}	11000	
		NOEC	800	
Scenedesmus subspicatus (Merpan 80 WDG)	72 hours Static	E_bC_{50}	50700 a.s.	Dengler (1996) R-8855
		NOEC	7960 a.s.	
		E_rC_{50}	271800 a.s.	
		NOEC	15100 a.s.	
Scenedesmus subspicatus (Malvin 83 WP)	72 hours Static	E_bC_{50}	1180 a.s.	Smyth (1993)
		NOEC	340 a.s.	
		E_rC_{50}	5100 a.s.	
		NOEC	340 a.s.	

Data on the toxicity of the major metabolites THPI and THPAM to aquatic organisms are presented in Table B.9.2.6.5.

Table B.9.2.6.5: Data on the toxicity of THPI and THPAM to aquatic organisms

Test organism (Test substance)	Exposure period	Endpoint	Result (µg /L)	Reference
Fish:				
Rainbow trout (THPI)	96 hours static	LC_{50}	>120000	Kent (1994a)
		NOEC	120000	
Rainbow trout (THPAM)	96 hours semi-static	LC_{50}	>120000	Kelso (1995a)
		NOEC	120000	
Invertebrates :				
Daphnia magna (THPI)	48 hours static	EC_{50}	>120000	Kent (1994b)
		NOEC	120000	
Daphnia magna (THPAM)	48 hours static	EC_{50}	220000	Kelso (1995b)
		NOEC	100000	
Algae:				
Selenastrum capricornutum (THPI)	96 hours static	E_bC_{50}	>180000	Kent (1994c)
		NOEC	180000	
		E_rC_{50}	>180000	
		NOEC	180000	
Selenastrum capricornutum (THPAM)	72 hours static	E_bC_{50}	33000	Smyth (1995)
		NOEbC	18000	
		E_rC_{50}	41000	
		NOErC	32000	

All values are based on nominal concentrations which were confirmed by analysis.

Risk assessment for aquatic organisms

Acute risk

Choice of relevant endpoints

Exposure of organisms in surface water will be to a short pulse of captan followed by transient exposure to hydrolytic degradation products. Therefore, the most relevant toxicity studies for use in the risk assessment are static (or semi-static) tests, which allow the breakdown of the parent compound within the test system. In such studies the *time:exposure* profile is relevant to shallow static water bodies the field.

Fish:

The choice of endpoint has been amended compared with the previous version.

Fish were the most sensitive group of aquatic organisms tested. Ninety-six hour flow-through studies on rainbow trout with artificially maintained concentrations have been conducted for both captan technical and 'Merpan' 80 WDG. Using either of these studies in the risk assessment will significantly over-estimate the risk to fish. **The most relevant available study for the risk assessment is the <u>static</u> acute toxicity study on rainbow trout (Jenkins, 2004a).**

A 28 day semi-static prolonged toxicity test on rainbow trout for Merpan 83 WP is available. In this study, test solutions were replaced three times per week (every 2 or 3 days), with a total of 12 renewals. Survival, behaviour, and growth were assessed. Given the rapid breakdown of captan directly after media replacement, this is actually a study of *multiple acute* exposures of the same individuals. Clearly, in the field the probability of the same individual fish receiving several sequential exposures is very unlikely. However, this study does demonstrate that if multiple exposures did occur in the field as a result of multiple spray drift inputs, there is unlikely to be any accumulated effect. The NOEC from this study was 199.2 µg a.s./l. Due to the likely rapid degradation of captan to THPI and THPAM in this study, the study is also considered to address potential long term toxicity of these metabolites to fish.

Fish: The appropriate endpoint for use in the first tier risk assessment is the **LC50 of 186 µg a.s./L** from the 96 h static acute toxicity study on the active substance.

Invertebrates:

The lowest 48 h EC_{50} for *Daphnia magna* for the active substance is > 3250 µg/L, which is from a static study with no replacement of test solutions. The 24 and 48 hour EC_{50} values from a semi-static study on 'Merpan' 80 WDG are 5200 and 3400 µg a.s./L, respectively (test solutions replaced after 24 hours). Hence, it is clear that the co-formulants do not enhance the toxicity of captan. The duration of any exposure to aquatic organisms in the field will be limited by the rapid hydrolysis of captan (DT_{50} 2.7 hours). Hence, the most relevant endpoint is the 24 hour EC_{50} for the formulation. As a precaution, TER values have also been calculated using the 24 hour EC50 of 3400 µg a.s./l from the static acute study on Malvin 83 WP (it should be noted that the WDG is the notified formulation). *(This final sentence has been added compared with previous version).*

Invertebrates: the relevant endpoint for use in the risk assessment is the 24 h EC_{50} for *Daphnia magna* (from the study on the WDG) of **5200 µg a.s./L.**

Algae:

'Merpan' 80 WDG

Algae: the lowest endpoint, which is the E_bC_{50} of **1600 µg a.s./L**, should be used in the risk assessment.

As a precaution the EbC50 for 'Malvin' 83 WP has also been used to derive TER values (it should be noted that the notified formulation is the WDG)(*This sentence has been added compared with previous version*):

Algae: the lowest endpoint, which is the E_bC_{50} of **1180 µg a.s./L** (based on a study with the 83% WP formulation), should be used in the risk assessment.

Metabolites:

Hydrolytic degradation products will have been present in the static and semi-static studies on the parent compound and formulation. Hence, their toxicity will have been taken into account in the endpoints from these studies. In addition, the products of hydrolysis (THPAM and THPI) have been tested in separate studies (Table B.9.2.6.5) and have been shown to be much less toxic than the parent compound. This explains why hydrolysis is an effective detoxification mechanism.

Toxicity Exposure Ratios

Fish have been identified as the most sensitive group of aquatic organisms tested. Hence, a risk assessment based on the relevant endpoint for fish will also be protective of aquatic invertebrates and algae. The appropriate value for use in the first tier risk assessment for fish is the LC50 of 186 µg a.s./L (see discussion above). Toxicity Exposure Ratios (TERs) calculated using this LC50, together with PEC_i values, are presented in Table B.9.2.6.6 and Table B.9.2.6.7. Worst case TERs for invertebrates and algae are also presented in Table B.9.2.6.8 to Table B.9.2.6.15.

Acute TERs for fish have been amended compared with previous version, to use the acute endpoint for rainbow trout (a standard approach).

Table B.9.2.6.6: Fish: acute TERs for use on pome fruit, peaches and nectarines, using an LC50 of 186 µg a.s./L

Dist. (m)	Late season Drift (%)	Pome fruit				Peaches, nectarines	
		1.25 kg as/ha		2.4 kg a.s./ha		2.5 kg a.s./ha	
		PEC_i µg a.s./L	TER*	PEC_i µg a.s./L	TER*	PEC_i µg a.s./L	TER*
3	15.73	65.54	2.84	125.84	1.48	131.08	1.41
5	8.41	35.04	5.31	67.28	2.76	70.08	2.65
10	3.60	15.00	12.4	28.80	6.46	30.00	6.20
15	1.81	7.54	24.7	14.48	12.8	15.08	12.3
20	1.09	4.54	50.0	8.72	21.3	9.08	20.5
30	0.54	2.25	82.7	4.32	43.1	4.50	41.3
40	0.32	1.33	140*	2.56	72.7	2.67	69.7
50	0.22	0.92	202*	1.76	106*	1.83	102*

*TER is greater than the relevant trigger of 100 at a distance of 40 m (North EU pome fruit) and 50 m (South EU pome fruit, and peaches/nectarines). Hence, there is a low risk to fish at these distances. A higher tier risk assessment is presented at the end of this section.

Table B.9.2.6.7: Fish: acute TERs for use on tomatoes, using an LC50 of 186 µg a.s./L

Distance (m)	Drift (%)	Tomatoes 1.8 kg a.s./ha	
		PEC_i (µg a.s./L)	TER
1	2.77	16.62	11.2
5	0.57	3.42	54.4
10	0.29	1.74	107*

*TER is greater than the relevant trigger of 100 at a distance of 10 m. Hence, there is a low risk to fish at this distance. A higher tier risk assessment is presented at the end of this section.

Table B.9.2.6.8: Invertebrates: acute TERs for use on pome fruit, peaches and nectarines, using an EC_{50} 5200 µg a.s./L for 'Merpan' 80 WDG

Dist. (m)	Late season Drift (%)	Pome fruit				Peaches, nectarines	
		1.25 kg as/ha		2.4 kg a.s./ha		2.5 kg a.s./ha	
		PEC_i µg a.s./L	TER	PEC_i µg a.s./L	TER	PEC_i µg a.s./L	TER
3	15.73	65.54	79.3	125.84	41.3	131.08	39.7
5	8.41	35.04	148*	67.28	77.3	70.08	74.2
10	3.60	15.00	347*	28.80	181*	30.00	173*

*All TERs are greater than the relevant trigger of 100 at a distance of 10 m. Hence, there is a low risk to aquatic invertebrates at this distance. No further consideration is required as the outcome of the overall assessment is driven by the risk to fish.

Table B.9.2.6.9: Invertebrates: acute TER for use on tomatoes, using an EC_{50} of 5,200 µg a.s./L for 'Merpan' 80 WDG

Distance (m)	Drift (%)	Tomatoes 1.8 kg a.s./ha	
		PEC_i (µg a.s./L)	TER
1	2.77	16.62	313*

*TER is greater than the relevant trigger of 100 at a distance of 1 m. Hence, there is a low risk to aquatic invertebrates.

Table B.9.2.6.10: Invertebrates: acute TERs for use on pome fruit, peaches and nectarines, using an EC_{50} of 3400 µg a.s./L for 'Malvin' WG

Dist. (m)	Late season Drift (%)	Pome fruit				Peaches, nectarines	
		1.25 kg as/ha		2.4 kg a.s./ha		2.5 kg a.s./ha	
		PEC_i µg a.s./L	TER	PEC_i µg a.s./L	TER	PEC_i µg a.s./L	TER
3	15.73	65.54	51.9	125.84	27.0	131.08	25.9
5	8.41	35.04	97.0	67.28	50.5	70.08	48.5
10	3.60	15.00	227*	28.80	118*	30.00	113*

*All TERs are greater than the relevant trigger of 100 at a distance of 10 m. Hence, there is a low risk to aquatic invertebrates at this distance. No further consideration is required as the outcome of the overall assessment is driven by the risk to fish.

Table B.9.2.6.11: Invertebrates: acute TER for use on tomatoes, using an EC_{50} of 3400 µg a.s./L for 'Malvin' WG

Distance (m)	Drift (%)	Tomatoes 1.8 kg a.s./ha	
		PEC_i (µg a.s./L)	TER
1	2.77	16.62	205*

*TER is greater than the relevant trigger of 100 at a distance of 1 m. Hence, there is a low risk to aquatic invertebrates.

Table B.9.2.6.12: Algae: short term TERs for use on pome fruit, peaches and nectarines, using an E_bC_{50} of 1,600 µg a.s./L for captan

Dist. (m)	Late season Drift (%)	Pome fruit				Peaches, nectarines	
		1.25 kg as/ha		2.4 kg a.s./ha		2.5 kg a.s./ha	
		PEC_i µg a.s./L	TER	PEC_i µg a.s./L	TER	PEC_i µg a.s./L	TER
3	15.73	65.54	24.4*	125.84	12.7*	131.08	12.2*

*All TERs are greater than the relevant trigger of 10 at a distance of 3 m. Hence, there is a low risk to algae.

Table B.9.2.6.13: Algae: short term TERs for use on tomatoes, using an E_bC_{50} of 1,600 µg a.s./L for captan

Distance (m)	Drift (%)	Tomatoes 1.8 kg a.s./ha	
		PEC_i (µg a.s./L)	TER
1	2.77	16.62	96.3*

*TER is greater than the relevant trigger of 10 at a distance of 1 m. Hence, there is a low risk to algae.

Table B.9.2.6.14: Algae: short term TERs for use on pome fruit, peaches and nectarines, using an E_bC_{50} of 1180 µg a.s./L for 'Malvin' WG

Dist. (m)	Late season Drift (%)	Pome fruit				Peaches, nectarines	
		1.25 kg as/ha		2.4 kg a.s./ha		2.5 kg a.s./ha	
		PEC_i µg a.s./L	TER	PEC_i µg a.s./L	TER	PEC_i µg a.s./L	TER
3	15.73	65.54	18.0*	125.84	9.4	131.08	9.0
5	8.41	35.04	33.7*	67.28	17.5*	70.08	16.8*

*All are TERs greater than the relevant trigger of 10 at a distance of 5 m. Hence, there is a low risk to algae.

Table B.9.2.6.15: Algae: short term TERs for use on tomatoes, using an E_bC_{50} of 1180 µg a.s./L for 'Malvin' WG

Distance (m)	Drift (%)	Tomatoes 1.8 kg a.s./ha	
		PEC_i (µg a.s./L)	TER
1	2.77	16.62	71.0*

*TER is greater than the relevant trigger of 10 at a distance of 1 m. Hence, there is a low risk to algae.

TER values can also be calculated for the two major metabolites THPI and THPAM. Based on the highest PEC_i for captan, the calculated peak PEC values are 33.23 µg THPI/L and 18.79 µg THPAM/L. Comparison with the acute EC/LC_{50} endpoints quoted gives TER values for THPI of > 3611 (fish), > 3611 (invertebrates), and > 5417 (algae); and TER values for THPAM of > 6386 (fish), 11708 (invertebrates), and 1756 (algae). All these TER values are significantly greater than the relevant Annex VI TER triggers. In addition, potential long term risk to fish from THPI and THPAM is addressed by the 28 day semi-static study on the Merpan 83 WP, which is likely to have included exposure to THPI and THPAM.

Following a run-off event, the instantaneous PEC_{sw} for either metabolites is estimated to be 710 µg/L. The consequent TER_a values for THPI are >169 (fish and invertebrates) and >254 (algae). For THPAM the corresponding TER_a values are >169 (fish), 310 (invertebrates) and 46.5 (algae). All these TER values are significantly greater than the relevant Annex VI TER triggers. The worst case PECsw values resulting from spray drift inputs following multiple applications in South EU pome fruit (worst case GAP) are 72.35 µg/l for THPI and 40.89 µg/l for THPAM (from Addendum on fate and behaviour). These PEC values are lower than the extreme worst case runoff PEC, which already gave TERs greater than the relevant trigger values. Hence, a low risk from metabolites can be concluded. (*the last three sentences of this paragraph have been added compared with the previous version*)

Long term risk

Due to the rapid hydrolysis of captan (whole system DT_{90} < 1 day), there is no potential for prolonged exposure of aquatic organisms in the field. Hence, it is not relevant to calculate chronic TER values. It can be concluded there will be a low chronic risk to aquatic life. Multiple applications have potential to result in multiple acute exposures, rather than chronic exposure. This issue is addressed by the 28 day semi-static study on rainbow trout for Merpan 83 WP. This study included 12 media exchanges. Given the rapid hydrolysis of captan, these exchanges represent a series of acute exposures. There were no effects in the study at 199.2 µg a.s./L. Hence, there was no accumulation of acute effects, and the issue of multiple applications is addressed.

Higher-tier risk assessment for acute risk to fish, utilising multiple single-species acute toxicity tests

The Guidance Document on Higher-tier Aquatic Risk Assessment for Pesticides (HARAP) (Campbell *et al*, 1999)[2], provides guidance on the use of data on additional species of aquatic organisms in order to reduce uncertainty over interspecific variation in sensitivity. Thus, allowing reductions in standard TER triggers.

The HARAP guidance states that the number and type of additional species that should be tested depends on what is known about the mode of action or selectivity of the pesticides. For captan, fish are known to be particularly sensitive compared with other groups of aquatic organisms. Hence, when undertaking a multispecies approach it is appropriate to focus only on fish. The fate and behaviour of captan, i.e. rapid hydrolysis leading only to acute exposure, indicates that only acute toxicity requires consideration. This is backed up by the purely acute mode of toxicity of captan, as an acute irritant to gill membranes. The HARAP guidance states that 'if fish are the most sensitive group, fewer species may be required [than invertebrates] because it is generally recognised that distributions of sensitivity are usually narrow. For this reason and for animal welfare considerations, five species are probably sufficient to describe the range of toxicities of fish'. Following this guidance, a set of acute toxicity studies on six species of fish has been undertaken. These studies were conducted using the same protocol (according to OECD guideline 203), at the same laboratory, at around the same time. Hence, any differences in results should directly reflect any differences in the sensitivity of the exposed species. In order for the exposure to be of

[2] Campbell, P.J., Arnold, D., Brock, T., Grandy, N., Heger, W., Heimbach, F., Maund, S.J. and Streloke, M. Higher-tier Aquatic Risk Assessment for Pesticides. From the SETAC-Europe/OECD/EC Workshop, Lacanau Ocean, France, April 1998 (1999).

relevance to the field, the studies were undertaken under static conditions with no replacement of test media. Hence, exposure in the studies (as in the field) would be have been to a pulse of captan, followed by the hydrolytic degradation products (THPAM and THPI). The initial nominal concentrations of captan were confirmed by analysis.

The LC_{50} and LC_{10} values are presented in Table B.9.2.6.12. In addition, the highest test concentration which resulted in no mortality (no observed lethality concentration, NOLC) has been specified.

Table B.9.2.6.16: Captan - LC_{50}, LC_{10} and NOLC values for six species of fish tested in 96 h static acute toxicity tests according to OECD guideline 203

Species	Exposure time	LC_{50} (µg a.s./L)	LC_{10} (µg a.s./L)	NOLC*	Ref:
Brown trout	24 h	98	-	-	Jenkins (2002b),
(Salmo trutta)	96 h	98	92	66.1	R-12336
Bream	24 h	227	-	-	Jenkins (2002e),
(Abramis brama)	96 h	119	53	42.3**	R-12340
Roach	24 h	189	-	-	Jenkins (2002f),
(*Rutilus rutilus*)	96 h	154	88	42.3	R-12339
Rainbow trout	24 h	215	-	-	Jenkins (2002a),
(*Oncorrhynchus mykiss*)	96 h	215	203	145	R-12335
3-Spined stickleback	24 h	367	-	-	Jenkins (2002d),
(*Gasterosteus aculeatus*)	96 h	275	243	113	R-12338
Carp	24 h	556	-	-	Jenkins (2002c),
(*Cyprinus carpio*)	96 h	492	434	248	R-12337

*** No observed lethality concentration.**
****One mortality occurred but was not treatment related.**

Considering the spread of sensitivities of the tested fish, it can be seen that the range is relatively narrow. The ratio of highest (carp) to the lowest (brown trout) LC_{50} values is only 5, and the ratio of the lowest (bream) and highest (carp) LC_{10} values is 8. Excluding carp, the ratios of highest to lowest LC_{50}, LC_{10}, and NOLC are only 3, 5, and 3 respectively. The narrow range in sensitivity can be explained by the toxic mode of action of captan as an irritant to gill membranes, to which different species of fish might be expected to be comparably sensitive. What can also be seen from the data is that the LC_{50} and LC_{10} values for an individual species are quite close together. This indicates that the concentration response curve is steep, and that individual fish within the treatment group were similar in sensitivity. Again, considering the toxic mode of action, this is not surprising.

It terms of a higher tier risk assessment, the LC50 for the most sensitive species, brown trout, should be used. The studies on the 6 species provide information on inter-species variation in sensitivity, which demonstrate that the range is narrow. Hence, this source of uncertainty has been minimised. Therefore, based on the use of the LC50 for brown trout, it is considered appropriate in the risk assessment to reduce the standard TER trigger of 100 down to 10. (*final sentence has been added compared with previous version*)

The data points in Table B.9.2.6.17 above have been analysed in order to derive a species sensitivity distribution (SSD). HC_5 values have been calculated according to the method of Aldenburg and Slob (1993)[3], assuming a log-logistic distribution of the

[3] **Aldenberg, T. and Slob, W. (1993). Confidence limits for hazardous concentrations based on logistically distributed NOEC data. Ecotoxicology and Environmental Safety 25, 48-63.**

sensitivities of fish species to captan. These values are presented in Table B.9.2.6.18 below.

Table B.9.2.6.17: LC_{50}, LC_{10} and NOLC -based HC_5 values in µg a.s./L

Parameter	LC_{50}	LC_{10}	NOLC*
HC_5 (50%)	65.1	35	24.2
HC_5 (95%)	20.3	7.57	6.0

*No observed lethality concentration.
** ie the upper 95% confidence interval for the HC_5

The NOLC-based HC_5 (95%) (ie the upper 95% confidence interval for the HC_5) represents a very certain estimate, and the NOLC-based HC_5 (50%) represents a *most likely* estimate of the concentration at which for 95% of the fish species in an ecosystem no mortality will occur. The LC_{10}-based HC_5 (95%) value represents a very certain estimate, and the LC_{10}-based HC_5 (50%) represents a *most likely* estimate of the concentration at which for 95% of the fish species in an ecosystem a level of 10% mortality will not be exceeded. Likewise, the LC_{50}-based HC_5 (95%) represents a very certain estimate, and the LC_{50}-based HC_5 (50%) represents an *most likely* estimate of the concentration at which for 95% of the fish species in an ecosystem the median lethal concentration will not be exceeded. In general, it is the HC_5 (50%) which is used in risk assessment, rather than the upper 95% confidence interval.

No guidance under Directive 91/414 EEC is currently available on the use of SSDs or the question of which is the most relevant endpoint to use in the risk assessment. Hence, in order to derive predicted no effect concentrations (PNEC) values it is proposed to follow the approach taken in EUSES (EU harmonised risk assessment scheme). The EUSES approach uses the HC_5 (50%) value as a valid PNEC for the protection of the aquatic environment. Formally this HC_5 (50%) value should be based on chronic NOEC values. However, for captan there is no potential for chronic exposure or risk (it is acute risk that drives the assessment). Hence, the acute NOLC-based HC_5 (50%) of 24.2 µg a.s./L may be considered a valid PNEC for the protection of fish.

Overall discussion of the risk to aquatic life

This section has been amended to include a change in EAC compared with previous version.

Fish have been identified as the most sensitive aquatic organisms tested. Hence, a risk assessment which is protective of fish will also be protective of other aquatic organisms (invertebrates, algae) as has been shown by the TER values in Table B.9.2.6.6 to Table B.9.2.6.11. Therefore, the following discussion focuses on the acute risk to fish.

In the first tier risk assessment, an LC50 for rainbow trout and the standard TER trigger of 100 have been used. On this basis, a low risk to fish has been demonstrated at a distance of 10 m for tomatoes, 40 m for North EU pome fruit and 50 m for South EU pome fruit and peaches/nectarines.

To support a higher tier risk assessment, a series of six static acute toxicity tests on species (including rainbow trout) has been undertaken. From the spread of the LC_{50} results it can be seen that the range of sensitivities is narrow (excluding carp, which is relatively insensitive, the ratio of highest to lowest LC50 is only 3). Hence, uncertainty has been minimised regarding inter-species variation in sensitivity. Therefore, using

the LC50 for the most sensitive species (brown trout: LC50 98 µg a.s./L) it is considered appropriate to reduce the TER trigger (uncertainty factor) from 100 to 10.

Ecologically Acceptable Concentration for fish: the above effectively sets the safe concentration for fish at 9.8 µg/L. This is backed-up by the SSD analysis of the endpoints for the six fish species, which gave a predicted no effect concentration (PNEC) for the protection of fish in the field of 24.2 µg a.s./L. **Overall, the Ecologically Acceptable Concentration for fish is concluded to be 9.8 µg a.s./L.**

For Member States which accept the use of Species Sensitivity Distributions (SSD) in aquatic risk assessment at the national level, the HC_5 of 24.2 µg/L may be used as an alternative EAC for fish. *This sentence has been added compared with previous version in response to comment from NL.*

Table B.9.2.6.18a and B.9.2.6.18b is shaded to show where the TER of 10 is exceeded, and hence at what spray drift distances the risk to fish is acceptable.

Table B.9.2.6.18a: TERs for use in tomatoes, based on the LC50 for brown trout (98 µg a,.s./L): shaded areas indicating a low risk to fish

Distance (m)	Drift (%)	Tomatoes 1.8 kg a.s./ha	
		PEC_i (µg a.s./L)	TER
1	2.77	16.62	5.90
5	0.57	3.42	**28.7**

The above table has been added compared with the previous version

Table B.9.2.6.18b: TERs for orchard uses, based on the LC50 for brown trout (98 µg a,.s./L): shaded areas indicating a low risk to fish

Dist. (m)	Late season Drift (%)	Pome fruit				Peaches, nectarines	
		1.25 kg as/ha		2.4 kg a.s./ha		2.5 kg a.s./ha	
		PEC_i µg a.s./L	TER	PEC_i µg a.s./L	TER	PEC_i µg a.s./L	TER
3	15.73	65.54	1.50	125.84	0.8	131.08	0.7
5	8.41	35.04	2.80	67.28	1.46	70.08	1.40
10	3.60	15.00	6.53	28.80	3.40	30.00	3.27
15	1.81	7.54	**13.0**	14.48	6.77	15.08	6.50
20	1.09	4.54	**21.6**	8.72	**11.2**	9.08	**10.8**

'Safe' distances have been amended compared with previous version of assessment.

From the above tables, TER values for fish of >10 (low risk) are achieved at a distance of 5 m for tomato, 15 m in North EU pome fruit, and 20 m in South EU pome fruit and nectarines/peaches. In addition, a low risk to aquatic invertebrates and algae has been demonstrated based on the lower tier assessment**. Hence, overall it can be concluded that the risk to aquatic life is acceptable. Appropriate risk mitigation measures should be considered as Member State level.**

It is considered that the above studies and revised risk assessment address the following comments from the Reporting Table: 5(24), 5(25), 5(26), 5(27), and the comment from Germany on validity of fish studies (contained in letter dated 29.10.04); and Open Points 5.9 (also see below) and 5.10.

For the following comments in the Reporting Table on the aquatic assessment, responses from the RMS are provided in the Reporting Table: 5(22), 5(23), 5(25), 5(26), 5(27), 5(28)

Responses to address other Open Points and comments in Reporting Table on the aquatic assessment:

Open point 5.8:

The evaluation of the sediment water fate study in the Addendum on fate and behaviour concluded that no change in the interpretation of the study or its use in the risk assessment was required. Hence, no specific change to the risk assessment is necessary in order to satisfy Open Point 5.8.

Comment from Germany (in letter dated 29.10.04), **Open Point 5.9**:

'It is doubted that the estimation and the use of the EAC in the aquatic risk assessment is appropriate and covers the possible risks to the whole aquatic community. According to the Guidance Document on Aquatic Ecotoxicology an EAC is estimated for the refined risk assessment, taking into account the overall evaluation of the compound in the aquatic environment.

a) In the DAR, the EAC is based on acute effects on one group of organisms (fish) only.
b) The uncentainty factor is reduced from 100 to 10 due to small interspecies sensitivity distribution. The new uncertainty factor is then applied to the NOEC from a 28 day semistatic toxicity test with rainbow trout. According to the Guidance Document on Aquatic Ecotoxicology "the full order of magnitude reduction is likely only to apply to acute risk assessments, e.g. Annex VI TER trigger for acute risk to fish and aquatic invertebrates." Since the uncertainty factor is applied to the NOEC of a chronic toxicity study, this approach is in dicordance with the Guidance Document.
c) In order to reduce the uncertainty of potential effects on the aquatic community and to derive a reliable EAC, the performance of a semi-realistic multispecies effect study would be helpful.'

Statement from Notifier (ref: Norman, 2005):

Fish are clearly the most sensitive group of aquatic organisms for captan. Hence, it is appropriate to base the EAC on acute toxicity data for fish. It is agreed that the whole aquatic community needs to be taken into account. This is achieved because considering the new EAC of 9.8 µg a.s./L, standard TER triggers are maintained for invertebrates (lowest 24 h EC50 for *D. magna* = 3400 µg a.s./L / 100 = 34 µg a.s./L) and algae (lowest EbC50 = 1600 µg a.s./L / 10 = 160 µg a.s./L).

Regarding part b) of comment: The EAC is now based on an acute endpoint (rather than from a long term study). Hence, the proposed approach is now in line with HARAP and the Guidance Document on Aquatic Ecotoxicology.

Regarding part c) of comment: The proposed assessment addresses each of the organism groups separately, which is the usual accepted practice. Hence, a multi-species study is not necessary in this case. Also, for practical experimental reasons (heavy predation pressure on invertebrates by fish), at least in small systems, it is not generally recommended to study fish and invertebrates together in the same test units.

The RMS agrees with the above statement.

Comment from Germany (in letter dated 29.10.04), **Open Point 5.9**:

'A fish early life-stage (FELS) test was not performed. According to EC Directive 96/12/EEC, this appears to be a data gap since the 96 h LC50 for rainbow trout was <0.1 mg/L (nominal value: 0.05 mg/L) and the BCF is >100 (140).'

Statement from Notifier (ref: Norman, 2005): The DT50 and DT90 for captan in the sediment water study was <1 day. Hence, long term exposure will not occur. Hence, an ELS study is not needed. Captan has an acute mode of toxicity (irritant to gill membranes), and the potential exposure duration in the field will be short (hydrolytic DT50: 3.84 hours at 20 °C). Therefore, the focus of the assessment should be on the *acute* risk to fish.

The RMS agrees with the above statement

Comment 5(29)(EFSA), **Open Point 5.11**:

'The measured concentrations of the freshly prepared stock solutions or measure concentrations at the start of test were far below 80% of the nominal for the following studies: acute toxicity to rainbow trout of a 83% WP formulation (Kent, 1993a) and acute toxicity to *Daphnia magna* of a 83% WP formulation (Kent, 1993b). Nevertheless the results of these studies are expressed in nominal concentrations which could underestimate the risk. Preferably the results of these studies are expressed in initial measured concentrations'.

Statement from Notifier (ref: Norman, 2005): Measured values for stocks and test media were low for the acute fish study with Malvin 83 WP (Kent, 1993a), and measured values in test media were low for the acute study on *D. magna* for Malvin 83 WP (however, the stock concentration was acceptable at 103% of nominal)(Kent, 1993b). Where the stock concentration is confirmed by analysis, as for the *D. magna* study, it is not necessary to express the results as initial measured values, as the correct *loading* of the test systems with test material has been confirmed (even if measured values in the test media were low). For the rainbow trout study, given the low results for measured concentration in stocks, it is simply proposed that the study is not used in the risk assessment (there are already sufficient data on acute toxicity to fish). Hence, the risk assessment does not need to be amended (as was raised as a possibility in Open Point 5.11).

The RMS agrees with the above statement

Comment 5(31)(EFSA) and **Data requirement 5.1**

'It is noted that for the risk assessment of the lead formulation Malvin WG, studies with Merpan 83 WP are used. A statement of the comparability of these formulations is considered necessary.'

Statement from Notifier (ref: Norman, 2005): In the aquatic risk assessment the lead formulation is Merpan 80 WDG (and Malvin 80 WG). A prolonged toxicity study on Merpan

83 WP has also been used to support the assessment, in terms of the risk from multiple acute exposures. The inherent toxicity of Merpan 80 WDG and 83 WP to fish has been assessed in acute flowthrough studies. For Merpan 80 WG, the 96h flowthrough LC50 is 122 µg a.s./L, and for Merpan 83 WP the value is 83 µg a.s./L. Hence, the LC50 value is lower for the 83WP. Therefore, the use of the prolonged study on Merpan 83 WP, to support Merpan 80 WDG is conservative.

The RMS agrees with the above statement

In addition, to satisfy **Data requirement 5.1**, formulation details of the tested formulation (Merpan 83 WP, 83% captan w/w) have been supplied by the Notifier. In comparison with the 80 WG (80% captan w/w) lead formulations, the WP is considered by the RMS to be comparable.

Comment 5(32)(EFSA), **Open Point 5.12**:

'Also THPAI is a major metabolite in the sediment. An argumentation concerning the necessity of a study with this metabolite is considered necessary.'

Statement from Notifier (ref: Norman, 2005): In the sediment water fate study (Travis and Simmons, 1993; p132 of DAR) THPAI was detected at low levels in the sediment phase. Two sediment water systems were tested. In one ('Virginia water') system, levels of THPAI were <5% AR for all assessed time points, apart from one at 30 days where the measured level of THPAI constituted 11.3% of applied radioactivity (at the next sampling time point it was <0.1% AR). In the other sediment water system ('Old Basing') again there was only one time point for which THPAI was >5% AR. This was after 14 days, when THPAI constituted 7.3% AR (at the next sampling time point THPAI was 3% AR, hence, it was declining). In addition, it was reported in the study that most of the THPAI detected in sediment was extracted in a second of two sediment extractions which was found (upon further investigation) to result in breakdown of THPAM to THPAI. As such, it is very likely that some of the THPAI recorded as in the sediment was probably originally THPAM and that the one detection above 10% was probably an artefact of the extraction procedure. Therefore, it appears unnecessary to designate THPAI as a sediment metabolite. In the context of the overall risk assessment, the possible and only limited occurrence in sediment is not considered to be significant. Captan, THPI and THPAM are of relatively low toxicity to *Daphnia magna*. THPAI is of similar structure to THPAM (one OH substituted by an NH_2), and there is no reason to suspect it will be of increased toxicity to invertebrates. Hence, the risk to sediment dwelling invertebrates from THPAI to be acceptable. The focus of the risk assessment should be on the acute risk to fish from captan itself.

The RMS agrees with the above statement

Overall conclusion of RMS on risk to aquatic organisms:

Risk to aquatic organisms is acceptable, with risk mitigation to minimise spray drift input. Risk mitigation measures should be considered at Member State level.

B.9.5 Effects on other arthropod species (Annex IIA 8.3.2; Annex IIIA 10.5)

Open point 5.13: RMS to prepare an addendum to revise the risk assessment for NTA.(see reporting table 5(38))
Open point 5.14: MS to discuss the acceptability of the laboratory toxicity test with *T. pyri* in an expert meeting. (see

reporting table 5(39))

Comments in the Reporting Table (5(43) and 5(44)) express concern over the application rates in non-target arthropod studies being too low to address the uses notified in the review. In response to these comments, the Notifier has submitted two new extended laboratory studies, together with a revised risk assessment. These are summarised below:

Report: Moll, M. (2004a). Effects of Merpan 80 WDG on the parasitoid *Aphidius rhopalosiphi*, extended laboratory study - aged residue test. IBACON, unpublished report No. 18191003 (Company file: R-16397).

Guidelines: Mead-Briggs *et al*. 2000, improvements by the ring test group (Mead-Briggs *et al*. 2002) and ESCORT 2 (2001).

GLP: Yes.

Material and methods:

The effects of 'Merpan' 80 WDG containing 805 g captan/kg, on the mortality and reproduction of the aphid parasitoid, *Aphidius rhopalosiphi*, were assessed in an extended laboratory test with a realistic substrate. Imagines (adults) were exposed to fresh, dried residues of the diluted 'Merpan' 80 WDG formulation sprayed onto bean plants (*Phaseolus vulgaris*). All treatments were applied outdoors in a volume equivalent to 400 L/ha. Bean plants (at BBCH 21-25), maintained outdoors, were sprayed with each treatment as follows: control (tap water), the toxic standard dimethoate at 40 g dimethoate/ha and 'Merpan' 80 WDG at 3.42 and 6.75 kg captan/ha.

Following spray application, bean leaves were excised and placed in exposure units (untreated glass plates 13 x 13 cm and held apart with an aluminium frame with ventilation holes and clamped together). The base glass plate in the exposure unit was covered with moistened paper tissue on which were placed four to five treated bean leaves. Into each exposure unit were placed 10 parasitoids (seven females, three males) with four replicate exposure units per treatment. The parasitoids were introduced to the exposure units within 25 to 40 minutes after spray application. A 10% fructose solution was sprayed onto the plants as food for the parasitoids before application of the test treatments. Additional food was supplied, via test tubes, during the exposure phase *ad libitum*.

The test conditions during exposure were 18 to 22°C, 60 to 88% relative humidity, 1500 to 2900 lux and a 16 hour daylength. The exposure units were ventilated during the test. The parasitoids were observed for mortality and behaviour after 2, 24 and 48 hours of exposure. Following the exposure period, for the assessment of parasitic (and hence reproductive) capacity, polyacrylic cylinders covering a pot with 18 to 25 barley seedlings, infested with 200 to 220 *Rhopalosiphi padi* aphids, were used. The soil surface of the pot was covered with sand. From each treatment, one surviving female was introduced to each of 20 replicate reproduction units to parasitise the aphids, for a 24 h period. The parasitised aphids (mummies) were counted after 12 days. Test conditions during the reproduction/parasitism phase were 18 to 22°C, 63 to 64% relative humidity, 4000 to 12000 lux and a 16 hour daylength.

Findings:

Results are summarised in Table 23 and 24. After 48 hours exposure on excised bean leaves, mortality was not statistically different in the 'Merpan' 80 WDG treatments compared to the tap water control. Mortality in the toxic standard, after 48 hours, was 100%. Reproductive capacity (as measured by the number of mummies on the barley plants) was statistically

significantly reduced at 3.42 kg captan/ha (19.4 mummies/female) but not at 6.75 kg captan/ha (29.5 mummies/female), compared to the control treatment (38.0 mummies/female). The reduction in parasitisation at 3.42 kg captan/ha was not considered to be related to treatment as there were no significant effects at the higher treatment rate. The reduction in reproduction in both 'Merpan' 80 WDG treatments was below the 'ESCORT 2' trigger of 50%. It was not necessary to conduct further testing with aged residues.

Table 23: Summary of mortality to *Aphidius rhopalosiphi* following exposure to 'Merpan' 80 WDG on excised bean leaves

Treatment	Mean mortality 48 hours (%)	Corrected mortality 48 hours (%)	Behavioural observations 48 hours	
			% affected	% moribund
Control (tap water)	7.5	-	0	0
'Merpan' 80 WDG: 3.42 kg captan/ha	7.5	0	0	0
'Merpan' 80 WDG: 6.75 kg captan/ha	20.0	13.5	7.5	0
Toxic standard	100*	100	0	0

* Significantly different from control at $p < 0.05$.

Table 24 Summary of reproduction of *A. rhopalosiphi* following exposure to 'Merpan' 80 WDG on excised bean leaves

Treatment	Parasitation rate (mummies/female)	Reduction in parasitation efficiency (%)
Control (tap water)	38.0	-
'Merpan' 80 WDG: 3.42 kg captan/ha	19.4*	48.8
'Merpan' 80 WDG: 6.75 kg captan/ha	29.5	22.2

* Significantly different from control at $p < 0.05$.

Conclusions: 'Merpan' 80 WDG, applied to bean plants at 6.75 kg captan/ha had no significant effect on survival and fecundity of *A. rhopalosiphi*. Differences from control were less than ESCORT 2 trigger of 50%.

Report: Moll, M (2004b). Effects of 'Merpan' 80 WDG on the ladybird beetle *Coccinella septempunctata*, extended laboratory study - aged residue test. IBACON, unpublished report No. 18193013 (Company file: R-16399).

Guidelines: Schmuck et al. 2000 and ESCORT 2 (2001).

GLP: Yes.

Material and methods:

The effects of 'Merpan' 80 WDG containing 805 g captan/kg, on the mortality and reproduction of *Coccinella septempunctata* were assessed in an extended laboratory test with a realistic substrate. Larvae, approximately three to four days old, were exposed to freshly dried (first bioassay) and aged (second bioassay) residues of diluted 'Merpan' 80 WDG sprayed onto bean plants (*Phaseolus vulgaris*). All treatments were applied outside in a volume equivalent to 400 L/ha. Bean plants (at BBCH 21-22 for the first bioassay and BBCH 51-55 for the second bioassay), maintained outdoors, were sprayed with each treatment as follows: control (tap water), the toxic standard (40 g dimethoate/ha) and 'Merpan' 80 WDG at 0.45, 1.89, 3.42 and 6.75 kg captan/ha. Following spray application, bean leaves were excised and 50 mm

discs cut and placed singly on wet cotton wool pads in petri dishes. Larval escape was prevented by placing a cylinder (40 mm diameter, 30 mm high) on each leaf disc. When larvae had pupated the cylinders were capped to prevent emerging beetles escaping. Each leaf disc supported one larva with 40 replicate leaf discs per treatment. The larvae were placed onto the leaf discs within 40 to 65 minutes (first bioassay) or after 14 days (second bioassay, which was only at 3.42 and 6.75 kg ai/ha) of spray application (residues aged outdoors but plants protected from rainfall). Larvae were fed with live aphids at regular intervals until pupation. The test conditions during exposure on leaf discs were 23 to 27°C, 60 to 87% relative humidity and 1200 to 4000 lux with a 16 hour daylength. Larvae, pupation and the number of hatched adults were observed at regular intervals until 20 or 18 days (95% to 100% hatch of viable pupae) for the first and second bioassay, respectively. Following the exposure period all survivors (maximum 37 individuals) were transferred to one 'post-exposure' test unit per treatment, consisting of 40 cm x 40 cm x 40 cm cages containing *Vicia faba* plants infested with live aphids. Folded tissue paper was also present as an egg laying surface. The 'post-exposure' lasted for 18 to 28 days. Adult mortality was assessed at regular intervals. The number of eggs laid was counted at regular intervals and the number of hatched larvae counted daily. The 'post-exposure' reproduction test was not carried out with the toxic standard treatment. Test conditions during the reproduction phase were the same as those in the exposure phase other than the light intensity which was 1700 to 4300 lux.

Findings:

In the first bioassay, with fresh dry residues, pre-imaginal survival of *C. septempunctata* was not significantly different to the control treatment at 0.45 and 1.89 kg captan/ha. At 3.42 and 6.75 kg captan/ha mortality was significantly increased compared to the controls but was less than ESCORT 2 trigger of 50%, when corrected for control mortality. In the second bioassay when larvae were exposed to 14-day old residues, pre-imaginal mortality was not significantly different at 3.42 kg captan/ha but was significantly increased at 6.75 kg captan/ha. As for the first bioassay, the control-corrected mortalities were less than 50%. Reproduction in the control treatment and for the 'Merpan' 80 WDG treatments in both bioassays was greater than two eggs per viable female per day, which is within the historical database for control treatments on *C. septempunctata*. Hence, there were no effects on reproduction.

Table 25: Summary of mortality to *Coccinella septempunctata* following exposure to 'Merpan' 80 WDG on excised bean leaf discs

Treatment	Freshly dried residues + 20 days exposure (bioassay 1)		14-day aged residues + 20 days exposure (bioassay 2)	
	Mean mortality (%)	Corrected mortality (%)	Mean mortality (%)	Corrected mortality (%)
Control (tap water)	15.0	-	7.5	-
0.45 kg captan/ha	15.0	0	-	-
1.89 kg captan/ha	22.5	8.8	-	-
3.42 kg captan/ha	42.5*	32.4	10.0	2.7
6.75 kg captan/ha	52.5*	44.1	40.0*	35.1
Toxic standard	100*	100	-	-

* Significantly different from control at $p < 0.05$.
- not applicable or no treatment tested.

Table 26: Summary of reproduction of *Coccinella septempunctata* following exposure to 'Merpan' 80 WDG on excised bean leaf discs

Treatment	Freshly dried residues (bioassay 1)			14-day aged residues (bioassay 2)		
	Eggs/female /day[a]	Fertile eggs/female/ day	Larval hatch rate (%)	Eggs/female /day	Fertile eggs/female/ day	Larval hatch rate (%)
Control (tap water)	4.1	3.7	91.1	6.1	5.2	85.1
'Merpan' 80 WDG: 0.45 kg captan/ha	5.2	4.8	93.3	-	-	-
'Merpan' 80 WDG: 1.89 kg captan/ha	7.7	7.0	90.2	-	-	-
'Merpan' 80 WDG: 3.42 kg captan/ha	11.0*	7.9	71.5*	7.4	5.8	80.5
'Merpan' 80 WDG: 6.75 kg captan/ha	16.2*	15.7*	96.3	16.7*	14.4*	87.0

[a] Oviposition started one week after the first egg laying was observed in the control and lasted two weeks.
* Significantly different from control at $p < 0.05$.
- not applicable or no treatment tested.

Conclusions: Following exposure to freshly dried residues of 'Merpan' 80 WDG at 0.45, 1.89, 3.42 and 6.75 kg captan/ha on bean leaf discs the control-corrected mortality of *C. septempunctata* was less than 50%, the ESCORT 2 trigger. Reproduction was greater than two fertile eggs/viable female/day. For residues at 3.42 and 6.75 kg captan/ha which had 'aged' for 14 days on bean plants, the reduction in mortality and reproduction were similarly less than 50% compared to the control.

Revised risk assessment submitted by the Notifier:

Report: Norman, S. (2004). EU Review of captan. Non-target arthropods: Updated risk assessment incorporating new extended laboratory studies at higher application rates than previously tested. Makhteshim Agan, unpublished report 3 March 2004.

Guidance: ESCORT 2 and EU guidance document on terrestrial ecotoxicology (SANCO/10329/2002)

Summary: Previous studies indicated a general low toxicity to arthropods. The application rates tested in the previous laboratory and extended laboratory studies did not cover the highest rates notified in the EU review. Hence, additional studies have been undertaken on *Aphidius rhopalosiphi* and *Coccinella septempunctata* which cover the proposed rates, and also the ESCORT 2 multiple application factor. *A. rhopalosiphi* was chosen for testing as previous glass plate studies identified this as the most sensitive species. *C. septempunctata* was selected as it is a recommended additional test species under ESCORT 2. In both new studies, effects were less than the ESCORT 2 trigger of 50% at the maximum rate tested (6.75 kg a.s./ha). The new studies confirm the low risk to non-target arthropods in-field and off-field.

In the new studies [summarised above] Merpan 80 WDG was applied once as a foliar spray to potted bean plants (*Phaseolus vulgaris*) which were grown outdoors. Rates for the test item were calculated based on ESCORT 2. Bean plants were selected for use in the test because they provide a three dimensional leaf matrix which can be extrapolated to other plants.

Risk assessment:

Available studies on the toxicity of captan (formulated) to non-target arthropods are summarised in Table 27 (including the two new extended laboratory studies).

Table 27: Captan: Summary of studies on non-target arthropods (including two new extended laboratory) studies

Species	Captan (kg/ha)	Test	Endpoint and value	Conclusion	Reference (as stated in DAR)
*Typhlodromus pyri**	1.49	laboratory, residues on glass	*mortality:* 1.49 kg/ha: 7.2% control: 17.4% *eggs/female*: 1.49 kg/ha: 2.0 control: 2.0 *hatch rate:* 1.49 kg/ha: 0.68 control: 0.82	Effects less than ESCORT 2 trigger (50%)	Krips, O.E. (1994a)
*Aphidius rhopalosiphi**	0.60	laboratory, residues on glass	*mortality:* 0.6 kg/ha: 100% control: 13.7%	Effect greater than ESCORT 2 trigger (50%)	Kühner, C. (1995a)
*Chrysoperla carnea**	0.56	laboratory, residues on glass	*mortality:* control: 7% 0.56 kg/ha: 7% *fertile eggs/female:* control: 1037 0.56 kg/ha: 1089	Effects less than ESCORT 2 trigger (50%)	Kühner, C. (1995b)
	0.20	laboratory, residues on glass	*mortality:* control: 20% 0.2 kg/ha: 23% *eggs/female:* control: 418 0.2 kg/ha: 461	Effects less than ESCORT 2 trigger (50%)	Klepka, S. and Petto, R. (1993)
Pardosa spec.	0.75	laboratory, spiders and sand treated	*mortality:* control: 0% 0.75 kg/ha: 0% food consumption not affected	Effects less than ESCORT 2 trigger (50%)	Schmitzer, S. (1995)
*Orius insidiosus**	1.49	laboratory, residues on glass	*mortality:* control: 15.9% 1.49 kg/ha: 8% *eggs/female:* control: 12.2 1.49 kg/ha: 11.8 *hatch rate:* control: 0.96 1.49 kg/ha: 0.94	Effects less than ESCORT 2 trigger (50%)	Krips, O.E. (1994b)
Pterostichus melanarius	3.6	laboratory, residues on soil	*mortality:* 0% no effect on feeding behaviour	Effects less than ESCORT 2 trigger (50%)	McMullin, L.C. *et.al.* (1992)
Trybliographa rapae	3.6	laboratory, residues on glass	*mortality:* control: 17% 3.6 kg/ha: 28% *parasitism:* control: 18% 3.6 kg/ha: 12%	Effects less than ESCORT 2 trigger (50%)	McMullin, L.C. *et.al.* (1992)
*Aphidius rhopalosiphi**	0.0042 to 1.868	extended laboratory, residues on apple leaves	*mortality:* control: 5% 1.868 kg/ha: 12% *parasitism mummies/female:* control: 9.4 1.868 kg/ha: 5.9	LR_{50} > 1.868, no significant effects on survival or reproduction (i.e. less than ESCORT 2 trigger (50%))	Schuld, M. (1999)

Table 27 continued

Species	Captan (kg/ha)	Test	Endpoint and value	Conclusion	Reference (as stated in DAR)
*Aphidius rhopalosiphi**	3.42 and 6.75	extended laboratory, residues on bean leaves	*corrected mort.:* 3.42 kg/ha: 0% 6.75 kg/ha: 13% *Reduction in parasitisation:* 3.42 kg/ha: 49% 6.75 kg/ha: 22%	No significant effect at 6.75 kg/ha. Effects less than ESCORT 2 trigger (50%)	**NEW STUDY** Moll, M (2004a)
Coccinella septem-punctata	0.45 – 6.75	extended laboratory, residues on bean leaves (fresh residues, and 14 day aged residues)	Fresh residues: *corrected mort:* 0.45 kg/ha: 0% 1.89 kg/ha: 9% 3.42 kg/ha: 32% 6.75 kg/ha: 44% *Fertile eggs/female/day:* control: 3.7 0.45 kg/ha: 4.8 1.89 kg/ha: 7.0 3.42 kg/ha: 7.9 6.75 kg/ha: 15.7	Effects on survival less than ESCORT 2 trigger (50%) for fresh residues at 6.75 kg/ha. No negative difference in reproduction compared with control.	**NEW STUDY** Moll, M (2004b)
*Typhlodromus pyri**	1.5	field (orchard) 10 applns	adult numbers mite eggs	No effects compared with 'harmless' ref. substance	Oberwalder, C. (1996)
*Typhlodromus pyri**	1.8	field (orchard) 10 applns	adult numbers. Generally no negative effects. Slightly lower numbers (by 27-36%) 4 wks after 10th appln compared with 'harmless' ref substance	No major effects compared with 'harmless' ref. substance	Oberwalder, C. (1997)
*Typhlodromus pyri**	0.75 to 2.6	field (vines), 8 applications	adult numbers: *1 wk after final application:* control: 157 treatment: 105 *4 wk after final application:* control: 169 treatment: 151	No significant effects.	Ipach, R. (1995)
*Typhlodromus pyri**	1.28 to 3.3	field (vines), 8 applications	adult numbers: *1 wk after final application:* control: 82 treatment: 62 *4 wk after final application:* control: 61 treatment: 40	No significant difference from control 4 wks after 8th application.	Silvanus, W. (1995)

* Recommended test species under ESCORT 2 (2000).

Standard species (Typhlodromus pyri and *Aphidius rhopalosiphi):*

ESCORT 2 requires laboratory testing on the two standard species, *Typhlodromus pyri* and *Aphidius rhopalosiphi*. Previously submitted studies on glass plates show no effects on *T. pyri* at 1.49 kg a.s./ha, compared with 100% mortality at 0.6 kg a.s./ha for *A. rhopalosiphi*. Hence, *A. rhopalosiphi* is most sensitive. This result triggered the need for an extended laboratory study on *A. rhopalosiphi* . A previously submitted dose response study for *A. rhopalosiphi* on leaf substrate (i.e. extended lab) gave an LR50 of >1.868 kg a.s./ha, with no effects on survival or parasitisation at the highest rate tested. However, the highest rate in this study (1.868 kg a.s./ha) does not cover the maximum rate in the proposed uses (including multiple applications). Hence, a new extended laboratory study on *A. rhopalosiphi* including higher application rates has been undertaken (ref: Moll, 2004a).

The worst case use in terms of the risk assessment is the proposed use on peaches/nectarines (see Table 1), with 4 applications at 2.5 kg a.s/ha. ESCORT 2 provides a default multiple application factor (MAF) for 4 applications of 2.7. Hence, the appropriate testing rate to address risk to non-target arthropods *in-field* is 2.7 x 2.5 kg a.s./ha = 6.75 kg a.s./ha. This was the highest application rate in the new extended laboratory study on *A. rhopalosiphi.* At this rate effects were less than the ESCORT 2 trigger of 50%, indicating an acceptable risk in-field.

Given that a low risk has been demonstrated for *in-field* application rates, it can also be concluded that the risk *off-field* from spray drift is acceptable.

Two additional species as required under ESCORT 2:

Data should be provided on two additional species selected from the options provided in ESCORT 2. For captan, data are available for *three* additional ESCORT 2 recommended species (*Orius insidiosus, Chrysoperla carnea,* and *Coccinella septempunctata*). The studies on *O. insidiosus* and *C. carnea* are both on glass plates (results are summarised in Table 2). Both these species showed a low toxicity at the rates tested, and they were less sensitive than *A. rhopalosiphi* (which gave 100% mortality in the glass plate test, at 0.6 kg a.s./ha). Hence, the risk to arthropods represented by *O. insidiosus* and *C. carnea* is addressed by the new extended laboratory study on *A. rhopalosiphi* (effects less than ESCORT 2 trigger at 6.75 kg a.s./ha).

A new study, on *C. septempunctata* has also been undertaken. This gave effects on survival and reproduction of less than the ESCORT 2 trigger of 50%, at 6.75 kg a.s./ha (Tables 2 and 3). Hence, this indicates a low risk in-field to species represented by *C. septempunctata*.

Given that a low risk has been demonstrated for *in-field* application rates, it can also be concluded that the risk *off-field* from spray drift is acceptable.

Conclusions:

Two new extended laboratory studies (on *A. rhopalosiphi* and *C. septempunctata*) at higher application rates than previously tested confirm that there is a low risk to non-target arthropods from the proposed uses.

Comments from RMS on new non-target arthropod studies and risk assessment:

The submitted studies are considered valid, and address the applications rates of the proposed uses in the review (including multiple applications, by the use of Multiple Application Factors). The RMS supports the risk assessment as presented above.

It is considered that the above studies and risk assessment address **Open point 5.13** and the following comments from the Reporting Table: 5(38), 5(41), 5(43), 5(44);

Responses to address Open points and comments in Reporting Table on non-target arthropods:

Comment 5(39)(EFSA), **Open point 5.13**:

'It is noted that the fecundity in the control during the laboratory study with *T. pyri* was rather low. Mean eggs per female was 2 while in the Guidelines to evaluate side-effects of plant protection products to non-target arthropods (Candolfi *et al*, 2000) a minimum of 4 is set as a validity criterion.'

Statement from Notifier (ref: Norman, 2005): The comment is noted. Under ESCORT2, for the Tier 1 risk assessment using glass plate tests reproduction results are not relevant (only survival). Hence, this shortcoming in the study does not affect the risk assessment. In addition, *T. pyri* is not the most sensitive standard species for captan (this is *A. rhopalosiphi*). Also, the risk to *T. pyri* is addressed by 3 field studies, which showed no major effects at the population level.

The RMS agrees with the above statement.

Comment 5(40)(EFSA):

'A more extensive argumentation regarding the comparability of the tested formulations to both lead formulations is considered necessary.'

Statement from Notifier (Ref: Norman, 2005): Most of the previous non-target arthropod studies were conducted with an 83 WP (83% w/w) formulation. This has a similar a.s. content to the lead formulations which are both 80 WG (80% w/w) formulations. Hence, it is considered appropriate to extrapolate between the WP and WG formulations. The tier 1 studies (glass plate, and sand substrate) on the 83 WP have been used in the above risk assessment to identify *Aphidius rhopalosiphi* as the most sensitive species. Consequently, a new extended laboratory study has been submitted on *A. rhopalisiphi* using the 80 WG (Merpan 80 WDG). An extended laboratory study has also been conducted for *Coccinella septempunctata* for the 80 WG. Hence, any potential for difference in the toxicity between the 83WP and the 80WG formulations has been addressed by the new studies, which are used as the basis of the assessment.

The RMS agrees with the above statement. In addition, as stated in the aquatic assessment, the Notifier has submitted the formulation details for Merpan 83 WP (83% captan w/w) (to satisfy Data Requirement 5.1) so that it can be compared with the lead formulations (80 WG, 80% captan w/w). The RMS considers that the formulations are comparable.

Comment 5(42)(EFSA):
'A more elaborate statement on the representativeness of the number of applications and the use rate in the field studies to the intended use in pome fruit for southern Europe is considered necessary'.

Statement from Notifier (ref: Norman, 2005): The two field studies on *T. pyri* by Oberwalder (1996 and 1997) cover the nine applications at 1.25 kg a.s./ha under the GAP for south EU pome fruit (for Scab control). However, they do not cover the additional 3 applications at 2.4 kg a.s./ha for Nectria control. Two *T. pyri* field studies on vines (Ipach, 1995; Silvanus, 1995) did include applications up to 2.6 kg a.s./ha (Ipach, 1995) and 3.76 kg a.s./ha (Silvanus, 1995). Hence, these studies do cover the potential exposure following an application at 2.5 kg a.s./ha for south EU pome fruit. In any case, *T. pyri* was not identified as the most sensitive species from the laboratory and extended laboratory studies. From tier 1 laboratory studies the most sensitive species was *A. rhopalosiphi*, and from the extended laboratory studies *Coccinella septempuncta* appeared to be marginally more sensitive than *A. rhopalosiphi* (although *Coccinella septempuncta* was not actually very sensitive: 44% mortality from a high rate of 6.75 kg a.s./ha). In general, captan has been shown to be of low toxicity to non-target arthropods and the available studies are considered sufficient to demonstrate low risk (including for south EU pome fruit).

The RMS agrees with the above statement.

Additional comment received from Germany (in letter dated 29.10.04):

'Many of the provided NTA limit tests were performed with very low application rates. So their results are nearly useless for a correct risk assessment (all HQ values are given as "<" values). In addition, both Tier I species (*T. pyri, A. rhopalosiphi*) are probably at risk, but only the former one is tested in the field. The performance of Tier I dose-response tests, Tier II tests with 3 species and, probably, a field test with *A. rhopalosiphi* are needed. According to the Terrestrial Guidance Document (2002), effects at Tier I cause the need for data with several species from extended laboratory tests (or field tests). Whether the new studies submitted by the notifier are appropriate and sufficient can only be decided when the evalaution and the revised risk assesment of the RMS is available.'

Statement from Notifier (ref: Norman, 2005):

Although the application rates in the glass plate tests are generally lower than the application rates for the proposed uses, the studies are useful for identifying what is the most sensitive species tested. Considering the studies using glass plate and sand substrates (summarised in Table 27), *Aphidius rhopalosiphi* is clearly the most sensitive species out of the four ESCORT 2 recommended species tested at Tier 1 (the other three species tested were *T. pyri*, *Chrysoperla carnea*, and *Orius insidiosus*). From the tier 1 test on *T. pyri*, there is no indication that this species is probably at risk. The reason why the field tests were conducted on *T. pyri* is because of its importance as a *beneficial* species in IPM. Given that *A. rhopalosiphi* was identified as the most sensitive species, a new extended laboratory study was submitted for this species. This study was conducted at high enough rates to address the proposed uses, including the use of the Multiple Application Factor. The highest rate tested in the new study was 6.75 kg a.s./ha. At this rate there was 13% mortality and 22% reduction in fecundity from exposure to fresh dry residues on leaves. Neither of these results was statistically significant, and both are below the ESCORT 2 trigger of 50%. Hence, they do not indicate the need for field testing.

To provide data on an additional ESCORT 2 recommended species an extended laboratory study on *Coccinella septempunctata* has also been conducted. At the highest rate tested (again

6.75 kg a.s./ha) there was 44% corrected mortality and no adverse effect on reproduction from exposure to fresh dry residues on leaves. Hence, effects were less than the ESCORT 2 trigger of 50% indicating low risk. Given that a conclusion on the risk assessment can be reached based on the available data, there is no need for lower Tier *dose-response* tests. If conducted, these tests would only trigger the need for extended laboratory tests, which have already been conducted.

The RMS agrees with the above statement.

Overall conclusion of the RMS on risk to non-target arthropods:

Low risk to non-target arthropods from the proposed uses.

B.9.6 Effects on earthworms (Annex IIA 8.4; Annex IIIA 10.6.1)

Open point 5.16: Pending on the discussion of the PECs in the section on Fate and behaviour, a revision of the risk to earthworms may be necessary. (see reporting table 5(46))
Open point 5.17: RMS to prepare an addendum to revise the risk assessment for earthworms.(see reporting table 5(47))

As agreed in **Open point 5.16**, a revised risk assessment is presented below to include new PECsoil values. Available studies on earthworms are already summarised in Annex B.9.6 of the DAR. For ease of reference the endpoints are also presented in Table 28 below.

Table 28: Summary of available toxicity data for earthworms (*Eisenia foetida*), for captan

Test material	Study type	Exposure duration	Endpoint mg a.s./kg soil	'Corrected' Endpoints*	Ref:
captan	acute	14 days	LC50: >519.3	LC50: >259.7	Roberts et al, 1985
Merpan 83 WP	acute	14 days	LC50: 839	419.5	Jackson et al, 1994
Merpan 80 WDG	reproduction	adults: 28 d total: 56 d	12.18 (11.25 kg a.s./ha)	6.09	Luhrs, 2002
Malvin 80 WDG	reproduction	adults: 28 d total: 56 d	11.60 (8.70 kg a.s./ha)	5.80	Stabler, 2002

* According to the EU terrestrial guidance and EPPO earthworm scheme 2002, the endpoints have been divided by 2 (as the log Kow of captan is >2) in order to account for the difference organic matter content of the test soil (10%) and field soils which lower organic matter content. If TER values are below their respective triggers, there may be scope to revisit this assumption based on the fate properties of captan in soil.

Risk assessment:

Based on a reassessment of fate in soil provided by the Notifier, a revised set of soil PEC values has also been provided by the Notifier. These values are stated in full in an Addendum to the DAR on fate and behaviour. Relevant PEC figures have been used to derive TER values for earthworms. The PEC and TER values are stated below in Table 29.

Table 29: Relevant PECsoil values and TER values for earthworms for the Notified uses of captan.

Crop use and max. number of applications	timescale	Toxicity endpoint	Maximum PEC*	TER	Annex VI Trigger
North EU pome fruit (10 applns)	acute	>259.7	1.003	258.9	10
	long term	5.80	1.003	5.78	5
South EU pome fruit (12 applns)	acute	>259.7	1.811	143.4	10
	long term	5.80	1.811	3.20	5
Tomatoes (4 applns)	acute	>259.7	1.354	191.8	10
	long term	5.80	1.354	4.28	5
peaches/nectarines (4 applns)	acute	>259.7	1.880	138.1	10
	long term	5.80	1.880	3.09	5

*PECsoil value directly after the final application. 70% foliar interception assumed for pome fruit and peaches/nectarine, in accordance with FOCUS ground water guidance.

For the notified use in North EU pome fruit TER values are greater than the relevant triggers, indicating a low risk.

For the notified use in peaches/nectarines and South EU pome fruit, the acute TER values are greater than the relevant trigger of 10, indicating low risk. The long term TER values are below the relevant trigger of 5. Hence, the risk requires further assessment (please see refined risk assessment below)

Refined long term risk assessment for use in South EU pome fruit and peaches/necarines:

Statement from Notifier on why correction factor of 2 should not apply to captan (ref: Norman, 2005): Captan degrades rapidly in soil by chemical hydrolysis with a DT50 and DT90 of <1 day in laboratory degradation studies. This hydrolytic degradation is not dependant on the presence of an active microbial population. All the earthworm studies used artificial 'soil' composed mainly of sand (70%) and peat (10%). Hence, this test medium is unlikely to have a high microbial activity. The soil is moistened in order to ensure the health of the earthworms in the controls. The presence of water would have meant the relatively rapid degradation of captan in the earthworm studies submitted. Hence, in the long term studies, after an initial short exposure to captan, subsequent exposure would mainly have been to the hydrolysis products THPI and THPAM. The logPow for captan (2.5) is >2, which means (according to EPPO, 2002, and EU terrestrial guidance document) that earthworm endpoints should be divided by 2. This is to account for the potential for greater sorption and hence potentially reduced bioavailability in the soil in the laboratory studies (10% organic matter) compared with exposure in field soils (where organic matter would less than in the study). However, the degradation of captan in the earthworm laboratory studies is likely to have been too fast for sorption to have significantly influenced exposure. Exposure in the studies would have been predominantly to THPI and THPAM. Neither of these compounds has a strong affinity for organic matter (Koc for THPI: 7.6 – 13, Koc for THPAM 3.8 – 110). Hence, the organic matter content of the laboratory soil is unlikely to have had a significant influence on extent of exposure. Therefore, in this case the correction factor of 2 is not necessary.

The RMS agrees with the above statement. This being the case, the long term TER values for peaches/nectarines (TER: 6.18), South EU pome fruit (TER: 6.4), and tomatoes (TER: 8.6) are greater than the relevant trigger of 5, indicating low risk.

The risk assessment above is considered to address Open Points 5.16 and 5.17 and the following comments in the Reporting Table: 5(46), 5(47), 5(48), 5(49), 5(50), 5(51) and the two comments received from Germany (in letter dated 29.10.04).

Additional responses on comments from Reporting Table on risk to earthworms:

Comment 5(45)(EFSA):

'A more extensive argumentation regarding the comparability of the tested formulation to both lead formulations is considered necessary.'

Statement from Notifier (ref: Norman, 2005): An acute toxicity study on an 83 WP formulation is available. This formulation is of similar a.s. content (83% w/w) to the lead formulations (80 WG: 80% w/w). Hence, it is considered reasonable to extrapolate. The acute risk assessment gives TER values much greater than the trigger of 10. Hence, any potential difference between formulations would not change the outcome of the risk assessment. For the long term assessment, earthworm reproduction studies are available for both Merpan 80 WDG and Malvin WG. Hence, there is no issue of extrapolation.

The RMS agrees with the above statement. In addition, as stated in the aquatic assessment, the Notifier has submitted the formulation details for Merpan 83 WP (83% captan w/w) (to satisfy Data Requirement 5.1) so that it can be compared with the lead formulations (80 WG, 80% captan w/w). The RMS considers that the formulations are comparable.

Overall conclusion of the RMS:

Low risk to earthworms from the notified uses.

Comments on other Open Points, and comments in the Reporting Table:

Comment 5(36)(EFSA):

'On p. 217 it is stated that the toxicity to bees for the lead formulation Malvin WG can be based on a study with a 50% WP formulation. A more extensive argumentation on the comparability of both formulations is considered necessary.'

Statement from Notifier (ref: Norman, 2005): In the study on the active substance, there were no treatment related mortalities or sublethal effects at the highest dose tested. Hence, the contact and oral LD50 values were >200 and >100 µg a.s./bee, respectively. Hence, captan is of low toxicity to bees. For Merpan 80 WDG, a justification for extrapolation from Merpan 83 WP (on which there is a study, showing low toxicity) is provided in the DAR. As noted in the comment above, there is no similar detailed statement to support an extrapolation from a study on a 50% WP to Malvin 80 WG. Given the low toxicity of captan and the 83WP (which has a similar a.s. content to Malvin 80 WG) to bees, it is concluded that Malvin 80 WG is also very likely to be of low toxicity to bees. Hence, further information is not needed. All hazard quotients are well below the trigger of 50, indicating low risk.

The RMS agrees with the above statement.

Comment 5(54)(EFSA), **Data requirement 5.2**: Effects on other flora and fauna:

Data requirement 5.2:
Notifier to address the risk to other non-target fauna and flora. (see reporting table 5(54))

(Comment from Germany in letter of 29.10.04, also raised need for screening data on plants).

Statement from Notifier (ref: Norman, 2005):

No data on effects on other flora and fauna are available. The product has been used for many years without reports of phytotoxicity on the target crops. Given that the captan is not a herbicide, it is considered that screening data for effects on plants are not needed.

The RMS agrees with the above statement.

Comment 5(54)(EFSA), **Open point 5.18**:

Open point 5.18:
Pending on the discussion of the PECgw values in the section on Fate and behaviour, data on pesticidal activity of the major ground water metabolites may be necessary (see reporting table 5(54))

Regarding the pesticidal activity of the metabolites THPI and THPAM, a study on their fungicidal activity has been submitted by the Notifier. This study has been evaluated by the RMS and is summarised below:

'Bioassay of captan and metabolites against Venturia and Botrytis. June 1999. Royal Research Station of Gorsem, Belgium':

A comparative test of the fungicidal activity of captan, THPI and THPAM was undertaken in the laboratory. Malt extract (15 g/L) and agar (18 g/L) were used as an artificial growth medium. The test substances were dissolved in acetone. Using a stock solution of concentration 10 g test substance/L (100 mg/10 mL), the concentration range was achieved through dilution in the agar. The acetone solution was added when the temperature of the agar had dropped to 45 °C.

The fungal strains of *Botrytis cinerea* (grey mold; isolated from strawberries) and *Venturia inaequalis* (apple scab; taken from the fungal collection of the research station) were tested. These are two of the main target organisms for captan. The endpoints of spore germination, and mycelial growth were assessed in the study.

To assess spore germination, 100 µL of a suspension containing 150000 conidies/mL (measured by a haemocytometer) was spread over the agar in plates containing 12 mL of the malt extract agar. This agar contained either no test material, acetone only, a series of concentrations of captan (1, 5, 25, 50 and 100 mg/L of test material), 100 mg THPI/L or 100 mg THPAM/L. For each substance and concentration, 4 x 50 conidies were evaluated on two duplicate agar plates (2 x 50 on each plate). Conidies were classified into 5 classes (RR, R, r, s, 0) depending on the length of the germination tube (RR = completely resistant, i.e. no effect; 0 = no resistance, i.e. germination inhibited). This classification scheme is also used in monitoring tests for resistance of fungi for specific fungicide families.

For mycelial growth, two agar plugs (5 mm diameter) cut from a freshly growing colony were transferred to agar plates containing the same concentrations of test materials as in the spore germination test. For each substance and concentration 4 plugs were evaluated on 2 agar plates (two on each plate). Inoculated plates were incubated at 20 °C, and the mean colony diameter was measured after 5 days incubation for *Botrytis cinerea*, and after 19 and 44 days for *Venturia inaequalis*.

Results are presented in Tables 30 and 31.

Table 30: Conidial germination of grey mold (*Botrytis cinerea*) and apple scab (*Venturia inaequalis*) classified by length of germination tube. Value are means of 4 assessments (each of 50 conidies).

		Botrytis cinerea **(after 24 h incubation)**					***Venturia inaequalis*** **(after 48 h incubation)**				
Test substance	**Conc. (mg/l)**	**RR**	**R**	**r**	**s**	**0**	**RR**	**R**	**r**	**s**	**0**
control	0	38.5				11.5	49.3				0.8
control (acetone)	0	39.0				11.0	48.8				1.3
captan	1			38.0		12.0	49.5				0.5
	5				10.8	39.3		44.5			5.5
	25					50.0					50.0
	50					50.0					50.0
	100					50.0					50.0
THPI	100	38.8				11.3	49.3				0.8
THPAM	100	38.5				11.5	49.3				0.8

RR= Complete resistence, i.e. no effect; 0 = no resistance, i.e. inhibition of germination

Table 31: Activity on mycelial growth of grey mould (*Botrytis cinerea*) and apple scab (*Venturia inaequalis*). Diameter of colonies on agar plates (mean value of 4 colonies, per concentration). Starting diameter was 5 mm (so a measurement of 5 mm indicates no growth).

Test substance:		***Botrytis cinerea*** **(after 5 days incubation) mean diameter of colony (mm)**	***Venturia inaequalis*** **(after 19 days incubation) mean diameter of colony (mm)**	***Venturia inaequalis*** **(after 44 days incubation) mean diameter of colony (mm)**
control		67.0	14.0	29.5
control (acetone)		57.5	14.5	32.5*
captan	1	59.3	12.5	24.0
	5	49.8	11.5	26.0
	25	5.0	5+	16.8
	50	5.0	5.0	12.8
	100	5.0	5.0	9.0
THPI	1	64.0	11.3	20.5
	5	50.5	12.5	28.0
	25	35.5	11.5	25.8
	50	39.5	13.8	28.0*
	100	39.3	13.3	25.8
THPAM	1	60.3	13.3	23.5*
	5	53.3	13.0	25.3
	25	52.8	13.3	26.0
	50	59.5	13.3	25.3
	100	58.0	13.0	I

I = no measurements were possible due to contamination of plates with other microorganisms. This was because of the long incubation time. * = mean of two plugs, as the other two could not be measured due to contamination of plates with other microorganisms.

In terms of conidial germination, for captan, there was a clear effect on both *Botrytis cinerea* and *Venturia inaequalis*. For *B. cinerea*, there was a clear effect at 1 mg/L, with complete inhibition of germination at 25 mg/L. For *V. inaequalis*, there was also complete inhibition of germination at 25 mg/L. THPI and THPAM had no effect on germination compared with the control, at 100 mg/L.

In terms of mycelial growth, there was complete inhibition for *B. cinerea* at 25 g captan/L. For *V. inaequalis*, there was almost complete inhibition at this concentration of captan ('5+' indicates a 'light growth' compared with at the start) after 19 days. After 44 days of incubation, some limited growth in the captan treated plates (25 – 100 mg/L) had occurred. For THPAM, there was no effect on mycelial growth for either species at any test concentration. For THPI, there was no effect on *V. inaequalis*. For THPI, there was a 35% reduction in growth of *B. cinerea* at 100 mg/L compared with the acetone control.

Comments from RMS:

The submitted study is considered sufficient to assess the pesticidal activity of THPI and THPAM. Hence, the potential data requirement as raised in Comment 5(54) is fulfilled.

In terms of fungicidal activity, THPAM showed no effects on *Botrytis cinerea* (grey mold) or *Venturia inaequalis* (apple scab) for conidial germination or mycelial growth. THPI showed no effects on *Venturia inaequalis* (apple scab) for either endpoint. For *Botrytis cinerea*, at 100 mg/L (the highest test level), THPI gave a 35% reduction in mycelial growth compared with

the control. This is compared with a 100% reduction for captan, at 25 mg/L, i.e. around a 3 x greater effect for captan at 4 x lower concentration.

Pesticidal activity of metabolites with the potential to reach groundwater should be assessed in the context of the Guidance Document on the Assessment of the Relevance of Metabolites in Groundwater (SANCO/221/2000 – rev 10- final, 25.2.2003). With respect to pesticidal activity, the document states the following: 'In screening assays it will often not be possible to determine and compare the biological activity of a parent molecule and its metabolites with great precision, and this will also not be necessary in most cases. As a line of orientation, it should be sufficient to demonstrate that the biological activity of a metabolite is clearly less than 50% of the activity of the parent molecule. Otherwise the biological activity should be considered as "comparable" '.

In terms of the above criteria of pesticidal activity, the RMS considers both THPI and THPAM to be non-relevant.

Comment from Germany in letter of 20.10.04, Comment 5(56), **Open Point 5.19**:

Open point 5.19:
MS to discuss the need for further data to address the risk to sewage treatment in an expert meeting. (see reporting table 5(56))

Statement from Notifier (ref: Norman, 2005): Data have been submitted which demonstrate the rapid degradation of captan (hydrolyis studies, and sediment water study). Also, given the use of the product as an agricultural fungicide it is very unlikely that the captan would enter the domestic drainage system, and reach sewage treatment plants.

The RMS agrees with the above statement.

Overall conclusion by RMS on the ecotoxicological risk assessment for captan:

The submitted information is sufficient to complete the risk assessment. Overall, a low risk to non-target organisms can be concluded for the notified uses of captan.

New references, by Annex point

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
Annex II					
IIA, 8.2.1	Jenkins	2004a	Captan: Acute toxicity to rainbow trout. [redacted] Project: MAK/836 (Company file: R-17596). 21 Sept. 2004 GLP, Unpublished.	Y	Makhteshim/ Calliope* (*formerly Tomen)
IIA, 8.2.1	Jenkins	2004b	Captan: Acute toxicity to three-spined stickleback. [redacted] Project: MAK/837 (Company file: R-17597). 21 Sept. 2004 GLP, Unpublished.	Y	Makhteshim/ Calliope* (*formerly Tomen)
IIA, 8.3.2	Moll, M.	2004	Effects of 'Merpan' 80 WDG on the parasitoid *Aphidius rhopalosiphi*, extended laboratory study - aged residue test. IBACON Report 18191003 (Company file: R-16397). GLP, Unpublished.	Y	Makhteshim/ Calliope* (*formerly Tomen)
IIA, 8.3.2	Moll, M., Bützler, B.	2004	Effects of 'Merpan' 80 WDG on the ladybird beetle *Coccinella septempunctata*, extended laboratory study - aged residue test. IBACON Report 18193013 (Company file: R-16399). GLP, Unpublished.	Y	Makhteshim/ Calliope* (*formerly Tomen)
-	Royal Research Station of Gorsem, Belgium	1999	Report 1999. Bioassay of captan and metabolites against Venturia and Botrytis. Royal Research Station of Gorsem, Brede Akker 3, B-3800, Belgium. June 1999. (Company file: R-11094) Non-GLP, Unpublished.	N	Makhteshim/ Calliope* (*formerly Tomen)
-	Norman, S	2005	Review of captan: Notifier responses to various comments on ecotoxicology raised in the official Reporting Table. Unpublished. February 2005.	Y	Makhteshim/ Calliope* (*formerly Tomen)
Annex III					
IIIA, 11.1	Norman, S., Wyness, L.	2003	Captan. Response to Rapporteur Member State request for a revised avian and mammalian risk assessment in accordance with EU guidance document on risk assessment for birds and mammals (SANCO/4145/2000. Makhteshim Agan and TSGE, report September 2003. Not GLP, Unpublished.	Y	Makhteshim/ Calliope* (*formerly Tomen)
IIIA, 11.5	Norman, S.	2004	EU Review of captan. Non-target arthropods: Updated risk assessment incorporating new extended laboratory studies at higher application rates than previously tested. Makhteshim Agan, report 3 March 2004. Not GLP, Unpublished.	Y	Makhteshim/ Calliope* (*formerly Tomen)

Captan

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Mammalian toxicology

Addendum to dossier

March 2005

Table of Contents

Introduction

This document contains new information on mammalian toxicology submitted by Makhteshim Chemical Works Ltd. and Arysta Paris to the RMS.

New information is presented here in the order of the Evaluation table for captan, cross-referencing the Open point numbers and Reporting table numbers. New information is summarised under the dossier numbering system.

Document D1: Critical Good Agricultural Practice

The GAP for peaches/nectarines is changed: the PHI is increased from 7 days to 21 days. No other changes have been made. The amended GAP is presented in the table below.

Critical Good Agricultural Practice for captan in the EU

Crop	Member state or country	Product name	F, G or I	Pests or group of pests controlled	Formulation		Application			Application rate per treatment			PHI (days)	Remarks:
					Type	Conc. of a.s.	method kind	growth stage/ timing	number[b] (max.)	kg a.s./hL (max.)	water L/ha	kg a.s./ha (max.)		
Pome fruit	North EU	'Merpan' 80 WDG / 'Malvin' WDG	F[a]	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 53 / April	9 - 10	0.125	1000	1.25	14	
	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69 / April	9 + 3 [c]	0.125 0.24	1000 1000	1.25 2.4	14	
Tomatoes	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Foliar spray; down-wards	From BBCH 60 to 87	4	0.15	1200	1.8	14	
Peaches/ nectarines	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69: petal fall	4	0.25	1000	2.5	21	

[a] F = field.
[b] Applications at a minimum of 7 days for all crops.
[c] Nine applications at 1.25 kg a.s./ha (scab control) followed by three applications at 2.4 kg a.s/ha (*Nectria* control).

New information on mammalian toxicology

Evaluation table number	Reporting table number	Open Point number
-	**2(1)**	**2.1**
Conclusions of the EFSA Evaluation Meeting: ***MS to discuss the cancerogenic properties in an expert meeting***		
-	**2(33)**	**2.15**
Conclusions of the EFSA Evaluation Meeting: ***Acceptability of the genotoxicity studies to be clarified by the RMS. If they are not acceptable they should be deleted from the reference list***		
-	**2(34)**	**2.16**
Conclusions of the EFSA Evaluation Meeting: ***The genotoxic effect of Captan to be clarified by the RMS and to be discussed at an expert meeting***.		
-	**2(35)**	**2.17**
Conclusions of the EFSA Evaluation Meeting: ***RMS to check the publications mentioned in the comment from GR (e.g.: Reuber MD, 1989; Cabral R et al., 1991; Hasegawa R et al., 1993; Perocco P et al, 1995) regarding the carcinogenicity of Captan and to summarize in an addendum.*** [This open point is also addressed by reports Reuber 1989 summarised under Point IIA 5.5.3/01 below, Cabal et al 1991 summarised under Point IIA 5.5.3/02 below, and Hasegawa et al. 1993 summarised under Point IIA 5.5.3/03 below.]		
-	**2(36)**	**2.18**
Conclusions of the EFSA Evaluation Meeting: ***RMS to review the study mentioned in the comment from GR (Mills PK, 1998 and MCDuffie HH et al, 2001) regarding medical data***. [This open point is also addressed by reports Mills 1998 summarised under Point IIA 5.9.3/02 below, McDuffie et al summarised under Point IIA 5.9.3/03 below.]		
2.4	**2(37)**	-
Conclusions of the EFSA Evaluation Meeting: ***Notifier to submit the two rat carcinogenicity studies by Goldenthal et al., 1982 and Bruyntjes, 1984.***		

The following paper is submitted in response to questions/comments made by the Greece authorities. The paper references additional studies which are summarised under Points IIA 5.10/03, 5.5.3/01, 5.5.3/02, 5.5.3/03, 5.9.3/02, 5.9.3/03. Please refer to the summaries of these studies presented below.

- **Point IIA, 5.10: Summary of mammalian toxicity and overall evaluation**

5.10/02

Report: Makhteshim Chemical Works and Calliope. (2005). Captan. Comments made by Greece on the toxicology section of the DAR. Response by Notifier. Makhteshim and Calliope, unpublished report.

Guidelines: Not applicable.

GLP: No.

Material and methods: The Member State (Greece) made several comments on the toxicological section of the DAR. Each of the comments are noted and the notifier response in detail is given in the document.

Executive Summary:

The Member State Greece submitted comments to the toxicology section of the captan DAR that addressed issues of mutagenicity (sections B.6.4, B.6.4.3), carcinogenicity (section B.6.5) and medical data (section B.6.9). The Notifier considered these comments and prepared responses that clarify the issues raised.

The genotoxicity of captan is well characterized and there are no data gaps in the genotoxicity database. Many studies have been conducted with captan, both *in vitro* and *in vivo*. The collective data are robust and provide a clear understanding of captan's actions in bacterial mutation assays as well as in whole animals. These data support the conclusion that captan is not genotoxic in humans.

The carcinogenicity of captan is equally well characterized. The mode of action for captan has been elucidated and accepted after peer review by a panel of independent experts as well as by a scientific panel in the US EPA. Captan is not a carcinogen in rats. The duodenal tumors that are associated with prolonged high doses of captan in mice result from a nonmutagenic cytotoxicity/regenerative hyperplasia response. This mode of action is reversible upon cessation of treatment and has a threshold. The database supporting the mode of action is sufficiently robust that captan is no longer classified as a probable human carcinogen (B2) by EPA.

The epidemiologic evidence suggesting an association of captan with human cancer is weak, at best. An association of captan with human cancer has not been established would not be expected in light of captan's established mode of action.

We address the Member State Greece's comments and reiterate the conclusions of independent experts that captan is not mutagenic and does not pose a cancer risk.

The paper addresses each of the points made by Greece and provides a full and comprehensive response with reference to existing data. In summary, the paper concludes:
1) There remain no data gaps in the genotoxicity database for captan.
2) Captan does not pose a risk of adverse mutagenicity *in vivo*.
3) Captan is not a carcinogen in rats.
4) There is insufficient epidemiologic evidence to link captan to human cancer.

Detailed responses to the issues raised are summarised below:

New information supplied to address open point 2.15

The table below lists the genotoxicity studies summarised in the original dossier and subsequent addenda:

Reference	Company reference	Guideline	GLP
(Carver and Richter 1985){Machado}	R-9246/TMN-0808	Not stated	No
(Carere, et al., 1978)	R-2615/TMN-806	Not stated	No
(Tezuka, et al., 1978)	R-1666/TMN-0824	Not stated	No
(Tezuka, et al., 1980)	R-2715/TMN-0816	Not stated	No
(Edgar, 1985)	R-4319	Not stated	No
(O'Neill, et al., 1981)	R-3487/TMN-0810	Not stated	No
(Jacoby, 1985)	R-3666	OECD 47	Yes
(Nguyen and McGowan, 1980)	TMN-0834	Not stated	No
(Bootman and Whalley, 1979)	R-1735	Not stated	No
(Feng and Lin, 1987)	TMN-0826	Not stated	No
(Fry and Fiscor, 1978)	R-2576/TMN-0825	Not stated	No
(Chidiac and Goldberg, 1987)	R-6346/TMN-0833	Not stated	No
(Kennelly, 1990)	TMN-0835	OECD 48	Yes
(Salaman, C. and Smith, S. 1977)	TMN-0850	Not stated	No

The studies listed are accepted for inclusion in the collective mutagenicity data for captan with the exception of one (Feng and Lin, 1987). This study has noted errors and is judged unreliable. Valid studies with scientific integrity should be included in the overall evaluation; the relative weight given to each study, however, is dependent on careful review of the study design, study conduct and consistency of results with the other collective data. It is noted that GLP status, *per se*, does not speak to the scientific validity of a study. It can be concluded that there remain no data gaps in the genotoxicity database for captan.

New information supplied to address open point 2.16
(see also new report submitted in connection with open points 2.16; 2.17 and 2.18).

It has been postulated that findings from the open literature studies and from the JMPR assessment for captan show that captan can interact with DNA and with the nucleic acid replication systems in a number of ways. In particular, the JMPR evaluation refers to the interaction of captan with tubulin, which affects the assembly and disassembly of microtubules in isolated tubulin and cultured mammalian cells (Stournaras, et al., 1991), (open literature not summarised in addendum or original dossier). However, judgement is erroneous here. The weight of evidence from data on captan does lead to a definite conclusion that the *in vivo* potential for genotoxicity of captan is low (essentially zero risk).

These data have been recently reviewed by independent experts as well as scientists at the U.S. EPA. Both parties conclude that captan is unlikely to be an *in vivo* mutagen (TERA, 2003[4], TERA, 2004[5]). This judgement was published November 24, 2004 (US-EPA, 2004). The collective data show that "captan induces adenomas and adenocarcinomas in the duodenum of the mouse by a non-genotoxic mode of action involving cytotoxicity and regenerative cell hyperplasia that exhibits a clear dose threshold …" (US-EPA, 2004, Page 68359).

[4] TERA. 2003. *Report of Peer Review Meeting Cancer Assessment for Captan September 3-4, 2003. Rep. CTF 0204*MRID 4619301.
[5] TERA. 2004. Peer reviewer comments on revised captan report.:

The work of Stournaras and co-workers (1991[6]) does not address the issue of captan's *in vivo* mutagenicity. Captan is a reactive chemical that produces a broad array of biochemical changes when contacting cells *in vitro*. The issue is not whether or not captan is capable of interacting with sensitive biological systems; it is, in contrast, whether or not captan ever exists long enough *in vivo* to actually come in contact with these systems. An abstract of Stournaras and co-workers (1991) work follows:

Using turbidometry, electron microscopy and immunofluorescent microscopy experiments we studied the effect of captan, a widely used pesticide, on mammalian microtubules and microfilaments. Turbidometry at 350 nm showed a dose-dependent inhibition of tubulin assembly incubated with captan. The pesticide, given at equimolar concentration with tubulin (30 microM), caused the total inhibition of microtubule formation, while at lower concentrations (5-20 microM) the inhibition of tubulin polymerization was less extensive. At the same concentration range (5-30 microM), captan also promoted the disassembly of preformed microtubules. The results of the *in vitro* effects of captan with microtubules were confirmed in parallel by electron microscopic studies. *In vivo*, captan also caused depolymerization of microtubules in cultured mouse fibroblasts as shown by indirect immunofluorescent staining of tubulin. The extent of microtubules disassembly was concentration- and time-dependent. While incubation of the cells with 10 microM captan for 3 h disturbs totally the microtubular structures, incubation with 5 microM captan needs 12 h for the same effect. Recovery of microtubules was observed, when pre-incubated cells were extensively washed. No interaction of this drug with equimolar concentration of G- or F-actin could be observed *in vitro*, as shown by polymerization experiments. In line with this, the fluorescent actin pattern in mouse fibroblasts incubated with 10 mM captan for up to 12 h did not seem to be altered. From these results it is concluded that captan interacts in equimolar concentrations with tubulin affecting the assembly and disassembly of microtubules in vitro and in cultures of mammalian cells.

Captan does not exist *in vivo* long enough to interact with sensitive biological systems. The half-life in human blood is less than one second (see Annex II, 5.1/07) and the half-life of the breakdown product thiophosgene is 0.6 seconds (see Annex II, 5.1/08). Metabolism studies show that these reactive molecules are rapidly and effectively neutralised by molecules such as glutathione. This rapid degradation and neutralisation eliminates captan *in vivo* and confounds the interpretation of *in vitro* studies with captan where concentrations of captan are maintained "artificially" high in systems where the natural detoxification mechanisms are not present.

JMPR noted that the data do not support an *in vivo* mutagenic component: "These studies provide no clear evidence for a reaction between captan or its breakdown products and DNA bases or deoxynucleosides. Furthermore, captan is, at best, an extremely weak genotoxin *in vivo*. Any binding of captan to DNA must be extremely low and would be impossible to measure by currently available methods" (Larsen 1995[7]).
It is concluded that captan does not pose a risk of mutagenicity *in vivo*.

New information added in accordance with reporting table point 2(37).

Bruyntjes JP. 1984. Incidence of tumours in CPB: WU Wistar random rats. Data of control animals from long-term studies. *Rep. V 84.132*, Netherlands

[6] Stournaras C, Saridakis I, Fostinis Y. 1991. Interaction of captan with mammalian microtubules. Cell Biochem Funct. 9: 23-8

[7] Larsen, J.-J. (1995). JMPR Evaluation of Captan (addendum), Institute of Toxicology, National Food Agency of Denmark, Ministry of Health, Soborg, Denmark, available at http://www.inchem.org./documents/jmpr/jmpmono/v95pr03.htm.

Organization for Applied Scientific Research, Division for Nutrition and Food Research TNO, Zeist, Netherlands.

In 1984 (Bruyntjes, 1984[8]) a response was provided to the U.S. EPA for historical control data relating to the previously submitted rat carcinogenicity study (current study - Til, et al., 1983). Based on these data, EPA judged that tumours of the islet cells were not treatment related. The Agency, however, associated uterine sarcomas with treatment[9] pending receipt of additional data confirming the original pathological findings.

The historical data are presented in the full document from Bruyntjes; a selection of relevant background details is presented here, including:

Pancreatic islet cells: adenomas (benign) and adenocarcinomas (malignant) in males.

Incidence in 8 studies:

Study Duration (months)	27	30	30	24	28	30	29[a]	30[b]
Incidence (%)	0	0	2	2	4	4	10	14

[a] 4% were malignant for 29 month study.

[b] 2% were malignant for last 30 month study

Merpan (captan) study	0	125	500	2000 ppm
Incidence (%)	1	2	0	5

Conclusion by US EPA: The high dose male rats had a combined incidence of pancreatic adenoma and adenocarcinoma of 5 out of 50 (10%). Although this is statistically increased over control values, the combined incidence is within the range of historical controls. There was also no evidence of progression toward malignancy from adenoma to adenocarcinoma. It does not appear the Merpan [captan] is associated with an increased incidence of islet cell tumours in the male rat.

Uterus polyp and sarcoma percent incidence in females:

Study Duration (months)	24	27	28	29	30	30	30	30
Fibromatous polyp	11	21	14	30	17	18	26	26
Fibrosarcoma	0	0	0	2	0	0	0	0

6% of the rats had multiple polyps, length 28 months

1-2% of the rats had multiple polyps, length 29, 30 (except last column)

Merpan (captan) study	0	125	500	2000 ppm
No. examined	48	49	50	50
Fibromatous polyp	8	12	13	12
Sarcoma	0	0	0	4

EPA noted: It appears that the ingestion of 2000 ppm of Merpan [captan] is associated with a small increased incidence of uterine sarcomas. The historical control range for the incidence of sarcomas in this laboratory is 0 to 2% as compared to 8% in the high dose treatment group. EPA comment: the company may wish to reread the uterine slides to confirm that sarcoma was the correct diagnosis.

[8] Bruyntjes JP. 1984. *Incidence of tumours in CPB: WU Wistar random rats. Data of control animals from long-term studies. Rep. V 84.132*, Netherlands Organization for Applied Scientific Research, Division for Nutrition and Food Research TNO, Zeist, Netherlands

[9] "…weakly oncogenic for increasing the incidence of uterine sarcomas in the SPG Wistar Cpb:WU strain of rat."

Subsequent to the 1986 data evaluation record cited above (Copley, et al., 1986), EPA has judged that the uterine sarcomas are not related to treatment with captan (US-EPA, 2004[10]).

New information submitted to meet open point 2.17. (See also new reports, Reuber 1989 summarised under Point IIA 5.5.3/01 below, Cabal et al 1991 summarised under Point IIA 5.5.3/02 below, and Hasegawa et al. 1993 summarised under Point IIA 5.5.3/03 below.)

These two studies Cabral et al. (1991) and Hasegawa R. et al. (1993) do not refer to the mode of action of captan in mice and are not reflected in the results of rat bioassays. Mode of action was also investigated by Perocco et al, 1995[11].

Cytotoxic and cell-transforming activities of the three fungicides, captan, captafol and folpet, have been studied in an experimental in vitro model by exposing BALB/c 3T3 cells to the chemicals with or without S-9 mix-induced bioactivation. Cytotoxicity of the three compounds was reduced in the presence of the metabolizing system. Each assayed pesticide displayed cell-transforming ability in the presence of the metabolizing system. The relative efficiency was: captafol > captan > folpet. Cell transformation was considered to be due to carcinogenesis-promoting activity. These data, obtained in a medium-term (6-8 weeks) experimental model, contribute to a better understanding of the action of the three pesticides in the multi-step carcinogenesis process and provide more information concerning the oncogenic risk of these xenobiotic compounds for humans.

The liver preparation S-9 does not "bioactivate" captan. This is a common misperception among researchers. The S-9 liver preparation serves to deactivate captan through the rapid reaction of captan with the available thiol groups of the S-9 enzymes. Since captan degrades nearly instantaneously *in vivo* (IIA 5.1/07 and 5.1/08), cytotoxic or cell-transforming activities measured *in vitro* have little relevance for human risk assessment. Captan is a very reactive molecule; thus, when biological systems are exposed in an artificial setting such as an *in vitro* petri dish, reactions will occur that are not relevant to the intact animal. These reactions are not relevant since there is no exposure in the animal. It does not follow, therefore, that effects seen *in vitro* will be mirrored by effects *in vivo*.

Okubo and coworkers (2004[12]) noted that captan was strongly suspected of being an antiestrogen:

Estrogenic activities of 20 selected pesticides-which are used for agricultural production as insecticides, fungicides and herbicides-were examined by estrogen receptor (ER)-dependent MCF-7 cell proliferation assay. Among them, chlordecone, dicofol, methoxychlor, gamma-HCH, fenarimol, EPN, triadimefon, and triadimenol had estrogenic activities, all of which were suppressed by the addition of pure antiestrogen ICI 182,780. The first 5 compounds exhibited binding capacities to ERalpha. The antiestrogenic activity of a compound was examined by estimating its suppressive effect on cell proliferation induced by 30 pM 17beta-estradiol. Strongly suspected antiestrogens were captan and myclobutanil, both of which were found to have the capacity to bind to ERalpha and which might exert their activities by competing at the level of ERalpha. Antiestrogenic activities of nitrofen, fenitrothion, fenarimol and triadimefon were also suggested. Affinities of the compounds for ERalpha and/or androgen receptor (AR) were lower than those of synthetic estrogen (diethylstilbestrol) and testosterone (mibolerone), respectively. Fenitrothion had the highest affinity to AR. Chlordecone, dicofol, methoxychlor, nitrofen, fenarimol, myclobutanil and pyridate had capacities to bind both ERalpha and AR. Chlordecone and pyridate were much more effective as competitors of estrogen binding to ERalpha than androgen binding to AR and, conversely, nitrofen was a more effective competitor of androgen binding to AR.

[10] Wilkinson CF, Arce G, Gordon EB. 2004. *Analysis of the appropriate cancer classification of captan under EPA's current guidelines. Rep. CTF 0304*, Captan Task Force. MRID 46247701

[11] Perocco P, Colacci A, Del Ciello C, Grilli S. 1995. Transformation of BALB/c 3T3 cells *in vitro* by the fungicides captan, captafol and folpet. *Jpn. J. Cancer Res.* 86: 941-7

[12] Okubo T. 2004. Estimation of estrogenic and antiestrogenic activities of selected pesticides by MCF-7 cell proliferation assay. *Arch Environ Contam Toxicol.* 46: 445-53

The MCF cell proliferation test is inappropriate for captan in that it does not reflect expected *in vivo* conditions. It does not follow that reactions seen *in vitro* with captan predict similar outcomes in vivo. The key factor to consider when evaluating such studies is to integrate the 0.97 second half-life of captan (Gordon, et al., 2001) (IIA 5.1/07) and the 0.6 second half-life of thiophosgene (Dohn and Arndt, 2004) (IIA 5.1/08) into the risk characterisation. When these degradation rates are considered, the predicted *in vivo* effects are not relevant.

The testicular atrophy in rats (Reuber, 1989, see 5.5.3/01 below) was not an accepted finding by EPA (although EPA's reasons for this judgment are not available) and would not be consistent with the MCF assay results, as noted above.

New information provided to meet open point 2.18. (See also report Mills 1998 summarised under Point IIA 5.9.3/02 below, McDuffie et al summarised under Point IIA 5.9.3/03 below)

A published study (Mills, 1998) conducted by the Cancer Registry of Central California, revealed elevated correlation between leukemia and captan in Hispanic males and captan and prostate cancer for black males. Another published study (McDuffie, et al., 2001) revealed statistically significant increased incidence of Non-Hodgkin's lymphoma induced by exposure to captan. An evaluation of the aforementioned studies is presented in Point IIA 5.9.3 below.

These epidemiology studies have suggested captan is associated with human cancer. The study conclusions are judged suspect in light of the well-established mode of action of captan, its rapid degradation in vivo, and the absence of collaborating cancers in populations of workers manufacturing captan (Palshaw, 1980, Palshaw, 1987). It should be concluded that there is insufficient epidemiologic evidence to link captan to human cancer.

Conclusions: Each of the comments made by the Member State Greece is addressed.

Evaluation table number	Reporting table number	Open Point number
-	**2(35)**	**2.17**

Conclusions of the EFSA Evaluation Meeting:
RMS to check the publications mentioned in the comment from GR (e.g.: Reuber MD, 1989; Cabral R et al., 1991; Hasegawa R et al., 1993; Perocco P et al, 1995) regarding the carcenogicity of Captan and to summarize in an addendum.

- **Point IIA, 5.5.3: Summary of long-term toxicity and carcinogenicity studies**

The following new reports are submitted:

5.5.3/01

Report: Reuber, M. (1989). Carcinogenicity of captan. Published in *Journal of Environmental Pathology Toxicology & Oncology* 9: 127-43).

Guidelines: Not applicable. Deviations: Not applicable.

GLP: Not applicable.

Conclusions: Melvin Reuber's conclusion that captan is highly carcinogenic in the rat and mouse (Reuber, 1989) was based on his reread of the microslides held in archival storage; he did not conduct the NCI rat bioassay nor were his findings embraced by EPA. It is noteworthy that his manuscript is not cited by EPA in any of their cancer reviews of captan. This paper is judged not reliable.

5.5.3/02

Report: Cabral et al. (1991). A Rapid *in vivo* Bioassay for the Carcinogenicity of Pesticides. *Tumori* 77: 185-8, published.

Guidelines: Not applicable. Deviations: Not applicable.

GLP: Not applicable.

Materials and Methods:
Eight pesticides were tested in a bioassay based on the induction of preneoplastic lesions in the liver. Rats were given diethylnitrosamine intraperitoneally at 200 mg/kg bw and two weeks later were treated with pesticides for six weeks and then killed; all rats had a partial hepatectomy at week 3. Hepatocarcinogenic potential was assessed by comparing the number and area of glutathione s-transferase (placental form) -positive foci in the liver with those of controls given diethylnitrosamine alone.

Findings:
This is one of two short-term studies (from the same laboratory) that suggest a carcinogenic potential of captan using rats that were first treated with known carcinogens.
Positive results were seen with Chinomethionat, Phosmet and Propiconazole; the results obtained with Captan and Prochloraz were borderline; Benomyl, Daminozide and Folpet gave negative results.

Conclusions: "Our findings provide enough experimental evidence to indicate that great care should be exercised in the use of these compounds."

This experimental design best addresses compounds that exist systemically and can act as promoters. Captan does not reach the target organs initiated by the carcinogens and THPI has been shown not to be carcinogenic in bioassays (as the immediate degradate of captan).

The purpose of these short-term studies is to screen for potential carcinogens. In the case of captan, full-term rodent bioassays have been conducted and the carcinogenic potential has been clearly described. Thus, these screening assays do not contribute meaningful data to our understanding of captan or its mode of action.

5.5.3/03
Report: Hasegawa R. et al. (1993). Carcinogenic Potential of Some Pesticides in a Medium-term Multi-organ Bioassay in Rats. *International Journal of Cancer* 54: 489-93, published.

Guidelines: Not applicable. Deviations: Not applicable.

GLP: Not applicable.

Material and methods: The carcinogenic potential of 5 pesticides was analyzed using a medium-term multi-organ bioassay for carcinogenicity. Male F344 rats were initially treated with 3 known carcinogens (diethylnitrosamine, N-methyl-N-nitrosourea and N-bis(2-hydroxypropyl)nitrosamine) during a period of 4 weeks to induce neoplastic changes in a variety of organs, and then given one of 5 pesticides in the diet for a further 16 weeks.

Findings:
Neoplastic and pre-neoplastic lesions were found in the thyroid, kidney and urinary bladder with propineb, in the forestomach, kidney and thyroid with captan and folpet. The number of glutathione S-transferase placental-form-positive liver-cell foci was significantly increased in the captan- and phosmet-treated groups. Based on these findings, captan and propineb can be considered as carcinogens and carcinogenicity is suspected for folpet and phosmet.

Conclusions: These results are in concordance with reported long-term carcinogenicity for captan, folpet and propineb. Daminozide was considered not to be carcinogenic. Thus, the present assay of 20 weeks' duration is useful for the prediction of potential carcinogens.

This experimental design best addresses compounds that exist systemically and can act as promoters. Captan does not reach the

target organs initiated by the carcinogens and THPI has been shown not to be carcinogenic in bioassays (as the immediate degradate of captan).

The purpose of these short-term studies is to screen for potential carcinogens. In the case of captan, full-term rodent bioassays have been conducted and the carcinogenic potential has been clearly described. Thus, these screening assays do not contribute meaningful data to our understanding of captan or its mode of action.

Evaluation table number	Reporting table number	Open Point number
-	**2(36)**	**2.18**

Conclusions of the EFSA Evaluation Meeting:
RMS to review the study mentioned in the comment from GR (Mills PK, 1998 and MCDuffie HH et al, 2001) regarding medical data.

- **Point IIA, 5.9.3: Observations on exposure of the general population and epidemiological studies if appropriate**

A published study (Mills, 1998) conducted by the Cancer Registry of Central California, revealed elevated correlation between leukemia and captan in Hispanic males and captan and prostate cancer for black males. Another published study (McDuffie, et al., 2001) revealed statistically significant increased incidence of Non-Hodgkin's lymphoma induced by exposure to captan. An evaluation of the aforementioned studies is presented below.

5.9.3/02

Report: Mills PK. (1998). Correlation analysis of pesticide use data and cancer incidence rates in California counties. Arch Environ Health 53: 410-3

Guidelines: Not applicable. Deviations: Not applicable.

GLP: Not applicable

Abstract from paper:
California, the leading agricultural state in the United States, has maintained a population-based cancer registry since 1988, and it also maintains a comprehensive, state-wide pesticide reporting system. Data on cancer incidence and pesticide use reporting are available, by county, for all 58 counties in California. Average annual age-adjusted cancer incidence rates (1988-1992), on a county-, sex-, and race/ethnicity-specific basis, were obtained from the California Cancer Registry (CCR), which maintains the population-based cancer registry throughout California. Pesticide use data (i.e., pounds of active ingredient applied annually in each county) were obtained from the California Department of Pesticide Regulation for 1993. Investigators used Pearson product-moment correlation coefficients (r) to correlate age-adjusted incidence rates for selected cancers with the use data for selected pesticides. For most sex- and race/ethnicity-specific groups, the correlation coefficients were very close to zero or negative in sign, indicating no correlation between pesticide use and cancer incidence. There were, however, several exceptions, particularly in Hispanic males for whom the following correlations were observed: leukemia and atrazine (r=.40), leukemia and 2,4-dichlorophenoxyacetic acid (r=.41), leukemia and captan (r=.46), atrazine and brain cancer (r=.54), and atrazine and testicular cancer (r=.41). For black males, we observed the following: atrazine and prostate cancer (r=.67) and Captan and prostate cancer (r=.49). In females, only a few of the correlations were elevated. Although most of the correlations examined in this analysis were not elevated, several of those in the Hispanic and black male populations were. These segments of the population have traditionally been employed as farm workers in California and have had the greatest potential for exposure to pesticides. This was an ecological study for which no data about exposure to pesticides at the individual level were available for analysis. In addition, no latency period was allowed between potential exposure and diagnosis with cancer. However, the results obtained in two minority groups

who represented the majority of farm workers in the fields suggested that additional research studies, in which more rigorous study designs are used, should be conducted in those groups.

Conclusions: The Cancer Registry notes a positive correlation of captan and leukemia in Hispanic males and captan and prostate cancer for black males but points out that exposure data were lacking and suggests that more rigorous study designs are used within the exposure groups to further determine any possible correlation.

5.9.3/03

Report: McDuffie H, Pahwa P, McLaughlin J, Spinelli J, F Incham S, et al. (2001). Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev.* 10: 1155-63

Guidelines: Not applicable. Deviations: Not applicable.

GLP: Not applicable

Abstract from paper:

Our objective in the study was to investigate the putative associations of specific pesticides with non-Hodgkin's Lymphoma [NHL; International Classification of Diseases, version 9 (ICD-9) 200, 202]. We conducted a Canadian multicenter population-based incident, case (n = 517)-control (n = 1506) study among men in a diversity of occupations using an initial postal questionnaire followed by a telephone interview for those reporting pesticide exposure of 10 h/year or more, and a 15% random sample of the remainder. Adjusted odds ratios (ORs) were computed using conditional logistic regression stratified by the matching variables of age and province of residence, and subsequently adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization treatment, and a positive history of cancer in first-degree relatives). We found that among major chemical classes of herbicides, the risk of NHL was statistically significantly increased by exposure to phenoxyherbicides [OR, 1.38; 95% confidence interval (CI), 1.06-1.81] and to dicamba (OR, 1.88; 95% CI, 1.32-2.68). Exposure to carbamate (OR, 1.92; 95% CI, 1.22-3.04) and to organophosphorus insecticides (OR, 1.73; 95% CI, 1.27-2.36), amide fungicides, and the fumigant carbon tetrachloride (OR, 2.42; 95% CI, 1.19-5.14) statistically significantly increased risk. Among individual compounds, in multivariate analyses, the risk of NHL was statistically significantly increased by exposure to the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D; OR, 1.32; 95% CI, 1.01-1.73), mecoprop (OR, 2.33; 95% CI, 1.58-3.44), and dicamba (OR, 1.68; 95% CI, 1.00-2.81); to the insecticides malathion (OR, 1.83; 95% CI, 1.31-2.55), 1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane (DDT), carbaryl (OR, 2.11; 95% CI, 1.21-3.69), aldrin, and lindane; and to the fungicides captan and sulfur compounds. In additional multivariate models, which included exposure to other major chemical classes or individual pesticides, personal antecedent cancer, a history of cancer among first-degree relatives, and exposure to mixtures containing dicamba (OR, 1.96; 95% CI, 1.40-2.75) or to mecoprop (OR, 2.22; 95% CI, 1.49-3.29) and to aldrin (OR, 3.42; 95% CI, 1.18-9.95) were significant independent predictors of an increased risk for NHL, whereas a personal history of measles and of allergy desensitization treatments lowered the risk. We concluded that NHL was associated with specific pesticides after adjustment for other independent predictors.

Conclusions: We concluded that NHL was associated with specific pesticides after adjustment for other independent predictors.

These epidemiology studies have suggested captan is associated with human cancer. The study conclusions are judged suspect in light of the well-established mode of action of captan, its rapid degradation in vivo, and the absence of collaborating cancers in populations of workers manufacturing captan (Palshaw, 1980, Palshaw, 1987). It should be concluded that there is insufficient epidemiologic evidence to link captan to human cancer.

Evaluation table number	Reporting table number	Open Point number
-	**2(3)**	**2.2**
Conclusions of the EFSA Evaluation Meeting: ***The setting of ARfD to be discussed at an expert meeting.***		
2.1	**2(3)**	**-**
Conclusions of the EFSA Evaluation Meeting: ***Notifier to submit the position paper Gordon and Kinzell (2004) and the study Moore and Creasey (2004).***		

- **Point IIA, 5.10: Summary of mammalian toxicity and overall evaluation**

The following new report is submitted:

5.10/01

Report: Gordon, E. and Kinzell, J. (2004). Captan. A summary basis for why an acute reference dose (aRfD) is not needed. Submitted to the JMPR for the 2004 toxicological evaluation of captan. Makhteshim-Agan and Arvesta, unpublished report R-17080.

Guidelines: Not applicable.

GLP: No.

Material and methods: An ARfD of 0.1 mg/kg bw is proposed in the DAR. Full and detailed comments on all aspects of the ARfD for captan are presented in a position paper.

Findings:

The position paper concludes:
1) There is minimal irritation seen in the gastrointestinal tract after one day exposures to captan at doses above 500 mg/kg.
2) Gastrointestinal irritation following repeated captan oral exposure is rapidly reversed upon cessation of treatment.
3) Captan is not present in the systemic circulation and is not a systemic toxin.
4) Captan will not induce adverse effects when residues are ingested continuously, even at the theoretical maximum residue values.
5) Captan's oral toxicity is greater than 5 g/kg.

This position paper is supported by a new previously unsubmitted acute intestinal irritation study (see Point IIA 5.8.2/06).

Conclusions: Based on an evaluation of the toxicology database for captan, an ARfD for captan is not required.

- **Point IIA, 5.8.2: Supplementary studies on the active substance**

The following new report is submitted:

5.8.2/06

Report: Moore, G.E. and Creasey, D. (2004). Intestinal irritation in CD-1 mice after a 24-hour exposure to folpet. [redacted] unpublished report number 13763 (Company file: R-16283).

Guidelines: In-house.
Deviations: Not applicable.

GLP: Yes (Study 1). Study 2 was not performed under GLP procedures but was performed under the same study director in a GLP compliant laboratory.

Material and methods: Test substance: folpet (a fungicide that shares a common mechanism of toxicity with captan), batch number 8133181, purity 96.9%. Two studies were conducted. These were initially designed as pilot studies but, as the data were unambiguous with regard to minimal irritation, they were integrated into a final report. In the first study the test substance was administered to groups of 3 female ICR (CD-1 equivalent) mice as an 18% w/w suspension in a 1% w/w solution of CMC in distilled water by oral gavage at 900 mg/kg/bw (followed by untreated diet) or in the diet at 200 or 5000 ppm over a 24-hour period; a fourth group of 3 animals received untreated diet only. Animals were terminated after 24 hours.

In the second study, the test substance was administered to groups of 15 female ICR (CD-1 equivalent) mice as an 18% w/w suspension in a 1% w/w solution of CMC by oral gavage at 900 mg/kg/bw (followed by untreated diet) or in the diet at 50, 200, 500 or 5000 ppm over a 24-hour period; a control group of 5 animals received untreated diet only. Animals were exposed to the treated diet for 24 hours (Day 1). The 5000 ppm dietary dose was equivalent to approximately 1000 mg/kg bw/day. In treated groups, five animals in each group were killed after 1 day, 3 days and 7 days, respectively. Of the five control animals, three were killed at 24 hours and one each at 3 and 7 days. Animals intended for sacrifice at 3 and 7 days were given control diet after the 24-hour exposure to test diets. These animals were designated recovery animals and were not evaluated histologically, as irritation was absent at Day 1.

Test concentrations in the suspension and diet were measured by HPLC. All animals were observed for mortality, signs of gross toxicity and behavioural changes. Food consumption was recorded during the first 24 hours (Day 1). Body weights were determined prior to administration (Study 1 and 2) and on Days 3 and 7 for animals on Study 2 maintained through Day 7.

At termination, mice in the first study were first injected with 2 mL/kg of 1% w/v Evans Blue Dye approximately 15 minutes before euthanasia with CO_2. This was done in an attempt to visualize areas of mucosal irritation. Following euthanasia, the stomach, and small intestine of each animal were removed and examined macroscopically using a binocular microscope. The number and size of lesions in the small and large intestines was recorded (large = > 2mm diameter, small = 1-2 mm diameter, punctiform = < 1 mm). For each tissue the severity of mucosal damage was estimated on a 0 to 5 scale, where 0 = no lesions, 1 = up to 5 punctiform lesions, 2 = more than 5 punctiform lesions, 3 = 1 to 5 small lesions, 4 = more than 5 small lesions or 1 large lesion and 5 = more than one large lesion. Lesions and samples taken from

the forestomach, fundic and pyloric glandular mucosa, pyloric duodenum and distal duodenum were processed and examined histologically.

Mice from the second study were not injected with Evans Blue Dye, as this procedure proved to be of little value. Following euthanasia, the stomach with the duodenum attached were removed intact, food contents flushed from the stomach after the forestomach was cut along the greater curvature. Ten percent neutral buffered formalin was injected into the open end of the duodenum so that it flowed into the stomach. This procedure was instituted to reduce artefacts caused by mechanical manipulation (including the pinning out of the longitudinally cut duodenum on a board for the macroscopic evaluation) in the first study. Samples were taken from the glandular fundic mucosa, non-glandular forestomach, and proximal (pyloric) duodenum and examined histologically from all mice. Additional samples (eight step serial sections) from mice dosed orally at 900 mg/kg/bw and at 5000 ppm in the diet were examined microscopically for evidence of irritation. This was done to confirm the absence of irritation seen in the initial sections.

Findings:

The first study showed some indications of apparent irritation (Table 5.8.2-1), but these findings were absent in the expanded second study. Extensive examination of multiple sections (eight step-serial sections) from the second study showed no irritation in the duodenum and only two instances of focal erosion in the stomach in mice administered a bolus gavage dose of folpet (Table 5.8.2-2).

While a definitive cause for the findings noted in the first study was not identified, mechanical manipulation of the tissues during necropsy and macroscopic evaluation (longitudinal cutting and pinning of the duodenums) may have contributed to the apparent irritation.

Food consumption data were used to calculate the intake of folpet. Individual body weights were used to calculate the mg/kg bw/day dose for those mice receiving folpet admixed in the diet. The mean dose (of three animals) in Study 1 was 31 and 845 mg/kg/day for the 200 and 5000 ppm groups, respectively. The actual dose for the 900 mg/kg group was 1430 mg/kg.

In the second study, the mean dose (of five animals) was 10, 44, 123, and 1060 mg/kg/day for the 50, 200, 500 and 5000 ppm groups, respectively. The actual dose for the 900 mg/kg group was 815 mg/kg.

In the first study, mice treated with folpet at 900 mg/kg/bw by gavage or 5000 ppm in the diet showed apparent changes in the proximal region of the duodenum, close to the junction with the pyloric sphincter, and also in the stomach. These initial findings included minimal to moderate focal areas of epithelial loss (erosions) or degeneration/regeneration of the epithelium characterised by basophilia and reduced cell height. Loss of villous structure was associated with the more severe lesions and congestion of the mucosal vasculature was also seen, with mucosal damage in all animals treated with folpet at 900 mg/kg/bw by gavage or 5000 ppm in the diet. Similar findings in the fundic mucosa of the glandular stomach were also seen in two of the three mice receiving the 900 mg/kg/bw dose. There were no microscopic findings in the distal duodenum. Findings in the 200 ppm treated group were equivocal or of negligible significance.

In the expanded second study, there were no gross abnormalities and there were no degenerative changes in the duodenum. The instances of erosion in the fundic stomach of two mice administered 900 mg/kg were judged “minimal.”

In summary, these data show that a 24-hour exposure to folpet at 5000 ppm, equivalent to approximately 1000 mg/kg bw/day, does not cause irritation to the duodenum or stomach (although a bolus dose of folpet at 900 mg/kg did cause minimal erosion in the stomachs of two of five mice). The data from the first study, however, indicated some irritation might be occurring (although possibly artifactual) and thus the conclusion was drawn that folpet at 5000 ppm causes minimal ("borderline") irritation in the duodenum of the mouse.

The duodenum is the site of tumor formation upon long-term dietary levels of 5000 ppm and has shown marked irritation after repetitive days dosing with a diet containing 5000 ppm folpet. This study shows that repetitive dosing is required for irritation in contrast to a single 24-hour period of dosing.

A single exposure of folpet at 5000 ppm over a 24-hour period (equivalent to approximately 1000 mg/kg bw/day) produces only minimal ("borderline") irritation to the mouse duodenal mucosa.

Table 5.8.2-1: Macroscopic and microscopic findings in the stomach and duodenum of mice treated with folpet (Study 1)

Finding*	Dose level			
	0	200 ppm/diet	5000 ppm/diet	900 mg/kg/bw by gavage
Number of large (> 2mm) lesions in stomach (individual scores)**	0/3	1/3 (1)	0/3	1/3 (2)
Number of large (> 2mm) lesions in proximal duodenum/pylorus (individual scores)	1/3 (1)	1/3 (1)	1/3 (1)	3/3 (1, 1, 1)
Erosion/epithelial degeneration of stomach (individual scores)	0/3	0/3	0/3	3/3 (2)
Mucosal congestion of stomach (individual scores)	0/3	0/3	0/3	2/3 (1,2)
Erosion/epithelial degeneration of proximal duodenum (individual scores)	0/3	1/3 (1)	3/3 (1, 2, 3)	3/3 (2, 3, 3)
Loss of villi in proximal duodenum (individual scores)	0/3	0/3	1/3 (3)	3/3 (1, 3, 3)
Mucosal congestion of proximal duodenum	0/3	1/3 (1)	1/3 (2)	2/3 (1, 1)
Effects on distal duodenum	0/3	0/3	0/3	0/3

* Determined in a total of 3 animals

** 1 = minimal, 2 = slight, 3 = moderate

Table 5.8.2-2: Macroscopic and microscopic findings in the stomach and duodenum of mice treated with folpet (Study 2)

Finding*	Dose level					
	0	50 ppm	200 ppm	500 ppm	5000 ppm	900 mg/kg
Macroscopic	0/5	0/5	0/5	0/5	0/5	0/5
Stomach, focal erosion (individual scores)**	0/3	0/5	0/5	0/5	0/5	2/5 (1, 1)
Proximal duodenum abnormalities	0/3	0/5	0/5	0/5	0/5	0/5

* Determined in a total of 5 animals (three controls were examined microscopically). Microscopic evaluation included eight step serial sections of the duodenum for mice administered 5000 ppm or 900 mg/kg.
**1= minimal

Conclusions:

Folpet, a fungicide that shares a common mechanism of toxicity with captan, administered by oral gavage at 900 mg/kg/bw or in the diet for 24 hours at 5000 ppm (as well as 500 ppm, 200 ppm, and 50 ppm) caused only minimal ("borderline") irritation of the proximal duodenum. The initial finding of apparent irritation in the first study was shown likely due to artefacts upon thorough (eight step serial section) examination of the expanded second study.

It was concluded that folpet was borderline for producing irritancy at 5000 ppm.

The common mechanism of toxicity for captan and folpet legitimize these data for the evaluation of captan.

Evaluation table number	Reporting table number	Open Point number
-	**2(6)**	**2.4**
Conclusions of the EFSA Evaluation Meeting: ***The dermal absorption value should be discussed at an expert meeting.***		

- **Point IIIA, 7.3: Dermal absorption**

The following response is provided to comments received from Member States on the dermal absorption studies with captan summarised in the DAR:

The 8-hour captan 50WP study is but one component of the weight of evidence determination of the captan skin penetration. These data show a maximum of 10% absorption, which appears to be a conservative estimate. Integrating these data with the *in vitro* studies gives an estimate of 3% dermal penetration.

The cited 8-hour captan 50WP *in vivo* study is not as extensively flawed as the NL comments indicate. The levels of absorbed radioactivity did not increase between 4 and 8 hours after dosing, indicating that penetration had reached a plateau, and that the skin was not a reservoir for captan to pass into the bloodstream in the 8-24 hour period i.e. after washoff. Recovery figures are quoted in the range 93.0% to 101.0% of applied radioactivity. While there is no mention of the exact area of treated skin, the values for absorption are not based on radioactivity per unit area, but are expressed as percentage penetration of applied radioactivity, independent of area. The two dose levels were an order of magnitude apart (0.5 mg/rat and 5.0 mg/rat), yet the similarity in the average values for percentage dermal penetration of radioactivity (6.4% and 9.0% of each dose level applied) indicate that the process was approximately linear and was not saturated; thus the precise area of skin treated did not affect the degree of penetration, and measurement of area treated in not important to the result obtained.

The higher dose level of 5 mg/rat was calculated to represent twice the estimated exposure of a worker mixing and loading the formulation at an orchard site, based on a human exposure study. As such, the value of 10% in the rat is considered conservative. In addition, comparison of rat and human *in vitro* data shows that the rat is a poor model for dermal penetration of captan in the human, with the technical material showing a 100:1 ratio in dermal penetration between rat and human. As such, repeating an *in vivo* study would not improve the available data in terms of assessing the dermal penetration in humans: any advantage in obtaining an arguably more accurate value for rats would be outweighed by the margin of error in estimating the species differences between rats and humans: to repeat the rat *in vivo* study simply to refine the data already obtained would be an needless repetition of experiments on vertebrate animals, and contrary to EU Directive 86/609/EEC of 24 November 1986 .

The ratio between rat and human skin *in vitro* varies from 100-fold for the technical material to ten, five and three times for varying concentrations of spray dilutions. The conventional logic in combining rat *in vivo* data and rat:human *in vitro* data is to divide the *in vivo* by the *in vitro* ratio to estimate human *in vivo* absorption (SANCO 222/2002 rev.6 of 27 November 2002). In taking a rat:human ratio of three, the Notifier has taken the smallest value from the available *in vitro* data, and taken the largest average value from the *in vivo* data. In being deliberately conservative, the Notifier has selected the worst-case data to accommodate any potential inherent inaccuracies in the experimental systems; the proposed estimate of 3% is almost certainly in excess of the real value, and can be considered protective.

Evaluation table number	Reporting table number	Open Point number
2.2	**2(11)**	**-**
Conclusions of the EFSA Evaluation Meeting: ***Notifier to submit new toxicokinetic study.***		
-	**2(11)**	**2.6**
Conclusions of the EFSA Evaluation Meeting: ***The RMS to provide a summary of the new toxicokinetic study in the addendum to be discussed in an expert meeting.***		

- **Point IIA, 5.1: Studies on absorption, distribution, excretion and metabolism in animals**

The following new report is submitted:

5.1/08

Report: Arndt, T. and Dohn, D. (2004). Measurement of the half-life of thiophosgene in human blood. PTRL West, Inc., unpublished report number 1146W (Company file: R-17121)

Guidelines: In-house.
Deviations: Not applicable.

GLP: Yes.

Material and methods: Test substance: thiophosgene, batch number 22123BO, purity 99.4%. Thiophosgene is an important degradate of captan. Data indicate that thiophosgene is produced if folpet or its analogue captan is present in the blood. Thiophosgene itself reacts rapidly with blood nucleophiles, but the reaction is quenched with phosphoric acid in acetone. A method of detecting thiophosgene in the blood was developed. Thiophosgene reacts with cysteine to produce 2-thioxo-4-thiazolidinecarboxylic acid (TTCA), which is capable of detection with UV light and quantification by HPLC. Human blood was collected under heparin from a single male volunteer, stored overnight at 10^{o}C and brought back to 37^{o}C before use. The experimental method involved adding 10 µL of 10 mg/mL thiophosgene to duplicate 1 mL samples of human whole blood at 37^{o}C, incubating for various times, quenching the reaction with chilled 1.5% phosphoric acid in acetone, and then adding cysteine buffer to produce TTCA, which was then quantified using HPLC. Thiophosgene was added to blood and allowed to react for <3, 3, 7.5, 15 and 30 seconds (kinetic samples). Positive and negative control samples were also prepared. The negative controls were blood samples that were not fortified with thiophosgene. Positive controls were blood samples that were quenched and chilled (to prevent thiophosgene reaction with blood nucleophiles) before addition of thiophosgene, such that the thiophosgene was fully able to react with the cysteine without competition from the blood nucleophiles. Positive control samples were prepared with 10, 30 or 100 µL of 10 mg/mL thiophosgene added to the quenched, chilled blood.

Findings:

The positive controls showed an average recovery of 42% ± 8.6% SD (n = 6 from the three duplicate positive control samples at 10, 30 and 100 µL) calculated from the mass of thiophosgene added to quenched chilled blood samples and the mass of thiophosgene

detected, calculated as thiophosgene equivalents from a TTCA standard curve. The recovery was very consistent; all kinetics sample values were corrected for 42% recovery. An exponential decline equation of the form $y = a + b*\exp^{(-kt)}$ was generated by plotting the reaction time (in seconds) versus normalised thiophosgene recovery data from <3 to 7.5 second timepoints. The half life was determined by inserting 50% as y and solving for t: where t = {Ln[50-a) ÷ -k.

No TTCA was detected in the negative control samples.

Thiophosgene rapidly disappeared from the whole blood samples. Samples from > 7.5 seconds showed a low, consistent, residual level of TTCA. This was considered to be the result of saturation of the active sites in the blood that react with thiophosgene. The sample recovery data were normalised for this residual level by subtracting the average corrected recovery from the 15 and 30 second samples from each of the corrected recovery kinetics samples. The resulting normalised % thiophosgene recovery data were fitted to the equation and a half-life of 0.6 seconds was derived.

Table 5.1-1: Kinetics sample summary

Kinetics Sample Identification	Actual Reaction Time (s)	Mass Thiophosgene Added (µg)	Mass Thiophosgene Detected (µg)	Corrected % Recovery[1]	Normalised % Recovery[2]
30 second rep.1	31.1	100	0.38	0.9	-0.2
30 second rep.2	30.7	100	0.46	1.1	0.1
15 second rep.1	16.3	100	0.40	1.0	0.0
15 second rep.2	15.8	100	0.50	1.2	0.2
7.5 second rep.1	7.3	100	0.54	1.2	0.2
7.5 second rep.2	7.3	100	0.51	1.2	0.2
3 second rep.1	4.4	100	0.74	1.7	0.7
3 second rep.2	3.7	100	2.55	6.2	5.2
<3 second rep.1	1.9	100	4.08	9.8	8.8
<3 second rep.2	2.4	100	5.58	13.3	12.3

[1] Corrected % Recovery = recovery based on TTCA standard curve divided by the average recovery value (42%) of positive control samples from initial blood test analysis

[2] Normalised % Recovery = Corrected % Recovery – average corrected recovery value (1.05%) of 15 and 30 second (nominal) samples.

Conclusions: Thiophosgene disappears rapidly when added in excess (100 µg/mL) to human whole blood *in vitro.* The half-life was calculated to be 0.6 seconds.
This study demonstrates why neither captan (with the DT_{50} of 0.97 sec. in human blood) nor thiophosgene are likely to reach sensitive target distant to the mucosal surface of the gastrointestinal tract and as part of the mechanism data it further supports the captan mode of action.

Evaluation table number	Reporting table number	Open Point number
-	**2(13)**	**2.7**

Conclusions of the EFSA Evaluation Meeting:
The need of performing a 90-day oral study in rat should be discussed at an expert meeting.

- **Point IIA, 5.3.2: Oral 90 day study**

The notifier contends that the requested waiver for the 90-day rat study should be granted for the following reasons:

1. The mode of action (MOA) for captan for toxicity is well established. This MOA is based on the rapid chemical reaction of captan and thiophosgene with thiol (-SH) groups.

2. The basis for the waiver as set forth in the DAR is believed adequate:

a. Given the well established captan MOA, it is unlikely that transitory changes in clinical chemistry or hematology, seen at 90 days in the two year study would lower the NOEL already established by the rat two year study, should a new 90-day study be initiated.

b. The collective data in mice, rats and dogs have not identified an organ, other than the gastrointestinal tract, that captan targets. It is unlikely that a 90-day study in rats will identify a new target or adverse effect that has not already been evaluated.

3. A 90-day oral rat is not likely to affect the endpoints or NOELs used for risk assessments. The mode of action for captan is constant over time and does not change with enzyme induction or other changes as test animals age.

The RMS also feels these reasons substantiate the 90-day rat waiver.

Evaluation table number	Reporting table number	Open Point number
-	**2(14)**	**2.8**

Conclusions of the EFSA Evaluation Meeting:
The setting of the NOAEL(C) in the 90-day inhalatory study should be discussed at an expert meeting.

- **Point IIA, 5.3.3: Other routes (90 day inhalation study)**

The notifier contends that the NOEL in the 90-day inhalation study in rat is 0.60 µg/L. This is supported by the following:

The primary action of captan is irritancy caused by its reaction with thiol (-SH) groups of tissues. The study director points out that irritant changes in the conducting pathways were an expected outcome to repeated captan exposure.

In the preliminary 3-week study, this sensitivity to particulate irritants was also mentioned. The study director notes:

> "The treatment related histopathological findings are consistent with captan having a direct irritant effect on the tissues where deposition occurs. Thus in the upper respiratory tract the nasal cavity and larynx, which are particularly sensitive to irritants, showed changes characteristic of those resulting from exposure to particulate irritants."

NL notes that references are not provided to support the statement that the rat larynx is extremely sensitive to particulate irritants. Page 32 of the 90-day report notes:

> "This apparent extreme sensitivity of the rat larynx to irritant particulates is considered to arise from anatomical, airflow, epithelial cell type and possible clearance rates (Klonne et al., 1988; Lewis, 1981; Walker et al., 1980)."

Reference citations are:

Klonne, DR, Garman, RH, Snellings, WM, Dodd, DE and Ballantyne, B. 1988. The larynx as a potential target organ in aerosol inhalation studies on rats. Abstract from 'Toxicologic Pathology of the Upper Respiratory System', a symposium organized by the National Toxicology Programme/National Institute of Environmental Health Sciences, Durham, NC.

Lewis, DJ, 1981. Factors affecting the distribution of tobacco smoke-induced lesions in the rodent larynx. Toxicol Letts 9:189-194.

Walker, D, Wilton, LV and Binns, R, 1978. Inhalation toxicity studied on cigarette smoke (VII) 6-week comparative experiments using modified flue-cured cigarettes: Histopathology of the conducting airways. Toxicology, 10, 241-259.

These references support the statement that the larynx is sensitive to particulate irritants.

It is clear that the irritant effects on the respiratory passages are local effects caused by captan deposition. The NOEC for toxicological effects, 0.60 µg/L is supported.

This conclusion is also supported by the RMS.

Evaluation table number	Reporting table number	Open Point number
-	**2(17)**	**2.9**
Conclusions of the EFSA Evaluation Meeting: ***MS to discuss the highest relevant NOAEL in the reproductive toxicity studies at an expert meeting.***		
2.3	**2(17)**	**-**
Conclusions of the EFSA Evaluation Meeting: ***Notifier to submit the position paper "Comments on captan Monograph Volume III" for RMS to provide a summary in an addendum.***		

- **Point IIA, 5.6.2: Developmental toxicity studies**

The following new report is submitted:

5.6.2.1/04 and 5.6.2.2/02

Report: Neal, B. (2004). Comments on captan monograph: section B 6.6 Reproductive toxicity. The Weinberg Group Inc, unpublished report 21 September 2004.

Guidelines: Not applicable.

GLP: No.

Material and methods:
The existing data on reproduction toxicity and developmental toxicity were reviewed following comments in the Captan DAR by the RMS that that new teratogenic studies in rat and rabbit were required with histopathological examination of the gastro-intestinal tract of the mothers.

Findings:

The findings are summarised as follows:

Reproductive toxicity studies
The NOAEL for pup body weight in the 3-generation reproductive toxicity study and one-generation reproductive toxicity studies is revised to 25 mg/kg bw/day, supported by evaluation of the study methodology for data collection and analyses, and the lack of effects in the one-generation study at that dose level. This dose level is equivalent to the parental NOEL, demonstrating a lack of unique susceptibility of the young to captan toxicity. Using 12.5 mg/kg bw/day as the NOEL for pup toxicity (and the basis for the captan ADI) provides a very conservative additional margin of safety for risk extrapolation.

Developmental toxicity studies
We concur with the RMS reviewer that the axial abnormalities observed at maternally toxic dose levels in several captan developmental toxicity studies may be related to the maternotoxic effect elicited by captan on the gastrointestinal tract. In addition to the noted irritant action of captan on the gastrointestinal mucosae, high bolus gavage doses of captan are likely to adversely affect the intestinal flora, leading to nutrient malabsorption or deficiencies.

The data from the rabbit studies support a developmental NOAEL of 30 mg/kg bw/day for the Tinston study and a developmental NOEL of 60 mg/kg bw/day for the Palmer et al. study, respectively. A weight-of-the evidence evaluation of the rabbit developmental toxicity studies concludes the malformations seen in the Tinston rabbit study are not related to treatment with captan, based on the nature of the findings in the Tinston study and the absence of treatment-related malformations in either the Rubin or Palmer *et al* studies. Further, distribution of captan to the foetus is considered unlikely because of the very short half-life of captan in aqueous media, and the primary metabolite THPI produced no malformations in a limited supplementary teratogenicity evaluation in rabbits.

Conclusions: The existing database provides adequate information regarding the reproductive and developmental toxicity of captan to permit informed and conservative risk assessment. There is no evidence that there is any unique developmental susceptibility of the developing young to captan. Further reproductive or developmental toxicity testing of captan should not be required.

Evaluation table number	Reporting table number	Open Point number
-	**2(30)**	**2.14**

Conclusions of the EFSA Evaluation Meeting:
The RMS to provide clarifications of the measurements of worker exposure in an addendum.The worker exposure should be discussed at an expert meeting.

- **Point IIIA, 7.2.3.3: Overall assessment of worker exposure**

The values in Table B.6.14.3.2.3 in the DAR are derived by multiplying the values measured on the patches by body surface areas. The totals are derived from the addition of exposure of uncovered body parts (face, back of neck, chest 'v' and hands) plus covered body parts (head, trunk, arms, legs and feet).

Harvest workers may wear clothing which leaves the arms and legs uncovered and, in such situations, a risk assessment assuming a complete layer of clothing may not be appropriate. Therefore, exposure has been recalculated from the values in the original report for unprotected arms and legs. The calculations are given in the Excel Spreadsheet below.

To assess risk to harvesters, the exposure measured in the exposure study is compared with the proposed AOEL for captan of 0.1 mg/kg bw/day assuming harvesters have uncovered arms and legs. A summary of the measured exposure values together with the proportion of the AOEL accounted for at each harvest date is given in Table 7.2.3.3-1.

Table 7.2.3.3-1 Harvester exposure to captan and the proportion of the AOEL accounted for

Days after application	Measured exposure (mg/kg bw/day)[1]		Systemic exposure[2] (mg/kg bw/day)	% of AOEL
	Dermal	Inhalation		
1	2.263	0.008	0.076	76
3	1.783	0.012	0.065	65
7	1.367	0.007	0.048	48
14	0.913	0.009	0.036	36

[1] Exposure recalculated from data in original report for unprotected arms and legs based on measured values for forearms and thighs without protection factor given by clothing. Assumes a body weight of 60 kg.
[2] Assumes 3% dermal exposure and 100% inhalation exposure is absorbed.

In a study, exposure to harvesters picking apples treated with captan at 3.36 kg/ha (i.e. 1.3 times the maximum GAP rate of 2.5 kg captan/ha for tree fruit) for eight hours in a day without protective gloves did not exceed 76% of the AOEL. With a harvest interval of 7 and 14 days exposure was only 48% and 36%, respectively, of the AOEL. Thus, the exposure measured in the study was lower than estimated by the German model. The study was conducted with a WP formulation but residues on treated crops have been shown to be similar with different formulations. Therefore, exposure during harvesting crops treated with a WG formulation will be similar to that from harvesting crops treated with a WP formulation. Exposure to captan for workers harvesting tomatoes or pruning and thinning any crop treated with captan is expected to be lower than for workers harvesting tree fruit.

In conclusion, the risk to all workers involved with the handling of crops treated with 'Merpan' 80 WDG/'Malvin' WDG in the absence of protective clothing is considered to be low. It is not necessary to set additional re-entry periods longer than the PHI for workers after the spray has dried or for workers to wear gloves when handling treated crops.

Calculations are given in Excel spread sheets below

Original worked example	Uncovered		
Dermal exposure in ug	180	25	4500
	82	4.2	344.4
	180	5.8	1044
			5888.4
			5593.98
	4400	5300	9700
			12125
			17718.98
	Covered		
	610	4	2440
	872	47	40984
	610	35	21350
	1990	23	45770
	1070	86	92020
	1070	42	44940
	1070	25	26750
			274254
			104216.5
			99005.69
	Total		116724.7

Dermal Exposure in ug. Modified calculations based on worked example in Attachment 3 of original report.

		area ratio				area ratio	
Rep 1, 1	Uncovered	skin/pad	total	Rep 1, 2	Uncovered	skin/pad	total
face	180	25	4500		270	25	6750
back of neck	82	4.2	344.4		120	4.2	504
forearms	1990	23	45770		650	23	14950
legs	1070	42	44940		850	42	35700
front of neck	180	5.8	1044		270	5.8	1566
total			96598.4				59470
total x recovery			91768.48				56496.5
hands	4400	5300	9700		9500	8200	17700
hands x 1.25			12125				22125
total uncovered			103893.5				78621.5
	Covered				Covered		
head	610	4	2440		670	4	2680
trunk	872	47	40984		1060	47	49820
upper arms	610	35	21350		670	35	23450
			0				0
thighs	1070	86	92020		850	86	73100
			0				0
feet	1070	25	26750		850	25	21250
subtotal			183544				170300
subtotal x 0.38			69746.72				64714
total x 0.95			66259.38				61478.3
covered plus uncovered	Total		170152.9		Total		140099.8

Rep 1, 3		area ratio skin/pad	total
	Uncovered		
	340	25	8500
	120	4.2	504
	2210	23	50830
	740	42	31080
	340	5.8	1972
			92886
			88241.7
	5100	4800	9900
			12375
			100616.7
	Covered		
	600	4	2400
	1060	47	49820
	600	35	21000
			0
	740	86	63640
			0
	740	25	18500
			155360
			59036.8
			56084.96
	Total		156701.7

Rep 1, 4		area ratio skin/pad	total
	Uncovered		
	110	25	2750
	57	4.2	239.4
	740	23	17020
	910	42	38220
	110	5.8	638
			58867.4
			55924.03
	5000	5800	10800
			13500
			69424.03
	Covered		
	370	4	1480
	537	47	25239
	370	35	12950
			0
	910	86	78260
			0
	910	25	22750
			140679
			53458.02
			50785.12
	Total		120209.1

Rep 1, 5		area ratio skin/pad	total
	Uncovered		
	63	25	1575
	75	4.2	315
	910	23	20930
	490	42	20580
	63	5.8	365.4
			43765.4
			41577.13
	5700	4700	10400
			13000
			54577.13
	Covered		
	510	4	2040
	648	47	30456
	510	35	17850
			0
	490	86	42140
			0
	490	25	12250
			104736
			39799.68
			37809.7
	Total		92386.83

Rep 2, 1			
	Uncovered		
	65	25	1625
	34	4.2	142.8
	840	23	19320
	1010	42	42420
	65	5.8	377
			63884.8
			60690.56
	7700	6000	13700
			17125
			77815.56
	Covered		
	440	4	1760
	539	47	25333
	440	35	15400
			0
	1010	86	86860
			0
	1010	25	25250
			154603
			58749.14
			55811.68
	Total		133627.2

Rep 2, 2			
	Uncovered		
	110	25	2750
	110	4.2	462
	950	23	21850
	590	42	24780
	110	5.8	638
			50480
			47956
	13000	12000	25000
			31250
			79206
	Covered		
	910	4	3640
	1130	47	53110
	910	35	31850
			0
	590	86	50740
			0
	590	25	14750
			154090
			58554.2
			55626.49
	Total		134832.5

Rep 2, 3	Uncovered		
	280	25	7000
	88	4.2	369.6
	730	23	16790
	400	42	16800
	280	5.8	1624
			42583.6
			40454.42
	7000	6800	13800
			17250
			57704.42
	Covered		
	556	4	2224
	924	47	43428
	556	35	19460
			0
	400	86	34400
			0
	400	25	10000
			109512
			41614.56
			39533.83
	Total		97238.25

Rep 2, 4	Uncovered		
	95	25	2375
	89	4.2	373.8
	460	23	10580
	450	42	18900
	95	5.8	551
			32779.8
			31140.81
	11000	11000	22000
			27500
			58640.81
	Covered		
	330	4	1320
	514	47	24158
	330	35	11550
			0
	450	86	38700
			0
	450	25	11250
			86978
			33051.64
			31399.06
	Total		90039.87

Rep 2, 5	Uncovered		
	38	25	950
	35	4.2	147
	470	23	10810
	510	42	21420
	38	5.8	220.4
			33547.4
			31870.03
	6500	6700	13200
			16500
			48370.03
	Covered		
	290	4	1160
	363	47	17061
	290	35	10150
			0
	510	86	43860
			0
	510	25	12750
			84981
			32292.78
			30678.14
	Total		79048.17

Rep 2, 1	Uncovered		
	65	25	1625
	34	4.2	142.8
	840	23	19320
	1010	42	42420
	65	5.8	377
			63884.8
			60690.56
	7700	6000	13700
			17125
			77815.56
	Covered		
	440	4	1760
	539	47	25333
	440	35	15400
			0
	1010	86	86860
			0
	1010	25	25250
			154603
			58749.14
			55811.68
	Total		133627.2

Rep 2, 2	Uncovered		
	110	25	2750
	110	4.2	462
	950	23	21850
	590	42	24780
	110	5.8	638
			50480
			47956
	13000	12000	25000
			31250
			79206
	Covered		
	910	4	3640
	1130	47	53110
	910	35	31850
			0
	590	86	50740
			0
	590	25	14750
			154090
			58554.2
			55626.49
	Total		134832.5

Rep 3, 1	Uncovered		
	92	25	2300
	32	4.2	134.4
	420	23	9660
	1010	42	42420
	92	5.8	533.6
			55048
			52295.6
	5400	4700	10100
			12625
			64920.6
	Covered		
	300	4	1200
	424	47	19928
	300	35	10500
			0
	1010	86	86860
			0
	1010	25	25250
			143738
			54620.44
			51889.42
	Total		116810

Rep 3, 2	Uncovered		
	130	25	3250
	69	4.2	289.8
	350	23	8050
	560	42	23520
	130	5.8	754
			35863.8
			34070.61
	9000	7900	16900
			21125
			55195.61
	Covered		
	300	4	1200
	499	47	23453
	300	35	10500
			0
	560	86	48160
			0
	560	25	14000
			97313
			36978.94
			35129.99
	Total		90325.6

Rep 3, 3	Uncovered		
	190	25	4750
	30	4.2	126
	520	23	11960
	240	42	10080
	190	5.8	1102
			28018
			26617.1
	4000	3600	7600
			9500
			36117.1
	Covered		
	250	4	1000
	470	47	22090
	250	35	8750
			0
	240	86	20640
			0
	240	25	6000
			58480
			22222.4
			21111.28
	Total		57228.38

Rep 3, 4	Uncovered		
	110	25	2750
	56	4.2	235.2
	700	23	16100
	560	42	23520
	110	5.8	638
			43243.2
			41081.04
	3700	4100	7800
			9750
			50831.04
	Covered		
	270	4	1080
	436	47	20492
	270	35	9450
			0
	560	86	48160
			0
	560	25	14000
			93182
			35409.16
			33638.7
	Total		84469.74

Rep 3, 5	Uncovered		
	33	25	825
	29	4.2	121.8
	590	23	13570
	360	42	15120
	33	5.8	191.4
			29828.2
			28336.79
	4300	3900	8200
			10250
			38586.79
	Covered		
	240	4	960
	302	47	14194
	240	35	8400
			0
	360	86	30960
			0
	360	25	9000
			63514
			24135.32
			22928.55
	Total		61515.34

Rep 2, 1	Uncovered			Rep 2, 2	Uncovered		
	65	25	1625		110	25	2750
	34	4.2	142.8		110	4.2	462
	840	23	19320		950	23	21850
	1010	42	42420		590	42	24780
	65	5.8	377		110	5.8	638
			63884.8				50480
			60690.56				47956
	7700	6000	13700		13000	12000	25000
			17125				31250
			77815.56				79206
	Covered				Covered		
	440	4	1760		910	4	3640
	539	47	25333		1130	47	53110
	440	35	15400		910	35	31850
			0				0
	1010	86	86860		590	86	50740
			0				0
	1010	25	25250		590	25	14750
			154603				154090
			58749.14				58554.2
			55811.68				55626.49
	Total		133627.2		Total		134832.5
Rep 4, 1	Uncovered			Rep 4, 2	Uncovered		
	140	25	3500		90	25	2250
	28	4.2	117.6		24	4.2	100.8
	340	23	7820		256	23	5888
	620	42	26040		260	42	10920
	140	5.8	812		90	5.8	522
			38289.6				19680.8
			36375.12				18696.76
	4500	4600	9100		6100	4800	10900
			11375				13625
			47750.12				32321.76
	Covered				Covered		
	260	4	1040		192	4	768
	428	47	20116		306	47	14382
	260	35	9100		192	35	6720
			0				0
	620	86	53320		260	86	22360
			0				0
	620	25	15500		260	25	6500
			99076				50730
			37648.88				19277.4
			35766.44				18313.53
	Total		83516.56		Total		50635.29

Rep 4, 3	Uncovered			Rep 4, 4	Uncovered			Rep 4, 5	Uncovered			
	100	25	2500		52	25	1300		25	25	625	
	21	4.2	88.2		34	4.2	142.8		28	4.2	117.6	
	260	23	5980		406	23	9338		320	23	7360	
	330	42	13860		220	42	9240		240	42	10080	
	100	5.8	580		52	5.8	301.6		25	5.8	145	
			23008.2				20322.4				18327.6	
			21857.79				19306.28				17411.22	
	3100	2500	5600		2900	3900	6800		3700	4000	7700	
			7000				8500				9625	
			28857.79				27806.28				27036.22	
	Covered				Covered				Covered			
	224	4	896		199	4	796		198	4	792	
	345	47	16215		285	47	13395		251	47	11797	
	224	35	7840		199	35	6965		198	35	6930	
			0				0				0	
	330	86	28380		220	86	18920		240	86	20640	
			0				0				0	
	330	25	8250		220	25	5500		240	25	6000	
			61581				45576				46159	
			23400.78				17318.88				17540.42	
			22230.74				16452.94				16663.4	
	Total		51088.53		Total		44259.22		Total		43699.62	

Dermal exposure in mg

	1	2	3	4	5	Total	Mean
PHI 1	170	140	157	120	92	679	135.8
PHI 3	134	135	97	90	79	535	107
PHI 7	117	90	57	84	62	410	82
PHI 14	84	51	51	44	44	274	54.8

Evaluation table number	Reporting table number	Open Point number
-	**3(7)**	**3.6**
Conclusions of the EFSA Evaluation Meeting: ***MSs to discuss residue definition for processed commodities and processing yields in an expert meeting.***		
-	**3(9)**	**3.7**
Conclusions of the EFSA Evaluation Meeting: ***MSs to discuss in an expert meeting the residue definition for animal products.***		

- **Point IIA, 5.8.1: Toxicity studies of metabolites**

The proposed definition of the residue in plants (including processed commodities) and animals commodities is captan alone.

The following new reports are submitted in support of the claim that is the relevant definition of the residue. These reports are also summarised in the new residues addendum under Point IIA 6.7.

5.8.1/01

Report: May, K. (2005). THPAM. Bacterial reverse mutation test. Huntingdon Life Sciences, unpublished report MAK 857/052225 (Company file: R-18026).

Guidelines: EC Commission Directive 2000/32/EC Annex 4D-B.13/14; OECD 471 (1997); US EPA (1998) OPPTS 870.5100 EPA 712-C-98-247.

GLP: Yes.

Material and methods: Test substance: THPAM (1,2,3,6-tetrahydrophthalamic acid), batch number 214-143, purity 97.3%; vehicle dimethyl sulphoxide (DMSO), lot number KB02145KB. Solubility of THPAM was demonstrated in DMSO at 50 mg/mL. Test concentrations were prepared by serial dilution. In a first test, the test substance was added to bacterial cultures of TA1535, TA1537, TA98 and TA100 *Salmonella typhimurium*, and WP2 *uvr*A (pKM101) *Escherichia coli* at levels of 5, 15, 50, 150, 500, 1500 and 5000 µg/plate in the presence of rat liver S-9 or phosphate buffer with agar containing histidine, biotin and tryptophan. In a second test, the test substance was added to the same bacterial species at levels of 50, 150, 500, 1500 and 5000 µg/plate in the presence of rat liver S-9 or phosphate buffer. There were three replicates for each concentration and Petri dishes were incubated at 37°C for 72 hours (first test) or pre-incubation assay where the mixtures of bacteria, buffer or S9 mix and test dilution were shaken for 30 minutes before addition of the top agar (second test). Further plates without test substance, with DMSO, with positive control article 2-nitrofluorene, sodium azide, 9-aminoacridine or 4-nitroquinolone-1-oxide in the absence of S-9 and positive control article benzo[a]pyrene or 2-aminoanthracene in the presence of S-9 were prepared. Numbers of revertant colonies were counted using an automatic colony counter.

Findings:

There were no substantial increases in revertant colony numbers in any tester strain following THPAM at up to 5000 μg/plate in the presence or absence of S9 mix compared to vehicle only controls. Positive controls, with and without S-9, induced marked increases in revertant colony numbers confirming sensitivity of the cultures and activity of the S-9 mix. The absence of colonies on sterility check plates confirmed the absence of microbial contamination.

The results of the two tests are summarised in Table 5.8.1-1 and Table 5.8.1-2.

Table 5.8.1-1: Mean revertant colony counts: test 1

Test substance (μg/plate)	Colony counts (mean of three replicates)									
	TA98		TA100		TA1535		TA1537		WP2	
	- S9	+ S9	- S9	+ S9	- S9	+ S9	- S9	+ S9	- S9	+ S9
THPAM (5)	28	35	85	123	16	25	13	38	107	130
THPAM (15)	32	32	74	118	15	16	14	28	103	152
THPAM (50)	34	41	81	131	18	18	14	34	105	151
THPAM (150)	34	37	95	101	20	16	13	34	126	150
THPAM (500)	36	38	95	99	22	17	10	34	117	135
THPAM (1500)	34	41	97	119	15	23	11	28	117	138
THPAM (5000)	27	34	75	97	12	17	15	34	125	144
DMSO (0.1mL)	36	40	98	118	18	23	15	28	117	136
2-nitrofluorene (2)	453	-	-	-	-	-	-	-	-	-
Benzo[a]pyrene (5)	-	286	-	-	-	-	-	118	-	-
Sodium azide (2)	-	-	816	-	1048	-	-	-	-	-
2-aminoanthracene (5/10)	-	-	-	539	-	391	-	-	-	386
9-aminoacridine (50)	-	-	-	-	-	-	390	-	-	-
4-nitroquinolone-1-oxide (2)	-	-	-	-	-	-	-	-	1159	-

Table 5.8.1-2: Mean revertant colony counts: test 2

Test substance (μg/plate)	Colony counts (mean of three replicates)									
	TA98		TA100		TA1535		TA1537		WP2	
	- S9	+ S9	- S9	+ S9	- S9	+ S9	- S9	+ S9	- S9	+ S9
THPAM (50)	38	52	132	147	24	24	20	25	106	142
THPAM (150)	41	55	143	151	19	16	15	28	117	115
THPAM (500)	37	53	126	177	21	22	16	24	101	132
THPAM (1500)	39	62	128	162	24	24	14	30	106	149
THPAM (5000)	38	51	97	156	21	24	14	26	110	128
DMSO (0.1mL)	44	56	149	181	24	27	15	27	114	116
2-nitrofluorene (2)	541	-	-	-	-	-	-	-	-	-
Benzo[a]pyrene (5)	-	136	-	-	-	-	-	107	-	-
Sodium azide (2)	-	-	1153	-	1115	-	-	-	-	-
2-aminoanthracene (5/10)	-	-	-	1240	-	262	-	-	-	526
9-aminoacridine (50)	-	-	-	-	-	-	505	-	-	-
4-nitroquinolone-1-oxide (2)	-	-	-	-	-	-	-	-	922	-

Conclusions: THPAM showed no mutagenic activity in the presence or absence of S-9 mix in any bacterial system at any concentration.

5.8.1/02

Report: Chaudhry, Q. (2005). Assessment of the activity, toxicity and mutagenicity potential of THPI and THPAM, using structure activity relationships. Central Science Laboratory, unpublished report dated 4 February 2005.

Guidelines: Not applicable.

GLP: No.

Material and methods: Captan, THPI and THPAM were evaluated for their potential for activity, toxicity and mutagenicity using a Structure Activity Relationship (SAR) approach. The technique, referred to as Deduction of Risk from Existing Knowledge (DEREK), uses specialist software 'DEREK for Windows' (DfW) developed by Llhasa Ltd. The software works by matching structural entities in a query structure with structural alerts that are associated with different toxicity endpoints (toxicophores). A structural alert is the set of structural features in a molecule that makes a toxicologist suspect that the substance may show a particular toxic effect. DfW can predict alerts for carcinogenicity, irritation (e.g. of the skin, eye and gastrointestinal tract), genotoxicity, respiratory sensitisation, skin sensitisation, thyroid toxicity and a range of miscellaneous effects for bacteria and a range of mammalian species including man. The programme used 482 structural alerts associated with the different endpoints.

DfW also predicts the likelihood of each effect using descriptive terms ranging from 'certain' to 'impossible' ('certain', 'probable', 'plausible', 'equivocal', 'doubted', 'improbable', 'impossible'), or 'open' or 'contradicted' in the case of findings where there is a prediction both that the proposition is true and that it is false.

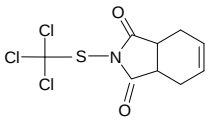
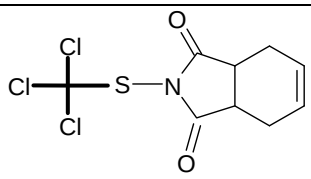
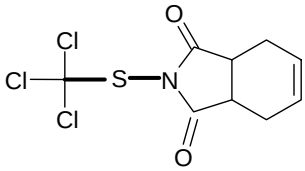
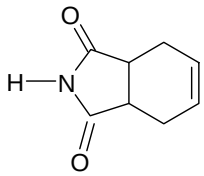
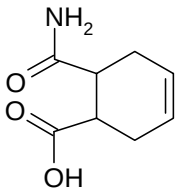
Findings:

DfW predicted that captan will exhibit mutagenicity in bacteria in vitro based on the presence of potentially labile halogen and skin sensitisation based on the thiol or thiol exchange agent. There were no structural alerts in THPI or THPAM.

These predictions are supported by experimental evidence which has demonstrated that captan is a skin sensitiser and can show mutagenicity in vitro.

The results are summarised in **Table 5.8.1-3**

Table 5.8.1-3: Structural alerts and DFW predictions for captan, THPI and THPAM

Test compound and structure	Description of alerts found	Endpoint	Species	Location of alert in molecule (in bold)	Likelihood of predicted effect
Captan 	potential labile halogen	mutagenicity (*in vitro*)	bacteria		plausible
	thiol or thiol exchange agent	skin sensitisation	guinea pig, hamster, human, mouse, primate, rat		plausible
THPI 	none	-	-	-	-
THPAM 	none	-	-	-	-

Conclusions: Computer predictions using DfW indicate that the captan metabolites THPUI and THPAM are not expected to exhibit the same fungicidal activity as captan or to exhibit mutagenic activity, genotoxicity, irritation, sensitisation or thyroid toxicity.

5.8.1/03

Report: Anon (1999). THPAM. Bioassay of captan and metabolites against Venturia and Botrytis. Royal Research Station of Gorsem, unpublished report (Company file: R-11094).

Guidelines: None.

GLP: No.

Material and methods: Captan (lot no. ASJ10097-01S), THPI (lot no. ASW01685-01A) and THPAM (lot no. ASW1584R) were dissolved in acetone and added to agar media at a range of concentrations. Activity of the compounds was tested against two fungal species

(*Botrytis cinerea* and *Venturia inaequalis*) isolated from field populations in two tests: (1) to measure spore germination and (2) to measure mycelial growth. Two Petri-dishes were prepared per compound/concentration/species/test.

For the spore germination test, 100 µL of suspension containing 150,000 conides/mL (concentration assessed by haemocytometer) was spread over the agar plates containing malt extract agar and test compound at 0 (untreated), 0 (acetone only), 1, 5, 25, 50 and 100 mg/L and incubated. Germination was assessed for four times 50 conides on two agar plates for each concentration after 24 hours (*B. cinerea*) or 48 hours (*V. inaequalis*).

For the mycelial growth test, two 5 mm agar plugs from a fresh growing colony were transferred to agar plates containing the same concentrations as for the spore germination test and incubated at 20˚C. The colony diameters were measured five days (*B. cinerea*) or 19 and 44 days (*V. inaequalis*).

Findings:

There was strong inhibition of germination with captan at concentrations of 1 mg/L and above (*B.cinerea*) and at 5 mg/L and above (*V. inaequalis*) compared to untreated and acetone only controls. At 25 mg/L and above germination of both fungal species was prevented (Table 5.8.1-4). THPI and THPAM had no effect on the germination of either species at 100 mg/L.

Captan at 25 mg/L and above gave total inhibition of mycelial growth of *B.cinerea* and there was a slight effect at lower doses. THPAM had no effect on mycelial growth of *B.cinerea* at any concentration compared to untreated and acetone only controls. THPI gave a slight reduction in mycelial growth (approximately 35% reduction) at 25, 50 and 100 mg/L compared to controls. Captan at 25 mg/L and above also inhibited mycelial growth of *V.inaequalis* after 19 and 44 days. THPAM and THPI had no effect on mycelial growth of *V.inaequalis* at any concentration compared to untreated and acetone only controls though the assessments for THPAM at 100 mg/L were obscured by the growth of other organisms on the agar plate (Table 5.8.1-5).

Table 5.8.1-4: Effect of treatments on conidial germination

Test substance (mg/L)	Length of germination tube for 50 conides (mean of 4 replicates)									
	B. cinerea					***V. inaequalis***				
	RR	**R**	**r**	**s**	**0**	**RR**	**R**	**r**	**s**	**0**
Untreated	38.5	-	-	-	115	49.3	-	-	-	0.8
Acetone only	39.0	-	-	-	11.0	48.8	-	-	-	1.3
Captan (1)	-	-	38.0	-	12.0	49.5	-	-	-	0.5
Captan (5)	-	-	-	10.8	39.3	-	44.5	-	-	5.5
Captan (25)	-	-	-	-	50.0	-	-	-		50.0
Captan (50)	-	-	-	-	50.0	-	-	-	-	50.0
Captan (100)	-	-	-	-	50.0	-	-	-	-	50.0
THPI (100)	38.8	-	-	-	11.3	49.3	-	-	-	0.8
THPAM (100)	38.5	-	-	-	11.5	49.3	-	-	-	0.8

RR, R , r, s, 0 = classes of germination tube length

Table 5.8.1-5: Effect of treatments on mycelial growth

Test substance (mg/L)	Mycelial growth (diameter in mm; mean of 4 replicates)		
	B. cinerea	*V. inaequalis*	
	5 days incubation	19 days incubation	44 days incubation
Untreated	67.0	14.0	29.5
Acetone only	57.5	14.5	32.5
Captan (1)	59.3	12.5	24.0
Captan (5)	49.8	11.5	26.0
Captan (25)	5.0	5+	16.8
Captan (50)	5.0	5.0	12.8
Captan (100)	5.0	5.0	9.0
THPI (1)	64.0	11.3	20.5
THPI (5)	50.5	12.5	28.0
THPI (25)	35.5	11.5	25.8
THPI (50)	39.5	13.8	28.0
THPI (100)	39.3	13.3	25.8
THPAM (1)	60.3	13.3	23.5
THPAM (5)	53.3	13.0	25.3
THPAM (25)	52.8	13.3	26.0
THPAM (50)	59.5	13.3	25.3
THPAM (100)	58.0	13.0	-*

* Growth could not be measured due to growth of other organisms.
5 = no growth
5+ = light growth

Conclusions: Captan showed marked activity against *B.cinerea* and *V. inaequalis* at a concentration of 25 mg/L and above, preventing germination and inhibiting mycelial growth. Lower doses of captan also affected germination. In contrast, THPAM and THPI showed no or negligible activity on either species at any concentration up to 100 mg/L.

5.8.1/04

Report: Gordon, E. (2005). Captan. Toxicological significance of relevant degradates. Makhteshim, unpublished report dated April 8, 2005.

Guidelines: Not applicable.

GLP: Not applicable.

Material and methods: The discussion paper expands on the discussion of the toxicological significance of the degradates of captan.

Findings:

The degradates of captan should not be included in the residue expression, as defined by the Guideline:

-Their basic toxicology

The physical and chemical properties of a chemical determine the nature and severity of effects in mammals. Captan has an active moiety that is responsible both for its fungicidal properties and its toxicological effects in

mammals. The degradate THPI and THPI's metabolites lack this active moiety and thus have a spectrum of effects distinct from their parent. These degradates are not acutely toxic, are not developmental or reproductive toxins, are not mutagenic, are not carcinogenic, and do not exhibit any relevant systemic long term or sub-chronic toxicity.

The absence of significant toxicity is reflected in a Structure Activity Relationship (SAR) analysis for the degradates of captan (Chaudhry 2005). Where predictions could be made (i.e., where similar molecules/functional groups existed in the database with associated toxicity), low potential for mutagenicity and carcinogenicity were calculated. Interestingly, the SAR analysis did predict mutagenicity for captan in the Ames Assay, providing some sense of validation for the analysis as captan is an *in vitro* mutagen but not mutagenic in vivo (Chaudhry 2005).

-Their presence in significant amounts
The definition of "significant amounts" is not clear in the guideline; however, THPI is only present as a minor residue in the environment. THPI, along with its metabolites are the main ring associated residues in mammals administered captan, but the expected amounts in livestock are judged not significant.

The toxicology of captan is based on its reactive trichloromethylthio side chain that reacts rapidly with thiol groups, destroying captan and, in the process, producing thiophosgene, itself a highly reactive compound. Thiophosgene reacts not only with thiol groups but a whole host of other functional groups. The half-life of these compounds in human blood reflects their reactivity: captan has a half-life of 0.9 seconds (Gordon, Mobley et al. 2001) and thiophosgene has a half-life of 0.6 seconds (Dohn and Arndt 2004).

The degradates/metabolites of captan lack the reactive sites present on the parent. Since the chemical properties govern in large measure the toxicity of compounds, it is not surprising that the toxicity of the degradates/metabolites of captan are essentially innocuous in comparison to the parent.

On plants, as noted in plant metabolism studies, the main residue is the parent compound; in animals, the parent is completely degraded, except where high oral doses are administered leading to some appearance in the faeces.

In animals, residues of captan are absent and are replaced by a variety of ring-based compounds generated from THPI, which are then excreted.

Since the main plant residue is captan and captan is the species that confers toxicity, it is concluded that the residue expression should be restricted to captan only.

The main animal residue is a collective of THPI-based molecules and do not confer toxicity that is considered toxicologically significant. None of these degradates or metabolites are judged candidates for inclusion in the residue expression.

The suggestion that THPI-based compounds be included in the residue definition since *they occur* in instances where the parent, captan, has been degraded (e.g., certain animal products) reflects a desires to *measure something*, regardless of the toxicological significance of the analyte. In truth, while the captan degradates or metabolites might provide some measure of

'exposure,'[13] its main metabolites do not meet the criteria for inclusion as part of the residue definition.

Conclusions: The collective data on captan degradates shows that the appropriate residue definition for captan is the parent molecule, only. This is in conformity with the JMPR (FAO/WHO 2000) and US-EPA. This is in conformance with the DG SANCO Guideline (European Commission 1997):

-Residues are expressed as parent compound if there are no metabolites or if the metabolites are known to be of no toxicological significance.

The metabolites present a significantly lower hazard to man than captan, evidenced by the complete lack of systemic toxicity observed in the captan long term and subchronic toxicity studies. In addition, direct comparisons of captan and THPI aquatic toxicity further reinforces the differences due primarily to its mode of action as a primary irritant. Key to resolving the differences in toxicity between captan, THPI and other systemically circulating THPI-metabolites is the exceptionally rapid degradation of captan in the presence of blood. As such, all systemic toxicity observed in captan studies is attributed to the metabolites along with secondary effects of captan's irritation of the GI tract.

The residue expression for captan should be captan alone.

[13] That is, measurements of THPI-based compounds would reflect the fact that captan had been applied some time in the past. Quantifying these THPI-based compounds would not, however, provide a validated estimate of how much captan had been applied. These compounds remain not relevant of human risk assessment following captan agricultural use.

New references, by Annex point

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
IIA, 5.1/08	Arndt, T., Dohn, D.	2004	Measurement of the half-life of thiophosgene in human blood. PTRL West, Inc., Report number 1146W (Company file: R-17121). GLP, Unpublished	Y	Makhteshim/ Arysta Paris
IIA, 5.5.3/01	Reuber, M.	1989	Carcinogenicity of captan. Published in *Journal of Environmental Pathology Toxicology & Oncology* 9: 127-43) Not GLP, Published.	N	-
IIA, 5.5.3/02	Cabral, et al	1991	A Rapid *in vivo* Bioassay for the Carcinogenicity of Pesticides. *Tumori* 77: 185-8. Not GLP, Published.	N	-
IIA, 5.5.3/03	Hasegawa, R. et al.	1993	Carcinogenic Potential of Some Pesticides in a Medium-term Multi-organ Bioassay in Rats. *International Journal of Cancer* 54: 489-93. Not GLP, Published.	N	-

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
IIA, 5.6.2.1/04	Neal, B.	2004	Comments on captan monograph: section B 6.6 Reproductive toxicity. The Weinberg Group Inc, unpublished report 21 September 2004. Not GLP, Unpublished.	N	Makhteshim/ Arysta Paris
IIA, 5.6.2.2/02	Neal, B.	2004	Comments on captan monograph: section B 6.6 Reproductive toxicity. The Weinberg Group Inc, unpublished report 21 September 2004. Not GLP, Unpublished.	N	Makhteshim/ Arysta Paris
IIA, 5.8.1./01	May, K.	2005	THPAM. Bacterial reverse mutation test. Huntingdon Life Sciences, unpublished report MAK 857/052225 (Company file: R-18026). GLP, Unpublished.	Y	Makhteshim
IIA, 5.8.1./02	Chaudhry, Q.	2005	Assessment of the activity, toxicity and mutagenicity potential of THPI and THPAM, using structure activity relationships. Central Science Laboratory, report dated 4 February 2005. Not GLP, Unpublished	Y	Makhteshim
IIA, 5.8.1./03	Anon	1999	THPAM. Bioassay of captan and metabolites against Venturia and Botrytis. Royal Research Station of Gorsem, report (Company file: R-11094). Not GLP, Unpublished	Y	Makhteshim
IIA, 5.8.1./04	Gordon, E.	2005	Captan. Toxicological significance of relevant degradates. Makhteshim, report dated April 8, 2005. Not GLP, Unpublished.	N	Makhteshim
IIA, 5.8.2./06	Moore, G.E., Creasey, D.	2004	Intestinal irritation in CD-1 mice after a 24-hour exposure to folpet. [redacted], Report number 13763 (Company file: R-16283). GLP, Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 5.9.3/02	Mills P.K.	1998	Correlation analysis of pesticide use data and cancer incidence rates in California counties. Arch Environ Health 53: 410-3. Not GLP, Published.	N	-
IIA, 5.9.3/03	McDuffie, H., Pahwa, P., McLaughlin, J., Spinelli, J.F., Incham, S. et al.	2001	Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev.* 10: 1155-63. Not GLP, Published.	N	-

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
IIA, 5.10./01	Gordon, E., Kinzell, J	2004	Captan. A summary basis for why an acute reference dose (aRfD) is not needed. Submitted to the JMPR for the 2004 toxicological evaluateioon of captan. Makhteshim-Agan and Arvesta (MCW company file R-17080). Not GLP, Unpublished.	N	Makhteshim/ Arysta Paris
IIA, 5.10./02	Makhteshim Chemical Works and Calliope	2005	Captan. Comments made by Greece on the toxicology section of the DAR. Response by Notifier. Makhteshim and Calliope, report April 6, 2005. Not GLP, Unpublished.	N	Makhteshim/ Arysta Paris

Captan

Dossier According to Directive 91/414/EEC

Summary Documentation

Tier II

Annex II and Annex III

Residues

Addendum to dossier

March 2005

Table of Contents

Introduction

This document contains new information on residues submitted by Makhteshim Chemical Works Ltd. and Arysta Paris to the RMS.

New information is presented here in the order of the Evaluation table for captan, cross-referencing the Open point numbers and Reporting table numbers. New information is summarised under the dossier numbering system.

Document D1: Critical Good Agricultural Practice

The GAP for peaches/nectarines is changed: the PHI is increased from 7 days to 21 days. No other changes have been made. The amended GAP is presented in the table below.

Critical Good Agricultural Practice for captan in the EU

Crop	Member state or country	Product name	F, G or I	Pests or group of pests controlled	Formulation		Application			Application rate per treatment			PHI (days)	Remarks:
					Type	Conc. of a.s.	method kind	growth stage/ timing	number[b] (max.)	kg a.s./hL (max.)	water L/ha	kg a.s./ha (max.)		
Pome fruit	North EU	'Merpan' 80 WDG / 'Malvin' WDG	F[a]	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 53 / April	9 - 10	0.125	1000	1.25	14	
	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69 / April	9 + 3 [c]	0.125 0.24	1000 1000	1.25 2.4	14	
Tomatoes	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Foliar spray; down-wards	From BBCH 60 to 87	4	0.15	1200	1.8	14	
Peaches/ nectarines	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69: petal fall	4	0.25	1000	2.5	21	

[a] F = field.
[b] Applications at a minimum of 7 days for all crops.
[c] Nine applications at 1.25 kg a.s./ha (scab control) followed by three applications at 2.4 kg a.s/ha (*Nectria* control).

New information on residues

Evaluation table number	Reporting table number	Open Point number
-	3(1)	3.1

Conclusions of the EFSA Evaluation Meeting:
RMS to provide an addendum to be considered in expert meeting with the new MRL proposal for peaches and nectarines, new TMDI and I(N)EDI calculations, as well as new STMR calculations.

- **Point IIA, 6.3: Residue trials (peaches and nectarines)**

The GAP for 'Malvin' WG and 'Merpan 80 WDG' is changed: the PHI is increased from 7 days to 21 days.

This amendment to the PHI changes only proposals for the MRL in peaches and consumer risk assessments. These changes are addressed in Points IIA 6.7 and IIA 6.9 below. The change in PHI for peaches/nectarines has no affect on the existing assessments of risk of captan to operators or the environment.

No new data are submitted to support this change. The same residue trials as those summarised in Table B.7.6.3.1 of the DAR are relevant to the amended GAP. The trials are listed in the table below. The relevant residue values according to the amended GAP are underlined.

Residues of captan in peaches and nectarines following applications of WG and WP formulations of captan in southern EU

Location Year Trial	Application					Portion analysed	PHI (days)	Captan residue (mg/kg)	Ref.
	Formuln (type, content)	No.	Method	kg a.s./ ha	kg a.s./ hL				
Peaches									
S.France 2000 TL1 Grenade sur Garonne, (31330)	WG, 800 g/kg	4	foliar; knap-sack	3.06 - 3.52	0.25	whole fruit	7	3.5	TMN-0651A (IIA 6.3/17)
							13	1.3	
							21	0.56	
Spain 2000 PA1 Lora del Rio (41440)	WG, 800 g/kg	4	foliar; knap-sack	2.96 - 3.27	0.15	whole fruit	11	4.9	
							15	6.3	
							22	2.2	
Spain 2000 ES1 Gualta (17257)	WG, 800 g/kg	4	foliar; knap-sack	3.05 - 3.17	0.15	whole fruit	9	3.7	
							14	2.8	
							21	1.7	
S. France 2001 Vacquiers (31340)	WG, 800 g/kg	4	foliar; knap-sack	2.94 - 3.08	0.25	whole fruit	8	4.4	TMN-0652 (IIA 6.3/20)
							13	1.6	
							20	0.66	
Nectarines									
Greece 1999 GR1 Veria (59100)	WP, 830 g/kg	4	foliar; knap-sack	2.80 - 2.99	0.125	whole fruit	7	5.6	TMN-0643 (IIA 6.3/18)
							14	4.1	
							21	1.5	
Greece 1999 GR2 Naoussa (59100)	WP, 830 g/kg	4	foliar; knap-sack	2.85 - 3.00	0.125	whole fruit	7	3.1	
							14	2.3	
							21	0.90	
Spain 1999 ES1 Gualta (17257)	WP, 500 g/kg	4	foliar; knap-sack	2.84 - 3.03	0.15	whole fruit	7	2.1	
							11	1.8	
							21	0.62	
Spain 1999 ES2 Pals (Girona, 17256)	WP, 500 g/kg	4	foliar; knap-sack	2.98 - 3.02	0.15	whole fruit	7	2.5	
							11	1.3	
							21	0.43	

- **Point IIA, 6.7: Proposed maximum residue Levels (MRLs) and residue definition**

No new data are submitted. Calculations of the MRL and STMR for peaches and nectarines according to Commission Directive 7039/VI/95 EN are presented below.

The relevant residue results arranged in ascending order are presented in Table 6.7-1.

Table 6.7-1 Residues of captan in peaches and nectarines for calculating a MRL and STMR

Location, Year, Trial	Application		PHI	Captan residue
	No.	kg a.s./ ha	(days)	(mg/kg)
Spain 1999, ES2 Pals	4	2.98 - 3.02	21	0.43
S.France, 2000, TL1 Grenade sur Garonne	4	3.06 - 3.52	21	0.56
Spain, 1999, ES1 Gualta	4	2.84 - 3.03	21	0.62
S. France, 2001, Vacquiers	4	2.94 - 3.08	20	0.66
Greece, 1999, GR2 Naoussa	4	2.85 - 3.00	21	0.90
Greece, 1999, GR1 Veria	4	2.80 - 2.99	21	1.5
Spain, 2000, ES1 Gualta	4	3.05 - 3.27	21	1.7
Spain , 2000, PA1 Lora del Rio	4	2.96 - 3.17	22	2.2

MRL calculation Method 1

$R(max) = R_{mean} + k \times s$
$= 1.07 + (3.188 \times 0.647)$

R(max) = 3.1 mg/kg.

k value from tables (according to Commission Working Document 7032, 1997)
s = standard deviation

MRL calculation Method 2

Number (n)	8
P = T/100	0.75
T = percentile value	75
J = integer of (n + 1) x P	6
G = modulus of (n + 1) x P	0.75
R(J) = residue value at point J	1.5
R(J + 1) = residue value at point J + 1	1.7

R(0.75) = (1 - G) x R(J) + G x R(J + 1)
= 0.375 + 1.275
= 1.65

R(calc) = 2 x R(0.75) in mg/kg = 3.3 mg/kg

Both methods of calculation indicate that a MRL of 3.0 mg/kg is appropriate for peaches and nectarines. A MRL of 3 mg/kg is proposed for peaches and nectarines.

STMR

STMR = 0.66 + 0.9/2 = 0.78 mg/kg.

- **Point IIA, 6.9: Estimation of the potential and actual exposure through diet and other means**

Chronic exposure

Theoretical Maximum Daily Intake (TMDI)
This is based on food consumption data and the existing or proposed MRLs for apples, pears, tomatoes, peaches and nectarines.

The TMDI assumes the following:

1) All the crop is treated and contains residues at the MRL.
2) Residues are not removed or reduced during storage, washing, processing or food preparation.

The TMDI is calculated by multiplying the MRL by the estimated average daily consumption for a given food commodity.

TMDI = ∑ MRL x F

where:
MRL = Maximum residue limit for a given food commodity
F = Consumption of that food commodity.

This calculation is performed using:

1) An International diet (European Region) based on data from the World Health Organisation (WHO)[14].
2) The UK Dietary model (PSD, 1999[15])
3) The German BBA average food consumption data (Federal Biological Office for Agriculture and Forestry, 1993[16])

WHO European diet

The TMDI calculation is presented in Table 6.9-1.

Table 6.9-1: TMDI calculation for captan based on WHO diet

Commodity	MRL (mg/kg)	Consumption (kg/person/day)	TMDI (mg/person/day)
Apples	5	0.0400	0.2000
Pears	5	0.0113	0.0565
Tomatoes	2	0.0660	0.1320
Peaches and nectarines	3	0.0125	0.0375
Total			**0.4260**

The total TMDI is 0.4260 mg/person/day day or 0.007 mg/kg bw/day for a 60 kg adult.

[14] WHO (1989). Guidelines for predicting dietary intake of pesticide residues. Prepared by the joint UNEP/FAO/WHO Food Contamination Monitoring Programme in collaboration with the Codex Committee on Pesticide Residues. World Health Organisation, Geneva.

[15] PSD (1999). Guidance on the estimation of dietary intakes of pesticides residues. The Registration Handbook. Pesticides Safety Directorate, Ministry of Agriculture, Fisheries and Food.

[16] Federal Biological Office for Agriculture and Forestry, (1993). Testing of the residue behaviour - Assessment of the intake of pesticide residues via food. Guidelines for pesticides testing in the registration procedure. Part IV 3 - 7.

UK diet

UK consumption data for adults, children, toddlers and infants (mean consumers and high, i.e. 97.5th percentile, consumers) are presented in Table 6.9-2.

The TMDI for adults, children, toddlers and infants based on the mean and 97.5th percentile consumption data for each commodity are presented in Table 6.9-3 and Table 6.9-4. Table 6.9-4 also includes the total TMDI calculated from the total of the two highest 97.5th percentile intakes plus the mean population intakes for the other crops.

Table 6.9-2: UK consumption data for adults, children, toddlers and infants

Commodity	Consumption data (kg/day)							
	Adults (70.1 kg bw)		Children (43.6 kg bw)		Toddlers (14.5 kg bw)		Infants (8.7 kg bw)	
	Mean	High [1]	Mean	High	Mean	High	Mean	High
Apples	0.0279	0.1566	0.0256	0.1328	0.0245	0.2186	0.0143	0.0751
Pears	0.0042	0.0988	0.0026	0.0634	0.0027	0.0974	0.0023	0.0254
Tomatoes	0.0228	0.0755	0.0086	0.0361	0.0061	0.0372	0.0013	0.0136
Peaches/ nectarines	0.0047	0.0958	0.0019	0.0478	0.0021	0.1074	0.0005	0.0194

[1] 97.5th percentile.

Table 6.9-3: TMDI calculation for captan for adults, children, toddlers and infants based on UK mean consumption intakes

Commodity	MRL (mg/kg)	TMDI (mg/kg bw/day) [1]			
		Adults (70.1 kg bw)	Children (43.6 kg bw)	Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
Apple	5	0.00199	0.00294	0.00845	0.00822
Pears	5	0.00030	0.00030	0.00093	0.00132
Tomatoes	2	0.00065	0.00039	0.00084	0.00030
Peaches/ nectarines	3	0.00020	0.00013	0.00043	0.00017

[1] Calculated for each crop from mean intakes.

Table 6.9-4: TMDI calculation for captan for adults, children, toddlers and infants based on UK high consumption intakes

Commodity	MRL (mg/kg)	TMDI (mg/kg bw/day) [1]			
		Adults (70.1 kg bw)	Children (43.6 kg bw)	Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
Apple	5	*0.01117*	*0.01523*	*0.07538*	*0.04316*
Pears	5	*0.00705*	*0.00727*	*0.03359*	*0.01460*
Tomatoes	2	0.00215	0.00166	0.00513	0.00313
Peaches/nectarines	3	0.00410	0.00329	0.02222	0.00669
Total exposure [2]		**0.01907**	**0.02302**	**0.11024**	**0.0582**

[1] Calculated for each crop from 97.5th percentile intakes.
[2] Calculated from total of the two highest 97.5th percentile intakes (*in italics*) plus mean population intakes for other crops (from Table 6.9-3).

The TMDIs are 0.019 mg/kg bw/day (adults), 0.023 mg/kg bw/day (children), 0.110 mg/kg bw/day (toddlers) and 0.058 mg/kg bw/day (infants).

German diet

The TMDI calculation for a 13.5 kg 4 to 6 year old girl is presented in Table 6.9-5.

Table 6.9-5: TMDI calculation for captan for a 4 to 6 year old girl based on German diet

Commodity	MRL (mg/kg)	Consumption (kg/person/day)	TMDI (mg/person/day)
Apples	5	0.0420	0.2100
Pears	5	0.0064	0.0320
Tomatoes	2	0.0151	0.0302
Peaches and nectarines	3	0.0079	0.0237
Total exposure	-	-	0.2959

The total TMDI is 0.2959 mg/person/day day or 0.022 mg/kg bw/day for a 13.5 kg girl.

Comparison of TMDI with ADI

The TMDI values for different consumer groups and diets are summarised in Table 6.9-6.

Table 6.9-6: TMDI values for different consumer groups and diets

Diet	Body weight (kg)	TMDI (mg/kg bw/day)
WHO adult	60	0.007
UK adult	70.1	0.019
UK child	43.6	0.023
UK toddler	14.5	0.110
UK infant	8.7	0.058
German child	13.5	0.022

Based on the proposed ADI for captan of 0.1 mg/kg bw/day, the TMDI represents 7% to 110% of the ADI for the different consumer groups and different dietary intakes.

The TMDI is less than the ADI for captan for adults (WHO and UK diets), children (UK and German diets) and infants (UK diet). There is therefore a large margin of safety for these consumer groups and more refined calculations of intake are not required.

The TMDI for toddlers using the UK dietary model exceeds the ADI and so it is necessary to carry out more refined calculations of intake for toddlers. These are presented below.

National Estimated Daily Intake (NEDI)

The NEDI is a more realistic estimate of pesticide residue intake. It takes into account distribution between edible and non-edible portions of crop, possible losses during processing or cooking and more realistic assessments of residue levels.

$NEDI = \sum F_i \times RL_i \times K$

where:
F_i = Consumption of that food commodity.
RL_i = Appropriate residue level for the food commodity (e.g. STMR).
K = Correction factor taking into account reduction or increase in residues during storage, processing, food preparation (washing, removing outer leaves), cooking.

The supervised trials median residue (STMR) is the residue value in the position of [0.5(n+1)], when residue values are placed in ascending order of magnitude, where n = number of residue values. STMR values for captan are as follows:
apples/pears – 1.7 mg/kg
tomatoes - 0.28 mg/kg
peaches/nectarines – 0.78 mg/kg

Since most of each of the commodities recommended for treatment with captan are consumed raw, no correction is made for loss of residues during processing for this calculation. No concentration of residues in edible commodities occurred in processing studies. Therefore, in the above equation K = 1.

STMR values and NEDI calculations for a 14.5 kg toddler based on UK mean and high consumption intakes are presented in Table 6.9-7. This table also includes the total NEDI calculated from the total of the two highest 97.5th percentile intakes plus the mean population intakes for the other crops.

Table 6.9-7: NEDI calculation for captan for toddlers based on UK mean and high consumption intakes

Commodity	STMR (mg/kg)	NEDI (mg/kg bw/day) for toddlers (14.5 kg bw)	
		Mean consumption intakes[1]	High consumption intakes[2]
Apple	1.7	0.0028	*0.0256*
Pears	1.7	0.0003	*0.0114*
Tomatoes	0.28	*0.00012*	0.00072
Peaches	0.78	*0.00011*	0.00578
Total exposure[3]		**0.03723**	

[1] Calculated for each crop from mean intakes.
[2] Calculated for each crop from 97.5th percentile intakes.
[3] Calculated from total of the two highest 97.5th percentile intakes (*in italics*) plus mean population intakes for other crops (*in italics*).

The NEDI values for toddlers is 0.037 mg/kg bw/day.

Comparison of NEDI with ADI

The NEDI value for toddlers represents 37% of the ADI for captan of 0.1 mg/kg bw/day. There is, therefore, a large margin of safety for toddler consumers, and no further calculations are required.

Acute exposure

Calculations of dietary exposure for assessing acute hazards posed by pesticide residues are based on consumption of a large portion of a single commodity containing residues assuming to be at the highest residue level detected (incorporating processing factors for processed commodities) .
An ARfD of 0.1 mg/kg bw has been proposed. Calculations of the acute dietary exposure (NESTI) for consumers were performed for adults and toddler by using UK models.

Acute intake estimates, termed National Estimates of Short-term Intake (NESTI), are calculated according to the recommendations of the PSD, on the basis of single day consumption data for adults and toddlers (UK registration handbook, 2001).

$$NESTI = \frac{\{U * HR\text{-}P * v\} + \{(F-U) * STMR\text{-}P\}}{\text{Mean body weight}}$$

Where:

- U is the weight of the first commodity unit (kg)
- F is the full portion consumption data (kg/person/day). Where F is less than or equal to U, then the second term of the equation drops out.
- HR-P is the highest residue level detected (mg/kg), incorporating processing or edible portion factors.
- v is the variability factor. It applies in case of commodities for which there may be a high variability of residue levels between the individual units within composite samples.
- STMR-P is the supervised trials median residue in the edible portion, incorporating processing factors.

The NESTI values for captan are presented in tables B.7.15.1.2.

Table B.7.15.1.1: Acute residue intake for captan (NESTI)

(ARfD =0.1 mg/kg bw)

Commodity	**U**	**HR-P**	**STMR-P**	**v**	**F**	**NESTI**	
	[kg]	[mg/kg]	[mg/kg]		[kg/person/day]	[mg/kg]	[%ARfD]
Adult (70.1 kg body weight)							
Apple fruit	0.112	4.2	1.7	7	0.308	0.0517	51.7
Apple juice	0.160	<0.21	<0.08	1	0.452	-	-
Pears	0.150	4.2	1.7	7	0.274	0.0659	65.9
Tomatoes	0.085	1.1	0.28	7	0.157	0.0096	9.6
Peaches	0.110	2.2	0.78	7	0.228	0.0255	25.5
Nectarines	0.149	2.2	0.78	7	0.172	0.033	33.0
Toddler 1½-4½ year-old (14.5 kg body weight)							
Apple fruit	0.112	4.2	1.7	7	0.199	0.2373	237.3
Apple juice	0.160	<0.21	<0.08	1	0.559		-
Pears	0.150	4.2	1.7	7	0.279	0.3193	319.3
Tomatoes	0.085	1.1	0.28	7	0.093	0.0453	45.3
Peaches	0.110	2.2	0.78	7	0.144	0.1187	118.7
Nectarines	0.149	2.2	0.78	7	0.152	0.1584	158.4

Using the UK model for the determination of the acute intake, the ARfD is exceeded in toddler by the 237 % for apples, 319% for pears, 118% for peaches and 158% for nectarines.

RMS comments

Risks for chronic exposure acceptable, since TMDI is less than the ADI for captan in adults (WHO and UK diets), children (UK and German diets) and infants (UK diet). TMDI exceed ADI in toddler (UK diet). However in these subjects (toddlers), NEDI is less than the ADI (UK model).
Risk for acute exposure unacceptable, since the ARfD is exceeded in toddler by the 237 % for apples, 319% for pears, 118% for peaches and 158% for nectarines (UK model).

Evaluation table number	Reporting table number	Open Point number
-	**3(2)**	**3.3**

Conclusions of the EFSA Evaluation Meeting:
RMS to prepare an addendum to be discussed in expert meeting addressing uncharacterized material in fruit wash, foliage, peel and pulp extracts of the metabolism study on apples (level and number of individual fractions…).

- **Point IIA, 6.1: Metabolism studies in plants**

The following information is provided to address questions concerning the nature of uncharacterised captan residues in apple fruit.

Information on the behaviour of captan in apples is provided in the study by DeBaun, J.R., Gruwell, L.A and Menn, J.J. (1975).

The distribution of radioactive residues in apples harvested at intervals after treatment with [carbonyl-^{14}C] captan is shown in the following table:

Identity of residue	% TRR			
	Tree 4 (0/0 DAT[1])	Tree 3 (20/20 DAT)	Tree 2 (50/20 DAT)	Tree 1 (80/20 DAT)
fruit wash				
captan	74.7	70.8	55.3	45.6
captan epoxide	< 1.0	< 0.9	< 0.8	< 0.6
THPI	7.3	5.1	5.0	3.3
THPI epoxide	< 1.0	< 0.9	< 1.0	< 0.9
THPAM	1.1	0.4	0.9	0.8
uncharacterised	~ 10.7	~ 11.6	~ 18.5	~ 12.8
foliage				
captan	83.1	63.2	48.2	60.1
captan epoxide	< 1.0	< 0.8	< 0.7	0.9
THPI	5.3	3.7	2.6	2.8
THPI epoxide	< 1.0	< 0.8	< 0.7	< 0.8
THPAM	2.1	2.0	1.4	0.6
unidentified	~ 6.0	~ 14.3	~ 17.9	~ 18.9
peel extract				
captan	1.5	1.7	1.2	1.9
captan epoxide	< 0.1	< 0.1	< 0.1	0.1
THPI	1.1	0.8	0.7	1.4
THPI epoxide	< 0.1	0.1	0.1	0.1
THPAM	0.3	0.5	0.6	1.1
unidentified	0.4	1.4	2.2	4.7
pulp extract				
captan	0.1	0.2	0.2	0.5
captan epoxide	< 0.1	0.1	0.2	0.2
THPI	0.4	0.8	1.4	2.3
THPI epoxide	< 0.1	< 0.1	0.4	0.6
THPAM	< 0.1	0.1	0.2	0.2
unidentified	0.3	1.6	5.3	13.5

[1] Days between first/last treatment and harvest.

In apple peel and pulp the proportion of the residue present as unidentified radioactivity increased with time during the study. A maximum level of 13.5% TRR was recorded in the sample harvested 80 days after first treatment. The unidentified residues were characterised by normal phase TLC as being predominantly polar, with 64.5% (11.1% TRR) of the pulp extract in the 80 day sample present as radioactivity remaining at the origin of the TLC plate.

Further information regarding the identity of this radioactivity was not given in the report; however information is available in the study by Chen, Y.A. (1988b) on the behaviour of captan in tomatoes and lettuce.

The distribution of radioactive residues in tomatoes and lettuce harvested at intervals after treatment with [cyclohexene-1, 2-^{14}C] captan is shown in the following table.

Identity of residue	% TRR (mg captan equivalents/kg)		
	Tomato plant[1]	Tomato fruit[2]	Lettuce leaves
captan	70.4	81.5	77.2
captan epoxide	0.4	0.4	0.6
THPI	4.6	4.5	9.5
THPI epoxide	-	-	0.9
other free metabolites	6.9	5.2	4.3
unidentified	8.9	7.5	4.5
non-extractable	8.8	0.9	3.0

[1] Leaves + stems.
[2] Determined by the addition of radioactivity in the acetone surface rinse, tomato juice and pulp calculated using weight/volume ratios for whole fruit, pulp, juice and acetone rinse.

A similar profile of radioactivity was observed in tomato and lettuce crops following treatment with captan and the profile is comparable to that observed in apples.

Unidentified radioactivity present in tomato and lettuce samples was attributed to polar and/or conjugated material and was characterised as multi-component, containing at least 7 metabolites in tomato plants, at least 4 metabolites in tomato fruit and at least 3 metabolites in lettuce.

Based on the information given above for apple, tomato and lettuce crops, it can be concluded that captan is metabolised via a common route in plants. It is therefore reasonable to conclude that unidentified residues observed in apples will be of a similar nature to those observed in tomato and lettuce and as such will be present as a multi-component residue composed of polar products most likely containing conjugates of captan metabolites.

This conclusion is consistent with the conclusion of the RMS in the reporting table 3(2).

RMS comments

Uncharacterised material (UM) likely represents polar products that are formed following the slow adsorption of captan into the peel and pulp. Based on the metabolism observed in tomato and lettuce these polar products are considered likely to be conjugates of captan metabolites. This is consistent with the observation that UM is low in fruit wash and foliage, increase in peel and is maximum in pulp.

Evaluation table number	Reporting table number	Open Point number
3.1	**3(4)** **3(22)**	**3.4**
Conclusions of the EFSA Evaluation Meeting: ***A hydrolysis study in representative hydrolytic conditions.***		

The notifier contends that a new study is not required as the effect of processing on captan can be accurately predicted from existing hydrolysis studies. This contention is supported by the position paper presented below. However, the RMS has indicated that this argument will not been accepted and so a new study has been done and will be available at the end of April 2005.

The position paper supporting the contention that a new study is not required is presented below.

- **Point IIA, 6.5.1: Effects on the nature of the residue**

The following new report is submitted:

6.5.1/01

Report: Goodyear, A.P. (2004). Captan. Position paper. Effects on the Nature of the Residue. TSGE, unpublished report July 2004.

Guidelines: Not applicable.

GLP: No.

Material and methods: The DAR volume 1 concludes that a hydrolysis study in representative hydrolytic conditions is required. The requirement for a new study and the response to the data requirement are addressed in the position paper.

Findings:

Several hydrolysis studies with captan and THPI have already been conducted. The studies cover a range of pH values and include high temperatures. The studies already conducted are considered to be adequate to evaluate the effects of processing. In the studies, captan degraded rapidly to THPI, and THPI was stable to hydrolysis under acid conditions. Further studies under simulated processing conditions would only provide data on the rate of formation of the known degradation products, the route of degradation will not be affected. Therefore, it is concluded that during simulated processing studies conducted at acid pH potentially toxic metabolites of captan will not be formed and additional studies are not required.

Conclusions: Sufficient data already exist to predict the effect of processing hydrolysis on the nature of the residue and therefore new studies are not required.

RMS comments

We feel that the studies on the nature of the residue are a key point to minimize consumer risks. The aim of the hydrolysis studies is to exclude that in “extreme” conditions potentially

toxic metabolites of captan are formed. Within the aim is to obtain information about unknown or unpredicted breakdown or reaction products which may require a separate risk assessment. This is therefore, by definition, to be addressed by specific studies.
Such specific studies are not available. **A hydrolysis study in representative hydrolytic conditions is therefore required**. This should be carried out with radiolabelled captan exploring the following conditions:
90°C x 20 min (pH4), representative of pasteurization
100°C x 60 min (pH5), representative of baking and boiling
120°C x 20 min (pH6), representative of sterilization.

Evaluation table number	Reporting table number	Open Point number
3.2	**3(4)**	**3.5**
Conclusions of the EFSA Evaluation Meeting: ***A whole balance study for tomato washed, peeled and canned or used for juice, plus a follow-up study in canned tomato and tomato juice.***		

- **Point IIA, 6.5.2: Effects on the residue levels**

Tomatoes

The following new reports are submitted:

6.5.2/07

Report: Faessel, V. (2004b). Residue study in and on tomatoes following 4 applications of the test item Malvin WG. Anadiag, unpublished report R A3154.
Perret, E. (2004a). Residue study in and on tomatoes following 4 applications of the test item Malvin WG. Viti RD, unpublished report FRC 0301 ARS.
Volle, C (2004a). Residue study in and on tomatoes following 4 applications of the test item Malvin WG. Viti R&D study plan FRC 0301 ARS and Viti R&D Processing Phase Plan No. TOM 0301 ARS.

6.5.2/08

Report: Faessel, V. (2004c). Residue study in and on tomatoes following applications of the test item Malvin WG. Anadiag, unpublished report R A3156.
Perret, E. (2004a). Residue study in and on tomatoes following 4 applications of the test item Malvin WG. Viti RD, unpublished report FRC 0302 ARS.
Volle, C (2004b). Residue study in and on tomatoes following 4 applications of the test item Malvin WG. Viti R&D study plan FRC 0302 ARS and Viti R&D Processing Phase Plan No. TOM 0302 ARS.

Analytical methods

Residues of captan were analysed by GC with ECD with a LOQ of 0.02 mg/kg.

Procedural recoveries

Mean procedural recoveries were within acceptable limits (70 to 110%) in the studies.

Storage stability

Captan residues were stable following storage at -20°C in apple fruit for 14 months, apple juice for 15 months, apple sauce, fruit pomace (tomato and grape) for 9 months, tomato fruit for 20 months and tomato sauce for 9.5 months (see Point IIA 6.3/01).

In the residue studies summarised here, samples were stored deep frozen at approximately -20°C for up to 5 months between sampling and extraction/analysis. Therefore, no reduction in residue levels recorded in tomato commodities in the studies is expected to have occurred during storage.

Residue results

Studies to investigate the effects on residue levels in tomato commodities after processing were carried out in France in 2003.

In France in 2003 (Table 6.5.2-1), residues in whole tomato fruit from two sites treated with captan (4 sprays at 1.8 to 1.9 kg a.s./ha) were < 0.02 and 0.16 mg/kg (PHI 13 days). In all processed samples, residues of captan were < 0.02 mg/kg at both sites.

Table 6.5.2-1 Residues of captan in processed tomatoes in France following applications of captan

Location Year Trial	Application				Portion analysed	PHI (days)	Captan residue (mg/kg)	Ref.
	Formul-ation (type and a.s. content)	No.	kg a.s./ ha	kg a.s./ hL				
France 2003 FRC 03 01 ARS	WG, 800 g/kg	4	1.8	0.15	whole fruit	13	< 0.02	(IIA 6.5.2/ 07)
					washed fruit	13	< 0.02	
					washing water	13	< 0.02	
					wet pomace	13	< 0.02	
					dry pomace	13	< 0.02	
					juice	13	< 0.02	
					peels	13	< 0.02	
					peeled fruit	13	< 0.02	
					canned fruit	13	< 0.02	
					puree	13	< 0.02	
					ketchup	13	< 0.02	
France 2003 FRC 03 02 ARS	WG, 800 g/kg	4	1.8-1.9	0.15	whole fruit	13	0.16	(IIA 6.5.2/ 08)
					juice	13	< 0.02	
					canned fruit	13	< 0.02	
					puree	13	< 0.02	
					ketchup	13	< 0.02	

Transfer factors

Transfer factors for tomato fruit to juice, canned fruit, puree and ketchup for trial FRC 03 02 ARS are summarised in Table 6.5.2-2. There was no concentration of residues in any processed tomato commodity. As the level of residues detected in the raw commodity in one of the trials was below the LOQ, an additional balance study will be conducted in 2005.

Table 6.5.2-2 Transfer factor values for processed tomato following applications of captan

Year Trial	Residue in whole fruit (mg/kg)	Juice		Canned fruit		Puree		Ketchup	
		Residue (mg/kg)	Trans. Factor	Residue (mg/kg)	Trans. Factor	Residue (mg/kg)	Trans. Factor	Residue (mg/kg)	Trans. Factor
2003 FRC 0302	0.16	< 0.02	< 0.1	< 0.02	< 0.1	< 0.02	< 0.1	< 0.02	< 0.1

RMS comments

Study evaluated are accepted. New TFs values included in the list of end points.
According to the statement of the MDS "the level of residues detected in the raw commodity in one of the trials was below the LOQ, an additional balance study will be conducted in 2005". Results will be evaluated when available.

Evaluation table number	Reporting table number	Open Point number
-	**3(7)**	**3.6**
Conclusions of the EFSA Evaluation Meeting: ***MSs to discuss residue definition for processed commodities and processing yields in an expert meeting.***		
-	**3(9)**	**3.7**
Conclusions of the EFSA Evaluation Meeting: ***MSs to discuss in an expert meeting the residue definition for animal products.***		
-	**3(9)**	**3.8**
Conclusions of the EFSA Evaluation Meeting: ***RMS to provide in an addendum informations in column 3 of comments 3(8) and 3(9) of the reporting table***		

- **Point IIA, 6.7: Proposed residue definition**

According to the MDS "the proposed definition of the residue in plants (including processed commodities) and animals commodities is captan alone".

The following new reports are submitted in support of the claim that is the relevant definition of the residue. These reports are also summarised in the new toxicological addendum under Point IIA 5.8.1.

- **Point IIA, 5.8.1: Toxicity studies of metabolites**

5.8.1/01

Report: May, K. (2005). THPAM. Bacterial reverse mutation test. Huntingdon Life Sciences, unpublished report MAK 857/052225 (Company file: R-18026).

Guidelines: EC Commission Directive 2000/32/EC Annex 4D-B.13/14; OECD 471 (1997); US EPA (1998) OPPTS 870.5100 EPA 712-C-98-247.

GLP: Yes.

Material and methods: Test substance: THPAM (1,2,3,6-tetrahydrophthalamic acid), batch number 214-143, purity 97.3%; vehicle dimethyl sulphoxide (DMSO), lot number KB02145KB. Solubility of THPAM was demonstrated in DMSO at 50 mg/mL. Test concentrations were prepared by serial dilution. In a first test, the test substance was added to bacterial cultures of TA1535, TA1537, TA98 and TA100 *Salmonella typhimurium*, and WP2 *uvr*A (pKM101) *Escherichia coli* at levels of 5, 15, 50, 150, 500, 1500 and 5000 µg/plate in the presence of rat liver S-9 or phosphate buffer with agar containing histidine, biotin and tryptophan. In a second test, the test substance was added to the same bacterial species at levels of 50, 150, 500, 1500 and 5000 µg/plate in the presence of rat liver S-9 or phosphate buffer. There were three replicates for each concentration and Petri dishes were incubated at 37°C for 72 hours (first test) or pre-incubation assay where the mixtures of bacteria, buffer or S9 mix and test dilution were shaken for 30 minutes before addition of the top agar (second test). Further plates without test substance, with DMSO, with positive control article 2-nitrofluorene, sodium azide, 9-aminoacridine or 4-nitroquinolone-1-oxide in the absence of S-9 and positive control article benzo[a]pyrene or 2-aminoanthracene in the presence of S-9 were prepared. Numbers of revertant colonies were counted using an automatic colony counter.

Findings:

There were no substantial increases in revertant colony numbers in any tester strain following THPAM at up to 5000 µg/plate in the presence or absence of S9 mix compared to vehicle only controls. Positive controls, with and without S-9, induced marked increases in revertant colony numbers confirming sensitivity of the cultures and activity of the S-9 mix. The absence of colonies on sterility check plates confirmed the absence of microbial contamination.

The results of the two tests are summarised in Table 5.8.1-1 and Table 5.8.1-2.

Table 5.8.1-6: Mean revertant colony counts: test 1

Test substance (μg/plate)	Colony counts (mean of three replicates)									
	TA98		TA100		TA1535		TA1537		WP2	
	- S9	+ S9	- S9	+ S9	- S9	+ S9	- S9	+ S9	- S9	+ S9
THPAM (5)	28	35	85	123	16	25	13	38	107	130
THPAM (15)	32	32	74	118	15	16	14	28	103	152
THPAM (50)	34	41	81	131	18	18	14	34	105	151
THPAM (150)	34	37	95	101	20	16	13	34	126	150
THPAM (500)	36	38	95	99	22	17	10	34	117	135
THPAM (1500)	34	41	97	119	15	23	11	28	117	138
THPAM (5000)	27	34	75	97	12	17	15	34	125	144
DMSO (0.1mL)	36	40	98	118	18	23	15	28	117	136
2-nitrofluorene (2)	453	-	-	-	-	-	-	-	-	-
Benzo[a]pyrene (5)	-	286	-	-	-	-	-	118	-	-
Sodium azide (2)	-	-	816	-	1048	-	-	-	-	-
2-aminoanthracene (5/10)	-	-	-	539	-	391	-	-	-	386
9-aminoacridine (50)	-	-	-	-	-	-	390	-	-	-
4-nitroquinolone-1-oxide (2)	-	-	-	-	-	-	-	-	1159	-

Table 5.8.1-7: Mean revertant colony counts: test 2

Test substance (μg/plate)	Colony counts (mean of three replicates)									
	TA98		TA100		TA1535		TA1537		WP2	
	- S9	+ S9	- S9	+ S9	- S9	+ S9	- S9	+ S9	- S9	+ S9
THPAM (50)	38	52	132	147	24	24	20	25	106	142
THPAM (150)	41	55	143	151	19	16	15	28	117	115
THPAM (500)	37	53	126	177	21	22	16	24	101	132
THPAM (1500)	39	62	128	162	24	24	14	30	106	149
THPAM (5000)	38	51	97	156	21	24	14	26	110	128
DMSO (0.1mL)	44	56	149	181	24	27	15	27	114	116
2-nitrofluorene (2)	541	-	-	-	-	-	-	-	-	-
Benzo[a]pyrene (5)	-	136	-	-	-	-	-	107	-	-
Sodium azide (2)	-	-	1153	-	1115	-	-	-	-	-
2-aminoanthracene (5/10)	-	-	-	1240	-	262	-	-	-	526
9-aminoacridine (50)	-	-	-	-	-	-	505	-	-	-
4-nitroquinolone-1-oxide (2)	-	-	-	-	-	-	-	-	922	-

Conclusions: THPAM showed no mutagenic activity in the presence or absence of S-9 mix in any bacterial system at any concentration.

5.8.1/02

Report: Chaudhry, Q. (2005). Assessment of the activity, toxicity and mutagenicity potential of THPI and THPAM, using structure activity relationships. Central Science Laboratory, unpublished report dated 4 February 2005.

Guidelines: Not applicable.

GLP: No.

Material and methods: Captan, THPI and THPAM were evaluated for their potential for activity, toxicity and mutagenicity using a Structure Activity Relationship (SAR) approach. The technique, referred to as Deduction of Risk from Existing Knowledge (DEREK), uses specialist software 'DEREK for Windows' (DfW) developed by Llhasa Ltd. The software works by matching structural entities in a query structure with structural alerts that are associated with different toxicity endpoints (toxicophores). A structural alert is the set of structural features in a molecule that makes a toxicologist suspect that the substance may show a particular toxic effect. DfW can predict alerts for carcinogenicity, irritation (e.g. of the skin, eye and gastrointestinal tract), genotoxicity, respiratory sensitisation, skin sensitisation, thyroid toxicity and a range of miscellaneous effects for bacteria and a range of mammalian species including man. The programme used 482 structural alerts associated with the different endpoints.

DfW also predicts the likelihood of each effect using descriptive terms ranging from 'certain' to 'impossible' ('certain', 'probable', 'plausible', 'equivocal', 'doubted', 'improbable', 'impossible'), or 'open' or 'contradicted' in the case of findings where there is a prediction both that the proposition is true and that it is false.

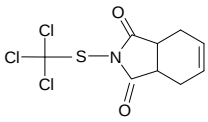
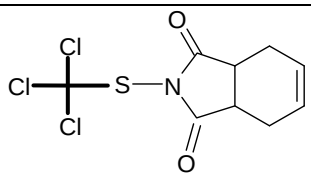
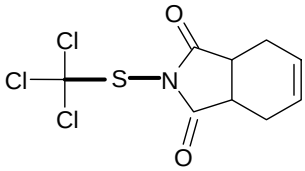
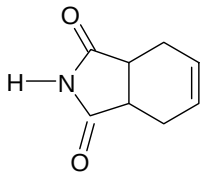
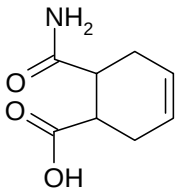
Findings:

DfW predicted that captan will exhibit mutagenicity in bacteria in vitro based on the presence of potentially labile halogen and skin sensitisation based on the thiol or thiol exchange agent. There were no structural alerts in THPI or THPAM.

These predictions are supported by experimental evidence which has demonstrated that captan is a skin sensitiser and can show mutagenicity in vitro.

The results are summarised in **Table 5.8.1-3**

Table 5.8.1-8: Structural alerts and DFW predictions for captan, THPI and THPAM

Test compound and structure	Description of alerts found	Endpoint	Species	Location of alert in molecule (in bold)	Likelihood of predicted effect
Captan 	potential labile halogen	mutagenicity (*in vitro*)	bacteria		plausible
	thiol or thiol exchange agent	skin sensitisation	guinea pig, hamster, human, mouse, primate, rat		plausible
THPI 	none	-	-	-	-
THPAM 	none	-	-	-	-

Conclusions: Computer predictions using DfW indicate that the captan metabolites THPI and THPAM are not expected to exhibit the same fungicidal activity as captan or to exhibit mutagenic activity, genotoxicity, irritation, sensitisation or thyroid toxicity.

5.8.1/03

Report: Anon (1999). THPAM. Bioassay of captan and metabolites against Venturia and Botrytis. Royal Research Station of Gorsem, unpublished report (Company file: R-11094).

Guidelines: None.

GLP: No.

Material and methods: Captan (lot no. ASJ10097-01S), THPI (lot no. ASW01685-01A) and THPAM (lot no. ASW1584R) were dissolved in acetone and added to agar media at a range of concentrations. Activity of the compounds was tested against two fungal species (*Botrytis*

cinerea and *Venturia inaequalis*) isolated from field populations in two tests: (1) to measure spore germination and (2) to measure mycelial growth. Two Petri-dishes were prepared per compound/concentration/species/test.

For the spore germination test, 100 µL of suspension containing 150,000 conides/mL (concentration assessed by haemocytometer) was spread over the agar plates containing malt extract agar and test compound at 0 (untreated), 0 (acetone only), 1, 5, 25, 50 and 100 mg/L and incubated. Germination was assessed for four times 50 conides on two agar plates for each concentration after 24 hours (*B. cinerea*) or 48 hours (*V. inaequalis*).

For the mycelial growth test, two 5 mm agar plugs from a fresh growing colony were transferred to agar plates containing the same concentrations as for the spore germination test and incubated at 20˚C. The colony diameters were measured five days (*B. cinerea*) or 19 and 44 days (*V. inaequalis*).

Findings:

There was strong inhibition of germination with captan at concentrations of 1 mg/L and above (*B.cinerea*) and at 5 mg/L and above (*V. inaequalis*) compared to untreated and acetone only controls. At 25 mg/L and above germination of both fungal species was prevented (Table 5.8.1-4). THPI and THPAM had no effect on the germination of either species at 100 mg/L.

Captan at 25 mg/L and above gave total inhibition of mycelial growth of *B.cinerea* and there was a slight effect at lower doses. THPAM had no effect on mycelial growth of *B.cinerea* at any concentration compared to untreated and acetone only controls. THPI gave a slight reduction in mycelial growth (approximately 35% reduction) at 25, 50 and 100 mg/L compared to controls. Captan at 25 mg/L and above also inhibited mycelial growth of *V.inaequalis* after 19 and 44 days. THPAM and THPI had no effect on mycelial growth of *V.inaequalis* at any concentration compared to untreated and acetone only controls though the assessments for THPAM at 100 mg/L were obscured by the growth of other organisms on the agar plate (Table 5.8.1-5).

Table 5.8.1-9: Effect of treatments on conidial germination

Test substance (mg/L)	Length of germination tube for 50 conides (mean of 4 replicates)									
	B. cinerea					***V. inaequalis***				
	RR	**R**	**r**	**s**	**0**	**RR**	**R**	**r**	**s**	**0**
Untreated	38.5	-	-	-	115	49.3	-	-	-	0.8
Acetone only	39.0	-	-	-	11.0	48.8	-	-	-	1.3
Captan (1)	-	-	38.0	-	12.0	49.5	-	-	-	0.5
Captan (5)	-	-	-	10.8	39.3	-	44.5	-	-	5.5
Captan (25)	-	-	-	-	50.0	-	-	-		50.0
Captan (50)	-	-	-	-	50.0	-	-	-	-	50.0
Captan (100)	-	-	-	-	50.0	-	-	-	-	50.0
THPI (100)	38.8	-	-	-	11.3	49.3	-	-	-	0.8
THPAM (100)	38.5	-	-	-	11.5	49.3	-	-	-	0.8

RR, R , r, s, 0 = classes of germination tube length

Table 5.8.1-10: Effect of treatments on mycelial growth

Test substance (mg/L)	Mycelial growth (diameter in mm; mean of 4 replicates)		
	B. cinerea	***V. inaequalis***	
	5 days incubation	**19 days incubation**	**44 days incubation**
Untreated	67.0	14.0	29.5
Acetone only	57.5	14.5	32.5
Captan (1)	59.3	12.5	24.0
Captan (5)	49.8	11.5	26.0
Captan (25)	5.0	5+	16.8
Captan (50)	5.0	5.0	12.8
Captan (100)	5.0	5.0	9.0
THPI (1)	64.0	11.3	20.5
THPI (5)	50.5	12.5	28.0
THPI (25)	35.5	11.5	25.8
THPI (50)	39.5	13.8	28.0
THPI (100)	39.3	13.3	25.8
THPAM (1)	60.3	13.3	23.5
THPAM (5)	53.3	13.0	25.3
THPAM (25)	52.8	13.3	26.0
THPAM (50)	59.5	13.3	25.3
THPAM (100)	58.0	13.0	-*

* Growth could not be measured due to growth of other organisms.
5 = no growth
5+ = light growth

Conclusions: Captan showed marked activity against *B.cinerea* and *V. inaequalis* at a concentration of 25 mg/L and above, preventing germination and inhibiting mycelial growth. Lower doses of captan also affected germination. In contrast, THPAM and THPI showed no or negligible activity on either species at any concentration up to 100 mg/L.

5.8.1/04

Report: Gordon, E. (2005). Captan. Toxicological significance of relevant degradates. Makhteshim, unpublished report dated April 8, 2005.

Guidelines: Not applicable.

GLP: Not applicable.

Material and methods: The discussion paper expands on the discussion of the toxicological significance of the degradates of captan.

Findings:

The degradates of captan should not be included in the residue expression, as defined by the Guideline:

-Their basic toxicology

The physical and chemical properties of a chemical determine the nature and severity of effects in mammals. Captan has an active moiety that is responsible both for its fungicidal properties and its toxicological effects in mammals. The degradate THPI and THPI's metabolites lack this active moiety and thus have

a spectrum of effects distinct from their parent. These degradates are not acutely toxic, are not developmental or reproductive toxins, are not mutagenic, are not carcinogenic, and do not exhibit any relevant systemic long term or sub-chronic toxicity.

The absence of significant toxicity is reflected in a Structure Activity Relationship (SAR) analysis for the degradates of captan (Chaudhry 2005). Where predictions could be made (i.e., where similar molecules/functional groups existed in the database with associated toxicity), low potential for mutagenicity and carcinogenicity were calculated. Interestingly, the SAR analysis did predict mutagenicity for captan in the Ames Assay, providing some sense of validation for the analysis as captan is an *in vitro* mutagen but not mutagenic in vivo (Chaudhry 2005).

-Their presence in significant amounts
The definition of "significant amounts" is not clear in the guideline; however, THPI is only present as a minor residue in the environment. THPI, along with its metabolites are the main ring associated residues in mammals administered captan, but the expected amounts in livestock are judged not significant.

The toxicology of captan is based on its reactive trichloromethylthio side chain that reacts rapidly with thiol groups, destroying captan and, in the process, producing thiophosgene, itself a highly reactive compound. Thiophosgene reacts not only with thiol groups but a whole host of other functional groups. The half-life of these compounds in human blood reflects their reactivity: captan has a half-life of 0.9 seconds (Gordon, Mobley et al. 2001) and thiophosgene has a half-life of 0.6 seconds (Dohn and Arndt 2004).

The degradates/metabolites of captan lack the reactive sites present on the parent. Since the chemical properties govern in large measure the toxicity of compounds, it is not surprising that the toxicity of the degradates/metabolites of captan are essentially innocuous in comparison to the parent.

On plants, as noted in plant metabolism studies, the main residue is the parent compound; in animals, the parent is completely degraded, except where high oral doses are administered leading to some appearance in the faeces.

In animals, residues of captan are absent and are replaced by a variety of ring-based compounds generated from THPI, which are then excreted.

Since the main plant residue is captan and captan is the species that confers toxicity, it is concluded that the residue expression should be restricted to captan only.

The main animal residue is a collective of THPI-based molecules and do not confer toxicity that is considered toxicologically significant. None of these degradates or metabolites are judged candidates for inclusion in the residue expression.

The suggestion that THPI-based compounds be included in the residue definition since *they occur* in instances where the parent, captan, has been degraded (e.g., certain animal products) reflects a desires to *measure something*, regardless of the toxicological significance of the analyte. In truth, while the captan degradates or metabolites might provide some measure of 'exposure,'[17] its main metabolites do not meet the criteria for inclusion as part of the residue definition.

[17] That is, measurements of THPI-based compounds would reflect the fact that captan had been applied some time in the past. Quantifying these THPI-based compounds would not, however, provide a

Conclusions: The collective data on captan degradates shows that the appropriate residue definition for captan is the parent molecule, only. This is in conformity with the JMPR (FAO/WHO 2000) and US-EPA. This is in conformance with the DG SANCO Guideline (European Commission 1997):

-Residues are expressed as parent compound if there are no metabolites or if the metabolites are known to be of no toxicological significance.

The metabolites present a significantly lower hazard to man than captan, evidenced by the complete lack of systemic toxicity observed in the captan long term and subchronic toxicity studies. In addition, direct comparisons of captan and THPI aquatic toxicity further reinforces the differences due primarily to its mode of action as a primary irritant. Key to resolving the differences in toxicity between captan, THPI and other systemically circulating THPI-metabolites is the exceptionally rapid degradation of captan in the presence of blood. As such, all systemic toxicity observed in captan studies is attributed to the metabolites along with secondary effects of captan's irritation of the GI tract.

The residue expression for captan in plants, processed plant commodities and animal products is captan alone.

RMS comments

For *row crops* THPI and THPAM represent only a minor part of the residue. The residue definition, for risk assessment and monitoring, should be therefore captan alone.

During processing, heating convert captan to THPI . Therefore in *processed commodities* for monitoring, residue definition should include captan plus THPI, expressed as captan equivalents, while for risk assessment only captan, since THPI is of low toxicological concern (new information provided by the MDS seems to confirm that the captan metabolite THPI is of low toxicological concern, compared to the parent compound captan). Accepting this view, residue definition in processed commodities should be therefore captan for Risk Assessment and captan plus THPI, expressed as captan equivalents, for monitoring.

In *animal commodities*, levels of parent captan are below the LOD since captan is rapidly converted to intermediate like THPI, THPI epoxide, 3-OH THPI and 5-OH THPI, that are subsequently incorporated into natural products. There is no evidence that they could be of toxicological concern and new information provided by the MDS seems to confirm that some captan metabolites (THPI, THPAM) are of low toxicological concern, compared to the parent compound. Moreover, after captan administration to lactating goats, only about 1-1.5% of the dose is retained in tissues and 2% in milk.

For residue definition in animal commodities we see three possibilities:

1) no needs for residue definition

validated estimate of how much captan had been applied. These compounds remain not relevant of human risk assessment following captan agricultural use.

2) sum of THPI, THPI epoxide, 3-OH THPI and 5-OH THPI (expressed as captan equivalents? And only for monitoring?)
3) the most abundant metabolite, 3-OH THPI ? (expressed as captan equivalents? And only for monitoring?).

This is open to discussion.

Evaluation table number	Reporting table number	Open Point number
-	**3(11)**	**3.9**

Conclusions of the EFSA Evaluation Meeting:
MSs to discuss the reliability of the residue of 8.0 mg/kg in pome fruits in an expert meeting.

- **Point IIA, 6.3: Residue trials (pome fruit)**

A MRL of 5 mg/kg for pome fruit has been proposed based on the results of supervised residue trials in apples and pears. The results used exclude the result of 8 mg/kg from the Brignano trial in Italy 2000 (IIA 6.3/12 TMN 0577A) which is out of step with all other residue values in apples and pears in north and south EU (17 observations) which ranged from 0.54 to 4.2 mg/kg.

The MRL of 5 mg/kg is supported by the results of monitoring trials in the EU in 2001 and 2002.

The following new reports are submitted. Both reports are considered together.

6.3/24
Report: Anon (2003). Monitoring of pesticide residues in products of plant origin in the European Union, Norway, Iceland and Lichtenstein. 2001 report. European Commission, published report number Sanco/20/03.

6.3/25
Report: Anon (2004). Monitoring of pesticide residues in products of plant origin in the European Union, Norway, Iceland and Lichtenstein. 2002 report. European Commission, published report number Sanco/17/04.

Guidelines: In-house.
Deviations: Not applicable.

GLP: No.

Material and methods: Products of plant origin were monitored in all countries of the European Union plus Norway, Iceland and Lichtenstein in 2001 and 2002. The monitoring included a co-ordinated monitoring exercise on five commodities, which included apples in 2001 and pears in 2002, following recommendations from the Commission via Commission recommendation 2001/42/EC and 2002/1/EC, respectively. Apples and pears were analysed

for various pesticides including captan. Details of the sampling methods, sample numbers, statistical analysis, methods of analysis used in each country are given in the reports.

Findings:

Various summaries of the results by country, crop, etc., appear in the reports. A summary of all the results for apples in 2001 and pears in 2002 appears in Annex 2 to the reports. The results for captan are summarised below.

A total of 2049 samples of apples and 1034 samples of pears were analysed for captan. Of these, 1634 samples of apples and 912 samples of pears (82.6% of the total) contained no detectable residues. Of the remaining 415 samples of apples and 122 samples of pears, only 1 (0.03% of the total) contained a residue value in excess of 5 mg/kg.

	Apples 2001	**Pears 2002**	**Total (% of total)**
Total number of samples	2049	1034	3083 (100%)
No. samples without residues	1634	912	2546 (82.6%)
No. samples with detectable residues	415	122	537 (17.4%)
No samples at residue level (mg/kg) up to and including:			
0.01	12	16	28 (0.9%)
0.02	49	8	57 (1.8%)
0.05	71	15	86 (2.8%)
0.1	59	14	73 (2.4%)
0.2	82	30	112 (3.6%)
0.5	76	25	101 (3.3%)
1	44	9	53 (1.7%)
2	16	3	19 (0.6%)
5	5	2	7 (0.2%)
10	1	0	1 (0.03%)
20	0	0	0
50	0	0	0
> 50	0	0	0

Conclusions: Monitoring data show that residues of captan were non-detectable in the majority of samples of apples and pears. 99.97% of the total number of samples contained residues at or below the proposed MRL of 5 mg/kg.

The monitoring results confirm that the result of 8 mg/kg from the Brignano trial in Italy 2000 is out of step with all other residue values in apples and pears in north and south EU. This conclusion is consistent with the conclusion of the RMS that the 8.0 mg/kg value is an outlier.

RMS comments

The 8.0 mg/kg residue on apple was considered an outlier according to EU regulations (EC document 7039/VI/95 EN, Appendix I, 4.1 Elimination of outlier).

The new evidences provided by the MDS (point IIA, residue trials, pome fruit) support this conclusion since the 99.97% of the samples from a two year EU co-ordinated programme of monitoring contained captan residues at or below 5 mg/kg.

This position is open to discussion.

Evaluation table number	Reporting table number	Open Point number
3.4	**3(16)**	**-**

Conclusions of the EFSA Evaluation Meeting:
Clarification of the results of the McKay study on storage stability, providing stability data for captan and THPI separately. If not available new experimental data are required.

- **Point IIA, 6.3: Stability of residues during storage of samples**

The results of the full study with stability data for captan and THPI separately are presented below.

In addition, the overall conclusions on the stability of captan residues in apple and tomato during storage of samples are discussed below.

6.3/01

Report: McKay, J.C. (1990) Captan and THPI - Storage stability study: various crops. Chevron unpublished report RR 90-368B (Company file: R-4785/TMN-0551).

Guidelines: USEPA 171-4. Deviations: None.

GLP: No.

Material and methods:
Crop commodities were fortified with known amounts of captan and THPI. Other samples were taken from field crops which had been sprayed with captan. Three separate studies were done. In studies 1 and 2, samples were macerated prior to storage. In study 3, whole crop samples such as tomato fruit were ground rather than macerated prior to storage. Captan and THPI were added after maceration to the fortified samples. The samples were stored at -20°C ± 10°C and analysed at intervals for captan and THPI by gas chromatography.

Findings:
The report gives results for a wide range of crop commodities. Only those relevant to the EU GAP are considered in this summary.

Following freezer storage, there was no significant degradation (i.e. less than 30% as defined by Commission Working Document 7032/VI/95 rev 5) of captan in apple commodities stored for at least 14 months (fruit), 15 months (juice) and 9.5 months (sauce). Captan residues were stable following freezer storage in tomato commodities for at least 9/9.5 months (fruit, sauce, pomace). Captan residues were stable following freezer storage in grape pomace for at least 9.5 months. Grapes are not included in the EU GAP but the results on grape pomace and tomato pomace can be extrapolated to apple pomace. Similarly, the results on apple juice can be extrapolated to tomato juice. The captan results are summarised in Table 6.3-1.

In one test using incurred residues, captan residues degraded in tomato fruit after the initial measured value. In this test, fruit samples were macerated prior to storage and this allowed the captan which would normally be on the outside of the fruit to come into contact with enzymes and juice inside the fruit and to degrade to THPI by hydrolysis (hydrolytic half life of captan is 2.6 hours at pH 7 to 11 hours at pH5). Levels of THPI increased after the initial measured value correspondingly (see Table 6.3-2). Similar results were not observed in macerated apple

fruit containing incurred captan residues and this can be attributed to the substantially lower water content of apples compared to tomato. In the test on tomato fruit with fortified captan residues, samples were ground sufficient for sampling prior to storage which conforms more closely to the process used when analysing residue samples from supervised trials. Under these conditions, captan was stable in fruit stored in the freezer for at least 9.5 months.

There was no significant degradation of THPI in apple and tomato commodities or grape pomace stored for the same period as those used to determine captan. In tomato fruit in one test with incurred residues, levels of THPI increased due to hydrolysis of captan during maceration (see above). The THPI results are summarised in Table 6.3-2.

Table 6.3-1 Stability of captan residues in crops following freezer storage

Crop commodity	Origin of residue / Treatment prior to storage	Storage time (months)	Captan residue (mg/kg)	Percentage of initial value
Apple fruit	Incurred / macerated	0	2.65	100
		3	2.75	104
		6	2.8	106
		14	2.9	109
Apple fruit	Fortified / coarsely ground	0	0.519	100
		1	0.41	79
		3	0.388	75
		6	0.382	74
		9.5	0.434	84
Apple juice	Fortified / stirred	0	0.413	100
		1	0.413	100
		3	0.579	140
		6	0.477	115
		15	0.309	75
Apple sauce	Fortified / stirred	0	0.47	100
		1	0.401	85
		3	0.369	79
		6	0.370	79
		9.5	0.348	74
Tomato fruit	Incurred / macerated	0	0.880	100
		1	0.404	46
		3	0.300	34
		6	0.283	32
		12	0.136	15
		20	0.147	17
Tomato fruit	Fortified / coarsely ground	0	0.461	100
		1	0.378	82
		3	0.376	82
		6	0.380	82
		9.5	0.396	86
Tomato dry pomace	Fortified / coarsely ground	0	0.433	100
		1	0.418	97
		3	0.378	87
		6	0.364	84
		9	0.378	87
Tomato sauce	Fortified / stirred	0	0.418	100
		1	0.508	122
		3	0.435	104
		6	0.422	101
		9.5	0.358	86
Grape dry pomace	Fortified / coarsely ground	0	0.406	100
		1	0.347	85
		3	0.408	100
		6	0.376	93
		9.5	0.374	92

Table 6.3-2 Stability of THPI residues in crops following freezer storage

Crop commodity	Origin of residue / Treatment prior to storage	Storage time (months)	THPI residue (mg/kg)	Percentage of initial value
Apple fruit	Incurred / macerated	0	0.095	100
		3	0.11	116
		6	0.12	126
		14	0.13	137
Apple fruit	Fortified / coarsely ground	0	0.417	100
		1	0.436	105
		3	0.400	96
		6	0.360	86
		9.5	0.487	117
Apple juice	Fortified / stirred	0	0.24	100
		1	0.26	108
		3	0.148	62
		6	0.145	60
		15	0.28	117
Apple sauce	Fortified / stirred	0	0.426	100
		1	0.371	87
		3	0.363	85
		6	0.417	98
		9.5	0.380	89
Tomato fruit	Incurred / macerated	0	0.089	100
		1	0.215	242
		3	0.248	279
		6	0.348	391
		12	0.338	380
		20	0.298	335
Tomato fruit	Fortified / coarsely ground	0	0.373	100
		1	0.422	113
		3	0.462	124
		6	0.427	114
		9.5	0.418	112
Tomato dry pomace	Fortified / coarsely ground	0	0.426	100
		1	0.381	89
		3	0.400	94
		6	0.392	92
		9	0.379	89
Tomato sauce	Fortified / stirred	0	0.411	100
		1	0.384	93
		3	0.529	129
		6	0.457	111
		9.5	0.394	96
Grape dry pomace	Fortified / coarsely ground	0	0.421	100
		1	0.361	86
		3	0.431	102
		6	0.378	90
		9.5	0.408	97

Conclusions: Captan residues were stable in apple and tomato commodities and grape pomace following storage at -20°C for 9 to 15 months.

- **Overall conclusions on the stability of captan residues in apple and tomato during storage of samples**

The critical residues data used to propose MRLs for apple and tomato was based on samples from residue trials which had been stored in the freezer prior to analysis. Apple samples were stored for up to 11 months and tomatoes were stored for up to 5 months. Freezer storage stability data have demonstrated that residues of captan are stable when stored for at least 14 months in apple fruit and for at least 9.5 months in tomato fruit. Therefore, no degradation is expected to have occurred during storage and all the trials in apple and tomato are validated by the freezer storage data.

Processed samples of apple and tomato were also stored in the freezer prior to analysis. The maximum period of storage in the various studies included in the DAR was as follows:

Study	Commodities	Maximum storage period (months)
6.5.2/01 (Company file: R-9077).	Apple juice, puree, dried fruit	5 months
6.5.2/02 (Company file: R-7784).	Apple juice, sauce	7 months
6.5.2/03 (Company file: R-4410/ TMN-0567	Apple pomace, juice	< 1 month
6.5.2/04 (Company file: R-7058/TMN-0570).	Apple sauce, juice	14 months
	Apple pomace	10 months
6.5.2/05 (Company file: R-7588/TMN-0572	Apple sauce, juice, pomace, dried fruit	12 months
6.5.2/06 (Company file: R-4410/TMN-0691)	Tomato pomace, puree, juice, ketchup	4 months
6.5.2/07 R A3154 (New data submitted September 2004)	Tomato pomace, juice, puree, peeled fruit, canned fruit, ketchup	5 months
6.5.2/08 R A3156 (New data submitted September 2004)	Tomato juice, canned fruit, puree, ketchup	5 months

Freezer storage stability data have demonstrated that residues of captan are stable when stored for 15 months in apple juice, 9.5 months in apple sauce (puree), 9.5 months in apple pomace (based on extrapolation from data on grape and tomato pomace), for 9/9.5 months in tomato pomace and tomato sauce (ketchup) and for 15 months in tomato juice (based on extrapolation from data on apple juice). All commodities were stored for less than the maximum period tested in all the available storage studies except for apple sauce in study 6.5.2/04 and 6.5.2/05 and apple pomace in study 6.5.2/05. No degradation is expected to have occurred during storage and the processing studies in apple and tomato are validated by the freezer storage data.

RMS comments

New evidences provided by the MDS seem to confirm storage stability of captan in the crops investigated: 14 months in apple fruit, 9.5 months in tomato fruit (not macerated) 15 months in apple juice, 9.5 months in apple sauce, 9 months in tomato pomace, 9.5 months tomato sauce (ketchup).

Evaluation table number	Reporting table number	Open Point number
-	**3(30)**	**3.13**

Conclusions of the EFSA Evaluation Meeting:
RMS to include calculations of the potential exposure of animals by consumption of apple pomace in an addendum to be considered in expert meeting.

- **Point IIA, 6.4: Livestock feeding studies**

Dietary Burden Calculation

Captan is recommended in pome fruit, tomatoes and peaches/nectarines. Fruit pomace (apple) can be used for cattle feed at a maximum of a 10% of the diet in dairy cattle and a 30% of the diet in beef cattle.

Captan is not recommended on any crops which are fed to hens or pigs and so feeding studies in hens or pigs are not required.

The potential dietary exposure of dairy and beef cattle to captan is calculated below based on a worst-case (using the MRL) and a more realistic case (using the STMR) according to Commission Working Document 7031/VI/95 rev 4 of 22 July 1996.

Worst-case calculation

Based on a MRL of 5 mg/kg for apple and a mean transfer factor of 1.1 in apple pomace (= 5.5 mg/kg), the maximum residue concentration for captan in feed of beef cattle is 107.8 mg captan/animal/day (Table 6.4-1). This gives an estimated worst-case daily feeding rate of 7.2 mg captan/kg diet (107.8/15), assuming 15 kg as the daily intake of dry matter for cattle of 350 kg body weight, or 0.31 mg/kg bw /day (107.8/350). The maximum dietary concentration is 5.5 mg captan/kg fresh diet (107.8/19.6).

For dairy cattle, the maximum residue concentration for captan in feed is 47.9 mg captan/animal/day (Table 6.4-1). This gives an estimated worst-case daily feeding rate of 2.4 mg captan/kg diet (47.9/20), assuming 20 kg as the daily intake of dry matter for cattle of 550 kg body weight, or 0.09 mg/kg bw /day (47.9/550). The maximum dietary concentration is 5.5 mg captan/kg fresh diet (47.9/8.7).

Table 6.4-1: Worst-case Calculation of Captan Dietary Exposure Level in Cattle

Animal/Crop	% Dry Matter	% Diet Contribution (dry weight)	Intake of Dry Matter (kg/animal /day)	Intake of Fresh Material (kg/animal/ day)	Captan Residue (mg/kg)	Captan Intake (mg/animal/day)
Beef cattle/ Apple	23	30	4.5	19.6	5.5	107.8
Dairy cattle/ Apple	23	10	2.0	8.7	5.5	47.9

Realistic calculation

Based on a STMR of 1.7 mg/kg for apple and a mean transfer factor of 1.1 in apple pomace (= 1.87 mg/kg), the maximum residue concentration for captan in feed of beef cattle is 33.3 mg captan/animal/day (Table 6.4-2). This gives an estimated worst-case daily feeding rate of 2.2 mg captan/kg diet (33.3/15), assuming 15 kg as the daily intake of dry matter for cattle of 350 kg body weight or 0.09 mg/kg bw /day (33.3/350). The maximum dietary concentration is 1.7 mg captan/kg fresh diet (33.3/19.6).

For dairy cattle, the maximum residue concentration for captan in feed is 16.2 mg captan/animal/day (Table 6.4-2). This gives an estimated worst-case daily feeding rate of 0.81 mg captan/kg diet (16.2/20), assuming 20 kg as the daily intake of dry matter for cattle of 550 kg body weight or 0.03 mg/kg bw /day (16.2/550). The maximum dietary concentration is 1.9 mg captan/kg fresh diet (16.2/8.7).

Table 6.4-2: More Realistic Calculation of Captan Dietary Exposure Level in Cattle

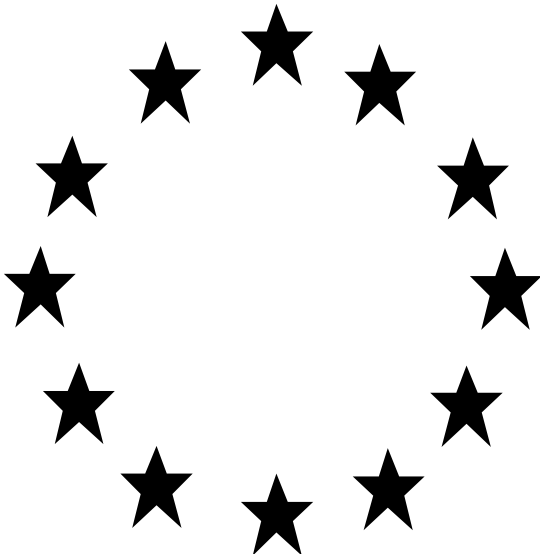
Animal/Crop	% Dry Matter	% Diet Contribution (dry weight)	Intake of Dry Matter (kg/animal /day)	Intake of Fresh Material (kg/animal/ day)	Captan Residue (mg/kg)	Captan Intake (mg/animal/day)
Beef cattle/ Apple	23	30	4.5	19.6	1.43	33.3
Dairy cattle/ Apple	23	10	2.0	8.7	1.43	16.2

In metabolism studies in goats, captan was administered at a dietary concentration of 50 mg/kg of diet for seven days and only 1-2% of the administered radioactivity was detected in animal tissues and milk; no parent captan was found in milk and tissues. The dietary concentration in the study was approximately 7 times the worst-case dietary burden (based on the MRL) and 26 times the realistic dietary burden (based on the STMR) for beef cattle, and approximately 21 times the worst-case dietary burden (based on the MRL) and 81 times the realistic dietary burden (based on the STMR) for dairy cattle.

New references, by Annex point

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
IIA, 6.3/01	McKay, J.C.	1990	Captan and THPI - Storage stability study: various crops. Chevron Report RR 90-368B. (Company file: R-4785/TMN-0551). Not GLP, Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 6.3/24	Anon	2003	Monitoring of pesticide residues in products of plant origin in the European Union, Norway, Iceland and Lichtenstein. 2001 report. European Commission, report number Sanco/20/03. Not GLP, Published.	N	-
IIA, 6.3/25	Anon	2004	Monitoring of pesticide residues in products of plant origin in the European Union, Norway, Iceland and Lichtenstein. 2002 report. European Commission, report number Sanco/17/04. Not GLP, Published.	N	-
IIA, 6.5.1./01	Goodyear, A.P.	2004	Captan. Position paper. Effects on the Nature of the Residue. TSGE report July 2004. Not GLP, Unpublished.	N	Makhteshim/ Arysta Paris
IIA, 6.5.2./07	Faessel, V. Perret, E. Volle, C	2004b 2004a 2004a	Residue study in and on tomatoes following 4 applications of the test item Malvin WG. Anadiag report R A3154. GLP, Unpublished. Residue study in and on tomatoes following 4 applications of the test item Malvin WG. Viti RD, unpublished report FRC 0301 ARS. GLP, Unpublished. Residue study in and on tomatoes following 4 applications of the test item Malvin WG. Viti R&D study plan FRC 0301 ARS and Viti R&D Processing Phase Plan No. TOM 0301 ARS.	Y	Arysta Paris
IIA, 6.5.2./08	Faessel, V. Perret, E. Volle, C	2004c 2004b 2004b	Residue study in and on tomatoes following 4 applications of the test item Malvin WG. Anadiag report R A3156. GLP, Unpublished. Residue study in and on tomatoes following 4 applications of the test item Malvin WG. Viti RD, unpublished report FRC 0302 ARS. GLP, Unpublished. Residue study in and on tomatoes following 4 applications of the test item Malvin WG. Viti R&D study plan FRC 0302 ARS and Viti R&D Processing Phase Plan No. TOM 0302 ARS.	Y	Arysta Paris

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
IIA, 5.8.1./01	May, K.	2005	THPAM. Bacterial reverse mutation test. Huntingdon Life Sciences, unpublished report MAK 857/052225 (Company file: R-18026). GLP, Unpublished.	Y	Makhteshim
IIA, 5.8.1./02	Chaudhry, Q.	2005	Assessment of the activity, toxicity and mutagenicity potential of THPI and THPAM, using structure activity relationships. Central Science Laboratory, report dated 4 February 2005. Not GLP, Unpublished	Y	Makhteshim
IIA, 5.8.1./03	Anon	1999	THPAM. Bioassay of captan and metabolites against Venturia and Botrytis. Royal Research Station of Gorsem, report (Company file: R-11094). Not GLP, Unpublished	Y	Makhteshim
IIA, 5.8.1./04	Gordon, E.	2005	Captan. Toxicological significance of relevant degradates. Makhteshim, report dated April 8, 2005. Not GLP, Unpublished.	N	Makhteshim



Final addendum to the

Draft Assessment Report (DAR)

- public version -

Initial risk assessment provided by the rapporteur Member State Italy for the existing active substance

CAPTAN

of the second stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC

part 2

January 2006

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Addendum
to the Draft Assessment Report

CAPTAN
Volume 3 **B.2, B.5**

May 2005

Rapporteur Member State: Italy

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.

Introduction

This document contains new information on identity, physical and chemical properties, details of uses and further information, and methods of analysis submitted by Makhteshim Chemical Works Ltd. and Arysta Paris to the RMS.

New information is presented here in the order of the Evaluation table for captan, cross-referencing the Open point numbers and Reporting table numbers. New information is summarised under the dossier numbering system.

Document D1: Critical Good Agricultural Practice

The GAP for peaches/nectarines is changed: the PHI is increased from 7 days to 21 days. No other changes have been made. The amended GAP is presented in the table below.

Critical Good Agricultural Practice for captan in the EU

Crop	Member state or country	Product name	F, G or I	Pests or group of pests controlled	Formulation		Application			Application rate per treatment			PHI (days)	Remarks:
					Type	Conc. of a.s.	method kind	growth stage/ timing	number[b] (max.)	kg a.s./hL (max.)	water L/ha	kg a.s./ha (max.)		
Pome fruit	North EU	'Merpan' 80 WDG / 'Malvin' WDG	F[a]	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 53 / April	9 - 10	0.125	1000	1.25	14	
	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69 / April	9 + 3 [c]	0.125 0.24	1000 1000	1.25 2.4	14	
Tomatoes	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Foliar spray; down-wards	From BBCH 60 to 87	4	0.15	1200	1.8	14	
Peaches/ nectarines	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69: petal fall	4	0.25	1000	2.5	21	

[a] F = field.
[b] Applications at a minimum of 7 days for all crops.
[c] Nine applications at 1.25 kg a.s./ha (scab control) followed by three applications at 2.4 kg a.s/ha (*Nectria* control).

- **Point IIA 2.1.2 Boiling point**
- **Point IIA 2.1.3 Decomposition or sublimation temperature**

Evaluation table number	Reporting table number	Open Point number
1.1	**1(13)**	**1.5**

Conclusions of the EFSA Evaluation Meeting:
Data regarding the boiling point or temperature of decomposition must be provided according to Directive 94/37/EC.

The following new information has been provided by Makhteshim:

Test or study & Annex point	Guideline and method	Test material and purity specification	Findings	Comments	GLP Y/N	Reference
Boiling point (IIA 2.1.2)	Test substance decomposes below its boiling point – See Annex point IIA 2.1.3					
Decompo-sition or sublimation temperature IIA 2.1.3/01	EEC A.2 OECD 103	214-49 98.9%	The test substance decomposed on melting starting at 173°C.	-	Y	Turner, 2005

Conclusions: Study acceptable. Data requirement addressed.

- **Point IIA 2.5.2 UV/VIS, IR, NMR, MS spectra of relevant impurities**

Evaluation table number	Reporting table number	Open Point number
1.4	**1(28)**	**--**

Conclusions of the EFSA Evaluation Meeting:
Spectra of relevant impurities have to be provided according to Directive 94/37/EC.

The following new information has been provided by Makhteshim (the spectra summary is reported into the amended Makhteshim Doc J.):

Test or study & Annex point	**Guideline and method**	**Test material and purity specification**	**Findings**	**Comments**	**GLP Y/N**	**Reference**
UV/VIS, IR, NMR, MS spectra of relevant impurities (IIA 2.5.2)	Folpet is the only significant impurity					
NMR: (IIA 2.5.2)	-	100-94 99.5%	The spectrum was consistent with the structure of folpet.	Proton NMR spectra in deuterated chloroform solution.	Y	Comb, 2000
Mass spectrum: (IIA 2.5.2)	-	100-194 99.5%	The M+ molecular ion was identified at m/z 295. This and other peaks confirmed the structure of folpet.	Folpet was analysed by GC/MS with EI ionisation	Y	Comb, 2000
Infrared spectrum: (IIA 2.5.2)	-	100-194 99.5%	The spectrum was consistent with the structure of folpet.	Fourier transform infrared spectrometry	Y	Comb, 2000
UV/Visible spectrum: (IIA 2.5.2)	OECD 101	100-194 99.5%	The spectrum was consistent with the structure of folpet.		Y	Comb, 2000

Conclusions: Study acceptable.

- **Point IIA 1.9 Specification of purity of the active substance in g/kg**

Evaluation table number	Reporting table number	Open Point number
-	**1(30)**	**1.8a**

Conclusions of the EFSA Evaluation Meeting:
RMS to clarify for transparency and better comprehensibility the given justification in respect to the given minimum purities of 920 g/kg and 910 g/kg, respectively.

The minimum specification of purity for technical captan is 92.0% for Makhteshim and 91.0% for Arysta Paris.

Details of the purity of the Makhteshim and Arysta Paris active substance are given in Document J now available (Document J Makhteshim updated March 2005 and Document J Arysta).
The given minimum purity provided by Arysta is in accord with the new five-batch analysis reports:
Rose, J.E. (2005) Analysis and certification of product ingredients in five batches of technical grade captan. Unpublished report no. 1262W-2 (Annex IIA, 1.9/01)
Rose, J.E. (2005) Analysis and certification of product ingredients in five batches of technical grade captan. Confidential business information supplement. Unpublished report no. 1262W-2 (Annex IIA, 1.9/02).

According to the Document J (updated March 2005), the given minimum purity provided by Makhteshim is 92.0%. Anyway, in a late Document J (updated May 2005), sent by Makhteshim two days before the EPCO meeting 25, the stated minimum purity of the Captan Technical has been increased to 93.0% (see addendum to Vol.4). This is the result of a significant improvement of the manufacturing process over the years which consequently cause the increase of the active ingredient purity. This level is still within the FAO specifications established back in 1990 which is 910 g/kg ±30g.

- **Point IIA 2.11.1 Flammability**
- **Point IIA 2.11.2 Auto-flammability**

Evaluation table number	Reporting table number	Open Point number
-	**1(30)** **1(32)**	**1.8b** **1.9**

Conclusions of the EFSA Evaluation Meeting:
RMS to clarify whether the justification that the two technical materials will not reveal significantly differences in the physical and chemical properties is based on practical experiences or on a theoretical assessment.
and
The need to conduct the studies regarding the flammability and autoflammability with both technical materials should be discussed in an expert meeting

A member state requested that each notifier provide physicochemical data performed on its own technical material. For the tests which are required to be performed on technical material (flammability and auto-flammability) data were provided in the original dossier from the Arysta Paris source. Additional data are presented here from Makhteshim.

Test or study & Annex point	Guideline and method	Test material and purity specification	Findings	Comments	GLP Y/N	Reference
Flammability (IIA 2.11.1)	EEC A.10	60138540 95.1%	Captan technical is not classified as highly flammable in terms of burning characteristics. In the preliminary test, the test substance melted on application of the test flame but failed to ignite.	-	Y	Turner, 2005b
Auto-flammability (IIA 2.11.2)	EEC A.16	60138540 95.1%	Under the conditions of the test, Captan technical does not self-ignite.	-	Y	Turner, 2005b

Conclusions : study acceptable.

Evaluation table number	Reporting table number	Open Point number
-	**1(37)**	**1.10**

Conclusions of the EFSA Evaluation Meeting:
The need for a measurement of the pH value of the in use concentration should be discussed in an expert meeting.

A member state noted that hydrolysis occurs very quickly in solution, particularly at higher pH. The implication of this observation is that working spray dispersions may undergo hydrolysis during use. It has been suggested that the pH of the 'in-use' dilution should be measured to indicate if hydrolysis may occur.

An 'in-use' dilution study is not required because captan has a low solubility and hence the products are formulated as water dispersible preparations, where the active ingredient is presented in the working spray liquor as a dispersed solid. Even for the lowest GAP concentration presented in the dossier (0.125 kg/hL), the solubility of captan is only 0.4% of the dispersed concentration. As hydrolysis is a solution state reaction, under conditions where over 99% of the in-use spray solution remains as a dispersed solid, hydrolysis will not occur to any meaningful extent with regards to the performance of captan. It is not therefore necessary to measure the pH of in-use dispersions.

A study was performed (Pollmann, 2004. Ref. IIIA 2.8.3/01) where the reproducibility of sprayer performance was tested using Merpan 80WDG. The sprayability study results confirm the explanation and demonstrate that the content of Captan in the spray tank remain stable. The report is summarised below.

IIIA 2.8.3/01

Report: Pollmann, B. (2004). Sprayability test with Merpan 80 WDG in a commercial agricultural boom sprayer. GAB, unpublished report 20031377/G1-FPPT (Company file R-16560).

Guidelines: None

GLP: Yes.

Material and methods: Merpan 80 WDG (captan content 808 g/kg), supplied by Makhteshim, batch number 8131041/1, was diluted at a rate of 0.75 kg product in 200 L of water (3.0 g a.s./L). 100 L water was first added to the 400 L spray tank of a commercial boom sprayer and agitation was started. 0.75 kg of formulated product (dissolved in water) was then added to the spray tank followed by the remaining 100 L water. A few drops of antifoam were added.

Samples were taken from the same three spray nozzles before the start of application, at the start of spraying, when the tank was approximately half empty and when the tank was nearly empty. The samples were analysed for captan content (HPLC with photodiodearray detection). The contents of the spray tank were also visually observed.

Findings:
The tank contents remained visually homogeneous. There was no degradation of captan during application. Analytical results are given in the table below:

Sampling time	Mean captan concentration (g/L)
Before application	2.61
Start of application	2.65
Mid application	2.79
End of application	2.46

Conclusions: The spray solution containing captan remained homogenous throughout the spraying operation. There was no change in captan concentration during spraying.
Study acceptable.

- **Point IIIA, 2.7.1: Storage stability after 14 days at 54°C**

Evaluation table number	Reporting table number	Open Point number
-	**1(39)**	**1.11**

Conclusions of the EFSA Evaluation Meeting:
RMS to clarify whether the physical stability (in terms of physical/technical properties) was examined after the accelerated storage.

An accelerated storage stability test was performed on Merpan 80 WDG (Captan 80 WDG). In this study the captan content was measured before and after storage at 54°C for 14 days and the test substance was visually inspected after the accelerated storage for changes in physical characteristics (color, phase separation, crystallization and clumping) and no changes were observed. Although technical properties of the formulated product were not examined in this study, complete data are provided from the ambient shelf life study. These data are adequate to conclude that the technical properties of Merpan 80 WDG do not change significantly during storage.

It should be noted that the accelerated storage study is only performed to provide an indication of and not an evaluation of stability. As stated in GIFAP (CropLife International) Monograph 17, accelerated tests are only performed at elevated temperatures in an attempt to get information on the shelf life of a formulation in a relatively short time. If ambient shelf life studies are available then accelerated data has little value. It should also be noted that in the proposed amendments to 91/414/EEC Point IIIA, 2.7.1, accelerated stability studies are not required if two-year ambient shelf life studies are provided.

- **Point IIIA 2.8.1: Wettability**

Evaluation table number	Reporting table number	Open Point number
1.7	**1(41)**	**-**
Conclusions of the EFSA Evaluation Meeting: ***Notifer to clarify the test conditions to determine the wettability for "Captan 80 WDG".***		
-	**1(49)**	**1.14**
Conclusions of the EFSA Evaluation Meeting: ***EFSA to highlight the concern of wettability of the formulation in its conclusion.***		

A member state noted that for the Malvin formulation, one result for the non-swirled wettability was greater than one minute, which is undesirable. It should be noted that this one result was obtained at the beginning of a 24 month shelf-life study. At the end of the shelf-life study the non-swirled wettability was less than one minute. In addition, the wettability of a similar Captan WG formulation was also reported to be less than one minute. It is concluded therefore that since the wettability was acceptable after storage, the 'before storage' result was anomalous.

- **Sprayability**

Evaluation table number	Reporting table number	Open Point number
-	**1(42)**	**1.12**

Conclusions of the EFSA Evaluation Meeting:
The need for a sprayability study should be discussed in an expert meeting.

A member state noted that for the Merpan 80 WG formulation, the suspensibility was outside the minimum acceptable level after storage, which may affect spray performance and homogeneity. A sprayability study was performed to confirm that the preparation performs acceptably in the field. A study was conducted (Pollmann, 2004. Ref. IIIA 2.8.3/01) where the reproducibility of sprayer performance was tested using Merpan 80WDG.

IIIA 2.8.3/01

Report: Pollmann, B. (2004). Sprayability test with Merpan 80 WDG in a commercial agricultural boom sprayer. GAB, unpublished report 20031377/G1-FPPT (Company file R-16560).

Guidelines: None

GLP: Yes.

Material and methods: Merpan 80 WDG (captan content 808 g/kg), supplied by Makhteshim, batch number 8131041/1, was diluted at a rate of 0.75 kg product in 200 L of water (3.0 g a.s./L). 100 L water was first added to the 400 L spray tank of a commercial boom sprayer and agitation was started. 0.75 kg of formulated product (dissolved in water) was then added to the spray tank followed by the remaining 100 L water. A few drops of antifoam were added.

Samples were taken from the same three spray nozzles before the start of application, at the start of spraying, when the tank was approximately half empty and when the tank was nearly empty. The samples were analysed for captan content (HPLC with UV-DAD detection). The contents of the spray tank were also visually observed.

Findings:
The tank contents remained visually homogeneous. There was no degradation of captan during application. Analytical results are given in the table below:

Sampling time	Mean captan concentration (g/L)
Before application	2.61
Start of application	2.65
Mid application	2.79
End of application	2.46

Conclusions: The spray solution containing captan remained homogenous throughout the spraying operation. There was no change in captan concentration during spraying. Study acceptable.

- **Point IIIA 2.8.6.3: Friability and attrition characteristics**

Evaluation table number	Reporting table number	Open Point number
-	**1(47)**	**1.13**

Conclusions of the EFSA Evaluation Meeting:
The need for further investigation regarding the friability and attrition for "Captan 80 WDG" should be discussed in an expert meeting.

Both Notifiers submitted data on friability and attrition characteristics, but the work was performed before the CIPAC test (MT 178) was widely available to users. The results from both Notifers indicated that both formulated products were resistant to attrition. Makhteshim are now submitting a new study designed to determine the resistance to the attrition of the test substance according to CIPAC MT 178.

IIIA 2.8.6.3/01

Report: Comb, A.L. (2001). Merpan 80 WDG attrition resistance, Huntingdon Life Sciences Ltd., unpublished report MAK651/004810. 12 January 2001.

Guidelines: CIPAC MT 178

GLP: Yes.

Material and methods: Merpan 80 WDG (captan content 814 g/kg), supplied by Makhteshim, batch number 01310002, was sieved to remove fine particles. A portion (50 g) of the granules were accurately weighed into a glass jar to which 50 g of glass beads were added. The jar was stoppered and placed on a horizontal roller and rolled at 100 rpm for 45 minute. The granules were then sieved again to remove fine particles and re-weighed. The attrition resistance is the ratio of the weight of the granules after testing to the weight before, expressed as a %.

Findings:
The attrition resistance was 99.6%.

Conclusions: Merpan 80 WDG is resistant to attrition, confirming the results previously obtained. Study acceptable.

- **Point IIA, 4.2.1: Residues in and/or on plants, plant products, foodstuffs (of plant and animal origin), feedingstuffs**

Evaluation table number	Reporting table number	Open Point number
-	**1(55)**	**1.16, 3.6, 3.7**

Conclusions of the EFSA Evaluation Meeting:
Analytical methods for the determination of residues in food could be required depending on the outcome of the discussion concerning the residue definition and the evaluation of the recently submitted methods.

The following new reports are submitted:

4.2.1/07
Report: Burden, A.N. (2004). Captan . Position paper on residue analytical methods. TSGE, unpublished report April 2004.

Guidelines: Not applicable.

GLP: No.

Material and methods: The DAR volume 1 concludes the following:
Four analytical methods are available for non-oily crops. One of them (Iwata ,1989) is not acceptable; the others have been validated for apples and tomatoes (but not for processed fractions) and require for final acceptance a suitable confirmatory assay.
The DAR volume 1 also concludes that independent laboratory validation and a confirmatory assay are required for residues in animal tissues and milk.
The position paper includes summaries of all the analytical methods, the validation data, a summary of the various chromatographic methods available for determination of captan and the response to the data requirements/deficiencies.

Findings:

Overall validation data available for crop methods:

IIA, 4.2.1/01: This method has been adequately validated for all crops in the critical GAP (apple, tomato and nectarine). The use of a packed gas chromatography column does not indicate that there are problems with specificity. The report provides two sets of chromatographic conditions for captan with two different selective detectors (ECD and NPD). Therefore, any apparent positive residues can be confirmed using the alternative conditions. No specific validation has been carried out for processed fractions. However, based on the good validation data obtained for the different raw agricultural commodities, it is considered that this method will be applicable to processed fractions.

IIA, 4.2.1/02: The method has been adequately validated for two relevant crops (apple and tomato). In addition, comprehensive validation data are available for a range of apple processed fractions (juice, puree, dry pomace, wet pomace, sauce). It is accepted that the validation of processed fractions does not completely meet the current requirements of SANCO/825/00 with respect to the size of sample sets. Current guidance for validation of analytical methods recommends that five replicate recovery values are determined at two concentrations. In this case sample sets are reduced, but a significant amount of acceptable data has been generated to demonstrate the validity of the method. The method was validated

before the current guidance was available, the study design is based on sound analytical principles and is not atypical of validation work carried out at that time. The validation data presented clearly demonstrate that the method is both accurate and precise, and it is considered that any minor deviations in the size of the sample sets compared to the current guidance is not significant. There is no scientific basis on which to reject the results of this method validation study and a pragmatic evaluation will confirm that the requirements of the Commission Directive 96/48/EC, in terms of method validity, have been adequately met and the method presented is suitable for monitoring purposes. Based on the good validation data obtained for apple and tomato raw agricultural commodities, and a wide range of apple processed fractions, it is considered that this method will be applicable to tomato processed fractions and peaches/nectarines. No additional validation work is considered to be necessary.

IIA, 4.2.1/03: The method has been adequately validated for apples. It is accepted, as stated by the report author, that alternative confirmatory conditions are required for unexpected positive results. However, it is not accepted that these conditions must be based on a mass selective detector. See comments below for further considerations of the confirmatory procedures.

IIA, 4.2.1/06: The method has been adequately validated for tomato. See comments below for further considerations of the confirmatory procedures.

Confirmatory procedure:

Firstly, it should be noted that the reports described under IIA, 4.2.1/01 and IIA, 4.2.1/06 do contain additional chromatographic conditions for confirmatory purposes. For the other crop methods, it is considered that residues may be confirmed using the many other chromatographic conditions presented for captan residue determination (other crops, soil, water, air etc.). These methods are based on packed or capillary GC with electron capture, nitrogen specific or mass selective detection using a range of stationary phases of varying polarity, and the various conditions will be sufficient for use in confirmation of captan residues. Therefore, it is considered unnecessary to conduct further work on confirmation when there are numerous existing chromatographic conditions available.

Determination of captan residues in animal products

The report of Tilkes described under Annex Point IIA, 4.2.1/05 was included to demonstrate that the standard multi-residue method DFG S19 is not directly applicable to determination of captan residues in animal products. It is accepted that this method has not been adequately validated.

It is considered that the analytical method described by Mende under Annex Point IIA, 4.2.1/04 has been adequately validated in all respects except that an independent laboratory validation has not been conducted. The comments above regarding confirmation for crop residue methods also apply to animal tissue methods - it is considered that residues may be confirmed using the many other chromatographic conditions presented for captan residue determination (crops, soil, water, air etc.). These methods are based on packed or capillary GC with electron capture, nitrogen specific or mass selective detection using a range of stationary phases of varying polarity, and the various conditions will be sufficient for use in confirmation of captan residues. Therefore, it is considered unnecessary to conduct further work on confirmation when there are numerous existing chromatographic conditions available.

It is considered appropriate to retract the original claim in the dossier that the method is suitable for monitoring purposes. However, further validation work is not required for the following reason. The metabolism studies in the goat demonstrated that significant captan residues did not occur in edible animal tissues following administration of a worst-case dietary concentration. Consequently, MRLs for animal tissues, milk and eggs are not applicable. Therefore, an analytical method for monitoring purposes is not required under these circumstances (as defined by Commission Directive 96/46/EC) and the validity of the methods presented need not be evaluated. The methods presented for determination of captan in animal tissues and milk should be considered as supporting information for the methods dossier and any deficiencies in their validation are irrelevant.

Conclusions: The notifiers conclude that no additional data are necessary to fulfil the Annex point requirement. For animal tissues, it is considered unnecessary to conduct further work or confirmation when there are numerous existing chromatographic conditions available and an analytical method for monitoring purposes is not required due to the lack of residues of captan in edible animal tissues.

Conclusions regarding the methods of analysis for residues in plants and plant products can not be acceptable form an analytical point of view, because none of the submitted methods has been fully validated, and no validated methods have been provided for determination of captan in processed fractions, i.e. commodities with high water content). Regarding the need of analytical methods for food of animal origin, conclusions are acceptable, if no MRLs are proposed. Analytical methods for the determination of residues in food could be required depending on the outcome of the discussion concerning the residue definition.

Evaluation table number	Reporting table number	Open Point number
-	1(55)	1.16

Conclusions of the EFSA Evaluation Meeting:
Analytical methods for the determination of residues in food could be required depending on the outcome of the discussion concerning the residue definition and the evaluation of the recently submitted methods.

The following report is submitted (previously submitted in September 2004) in response to the RMS comment in Reporting Table 1(55).

4.2.1/08

Report: Faessel, V. (2004a). Validation study of the analytical method for the determination of captan and tetrahydrophthalimide (THPI) in tomato processed fractions. Anadiag, unpublished report R A3153.

Guidelines: Not stated in report. However, the study complies with the requirements of EU guidance document SANCO/3029/99.

GLP: Yes.

Material and methods: Residues of captan are extracted by blending the crop samples in the presence of sodium sulphate, ethyl acetate and phosphoric acid. The filtered extract is washed with phosphoric acid solution, evaporated to dryness and reconstituted in dichloromethane. The extract is purified by gel permeation chromatography. Further clean-up and analyte separation is achieved by use of a silica gel column. Determination is by capillary GC/ECD for captan and capillary GC/NPD for THPI.

This method is based on procedures previously presented for the determination of captan in apple raw agricultural commodity (see Point IIA, 4.3.1/03).

Findings:

The method has been validated for application to tomato ketchup and washing water. Validation data for captan in the processed fractions are presented in Table 4.2.1-8.

Specificity: The method was shown to be selective for the determination of captan in the processed fractions. There were no peaks in the control samples that interfered with the determination of the analytes. Alternative gas chromatographic conditions and stationary phases are provided for confirmatory purposes.

Recovery: Recovery was determined at concentrations of 0.02 and 0.20 mg/kg for captan in both representative processing fractions. The overall mean captan recovery from ketchup and washing water was 75 and 86%, respectively. The recovery rates are within the acceptance criteria of 70 to 110% (as defined in the Uniform Principles decision-making criteria).

Repeatability: The recovery ranges of captan from ketchup and washing water at the limit of quantification (0.02 mg/kg) were 71 to 86% and 71 to 105%. The difference in the recovery ranges was 15 and 34%, which are all within the limit of acceptable repeatability as defined in the Uniform Principles decision-making criteria (≤ 41% at 0.02 mg/kg). Overall RSD values were less than 20% which is also indicative of good repeatability.

Limit of quantification: The limit of quantification is 0.02 mg/kg for captan and THPI.

Analyte	Matrix	Fortification level (mg/kg)	Recovery rate (%)		RSD (%)	n	Reference
			mean	range			
captan	tomato ketchup	0.02 [1]	77.1	70.9 – 85.7	7.5	5	Faessel, V. (2004) R A3153
		0.20	72.7	70.2 – 76.3	3.3	5	
		overall	74.9	70.2 – 85.7	6.4	10	
	washing water	0.02 [1]	80.6	75.3 – 88.6	6.8	5	
		0.20	90.5	70.5 – 104.6	17.5	5	
		overall	85.6	70.5 – 104.6	14.4	10	
THPI	tomato ketchup	0.02 [1]	90.2	77.2 – 108.4	13.6	5	
		0.20	88.0	78.5 – 94.7	7.0	5	
		overall	89.1	77.2 – 108.4	10.3	10	
	washing water	0.02 [1]	90.1	75.7 – 105.1	14.5	5	
		0.20	79.0	71.6 – 89.2	10.4	5	
		overall	84.6	71.6 – 105.1	14.0	10	

[1] Limit of quantification, defined by lowest validated fortification level.

Conclusions: The method has been demonstrated to be suitable for generation of pre-registration residue data. The validation data are within the acceptable limits as defined by guidance document SANCO/3029/99. Study acceptable.

- **Point IIA, 4.2.4: Residues in air**

Evaluation table number	Reporting table number	Open Point number
1.10	**1(57)**	**-**

Conclusions of the EFSA Evaluation Meeting:
Notifier to provide a validated analytical method for the determination of residues in air.

The following new report is submitted:

4.2.4/02

Report: Burden, A.N. (2004). Captan . Position paper on residue analytical methods. TSGE, unpublished report April 2004.

Guidelines: Not applicable.

GLP: No.

Material and methods: The DAR volume 1 concludes that for air, validation and a confirmatory method are required.
The position paper includes summaries of all the analytical methods and the validation data for determination of captan and the response to the data requirements/deficiencies.

Findings:

Specificity: As described in the dossier, the specificity of the method has been confirmed using blank samples containing no captan or interferences above 5% of the fortified values.

Linearity: Linearity is not defined as a requirement for residue analytical methods either in the Commission Directive 96/46/EC or SANCO/825/00 guidance document.

Method validation design: The method has been validated by fortification experiments - three replicate recovery values were determined at each of three concentrations. Current guidance for validation of analytical methods (SANCO/825/00) recommends that five replicate recovery values are determined at two concentrations.

The method was validated before the current guidance was available, but the study design is based on sound analytical principles and is not atypical of validation work carried out at that time. The validation data presented clearly demonstrate that the method is both accurate and precise, and it is considered that the minor deviation in the size of the sample set compared to the current guidance is not significant.

Confirmatory procedure
A specific confirmatory assay is not provided in the report. However, residues in air samples may be confirmed using the many other chromatographic conditions presented for captan residue determination in other substrates (crops, soil, water etc.). These methods are based on packed or capillary GC with electron capture, nitrogen specific or mass selective detection using a range of stationary phases of varying polarity, and the various conditions will be sufficient for use in confirmation of captan residues.

Conclusions: The Position paper on residue analytical methods concluded that the requirements of the Commission Directive 96/48/EC, in terms of method validity, have been adequately met and the method presented is suitable for monitoring. It is considered unnecessary to conduct further work on confirmation when there are numerous existing chromatographic conditions available. We disagree: because the previously submitted method (Jones and Freeman, 1994) has not been sufficiently validated, specific studies are still required. Data requirement not addressed.

- **Point IIA, 4.2.3: Residues in water (including drinking water, ground water and surface water**

Evaluation table number	Reporting table number	Open Point number
-	**1(65)**	**1.17** **4.17**

Conclusions of the EFSA Evaluation Meeting:
DT_{90} values must be confirmed by the fate and behaviour section. Provided that the values will be confirmed, an analytical method is not required.
=> ***Discussion in expert meeting (fate and behaviour)***

The following new report is submitted:

4.2.3/05
Report: Burden, A.N. (2004). Captan . Position paper on residue analytical methods. TSGE, unpublished report April 2004.

Guidelines: Not applicable.

GLP: No.

Material and methods: The DAR volume 1 concludes that a fully validated method with a suitable LOQ value for analysis of captan in water is required. The position paper includes summaries of all the analytical methods and the validation data for determination of captan and the response to the data requirements/deficiencies.

Findings:

It is accepted that the two methods for captan have not been shown to be sufficiently sensitive with respect to the EU drinking water limit of 0.1 µg/L. However, it should be noted that these methods are provided as supporting information and are not proposed as monitoring methods.

In fact, monitoring methods are not required for captan. According to the current guidance for residue monitoring methods, SANCO/825/00, a monitoring method for water is not required for an active substance with a DT_{90} in water of less than three days. It has been calculated from the hydrolysis data that the DT_{90} for captan is in the range 8 minutes to 1.3 days depending on pH. The DT_{90} values are newly calculated data which have not been previously submitted.

The hydrolysis degradation rate (DT_{90}) of captan under sterile conditions in aqueous buffer at pH 5, 7 and 9 was calculated using data reported by Pack, D.E, (1987a, Annex Point IIA, 7.2.1.1/01). These data are shown in the following table:

Sampling interval (hours)	Percent of applied radioactivity remaining as captan		
	pH 5	pH 7	pH 9
0	99.30	99.30	99.30
1 minute	-	-	71.82
2 minutes	-	-	43.52
3 minutes	-	-	36.79
5 minutes	-	-	32.16
10 minutes	-	-	11.45
20 minutes	-	-	1.68
1	90.79	71.78	-
2	74.91	-	-
3	72.93	45.64	-
7	-	18.36	-
17	-	1.78	-
24	20.48	-	-

The DT_{90} values were calculated using the Solver function in a Microsoft Excel spreadsheet to find the best fit between the experimental data and the following first order rate equation:

$C_T = C_0 \times \exp^{-KT}$

The line of best fit was determined by minimising the sum of the squares of the residuals between the actual data and the best fit line. This was achieved using the Solver function to change the values of C_0 and K and converge on a minimum value for the sum of the squares of the residuals. The rate constant, K, was then used to determine the DT_{90} value using the expression LN(10)/K.

The results obtained were as follows:

pH	DT_{90}	Co	K	R^2
5	1.3 days	94.418	0.0724	0.973
7	9 hours	97.018	0.2534	0.997
9	8 minutes	95.312	0.2891	0.962

In addition, the results of the water/sediment study described under IIA, 7.2.1.3.2/01, demonstrated that captan was not detectable in the surface water 24 hours after application.

Conclusions: As degradation of captan in water is extremely rapid, it would be practically impossible to monitor the active substance in the aquatic environment. Consequently, a monitoring method is not appropriate for captan. The evidences provided by the MDS seem to confirm that an analytical method is not required.

Evaluation table number	Reporting table number	Open Point number
-	**1(77)**	**1.21**

Conclusions of the EFSA Evaluation Meeting:
RMS to clarify the basis of the assumption that the CIPAC method for WP and DP formulations is also applicable for WG formulations.

A comparison of the composition of captan WP and WG products is presented in the 'confidential from both applicants' Document J. This concludes that water dispersible granules have very similar compositions to wettable powders. They have closely similar active ingredient content, the same wetting/dispersing agents at the same or similar concentrations, and the remaining ingredients are inorganic minerals. The CIPAC technical and WP analytical methods (40/TC/M 3/-, 40/TC/M 4/-, 40/WP/M 3/- or 40/WP/M 4/-) consists of a simple non-aqueous extraction which would be unaffected by the minor differences in composition. It can therefore be assumed that the CIPAC method for WP and DP formulations is also applicable to WG formulations.

- **Point IIA 1.1 Applicant**

Evaluation table number	Reporting table number	Open Point number
-	1(98)	1.22
Conclusions of the EFSA Evaluation Meeting: *For transparency and better comprehensibility, RMS to confirm that the notifier has changed from Tomen to Calliope and in this context to confirm which formulations belongs to which notifier.*		

Change of notifier from Tomen France S.A.S. to Arysta Paris, an affiliate of Calliope S.A.S., as detailed below:

Name:	Arysta Paris, an affiliate of Calliope SAS.
Address:	Route d'Artix, BP 80, 64150 Noguères, France
Contact name:	[redacted]
Contact position:	Registration and Regulatory Affairs Manager
Contact address:	Route d'Artix, BP 80, 64150 Noguères, France
Telephone number:	[redacted]
Telefax number:	[redacted]
e-mail address:	[redacted]
Local company name:	Calliope S.A.S
Local contact:	[redacted]
Local contact position:	National Europe Registration Manager
Local contact address:	Route d'Artix, BP 80, 64150 Noguères, France
Telephone number:	[redacted]
Telefax number:	[redacted]
e-mail address:	[redacted]

- **Point IIA 1.2 Manufacturer (name, address, etc., including location of plants)**

No change compared to original submission.

- **Point IIIA 1.1 Applicant (name, address, etc.)**

Change of notifier from Tomen France S.A.S. to Calliope SAS as detailed below:

Name:	Arysta Paris, an affiliate of Calliope SAS
Address:	Route d'Atrix, BP 80, 64150 Noguères, France
Contact name:	[redacted]
Contact position:	Registration and Regulatory Affairs Manager
Contact address:	Route d'Artix, BP 80, 64150 Noguères, France
Telephone number:	[redacted]
Telefax number:	[redacted]
e-mail address:	[redacted]
Local company name:	Calliope S.A.S
Local contact:	[redacted]
Local contact position:	National Europe Registration Manager
Local contact address:	Route d'Artix, BP 80, 64150 Noguères, France
Telephone number:	[redacted]
Telefax number:	[redacted]
e-mail address:	[redacted]

Change of manufacturer; formally Tomen Agro Inc. to Arvesta Corporation, as detailed below:

Manufacturer name and address:	[redacted]
Contact name:	[redacted]
Telephone number:	[redacted]
Telefax number:	[redacted]
Location of Plant(s):	[redacted]

The following new information is provided by Arysta Paris for 'Malvin WG'.

- **Point IIIA 2.7.3 Ambient temperature shelf life**

Test or study & Annex point / reference number	Guideline and method	Test material	Findings	Comments	GLP Y/N	Reference
Ambient temperature shelf life (IIIA 2.7.3/01)	GIFAP Technical Mono-graph 17 (1993)	Captan 80WDG, Lot no. 3111020-OS	There was no significant change to the active ingredient content when the product was stored over a 20 month period: Initial = 80.9% 20 months = 79.8%	HPLC/UV determin-ation of active ingredient.	Y	Robaugh, 2005

- **Point IIIA 2.8.3 Suspensibility and spontaneity of dispersion**

Test or study & Annex point / reference number	Guideline and method	Test material	Findings	Comments	GLP Y/N	Reference
Suspensibility and spontaneity of dispersion (IIIA 2.8.3/02)	CIPAC MT 174	Captan 80WDG, Lot no. 3111020-OS	Dispersibility at 20°C was: 93% (before storage) 89.4% (following storage for 20 months)	-	Y	Robaugh, 2005

Conclusions: study acceptable.

New references, by Annex point

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
IIA, 2.1.3/01	Turner, B.J.	2005a	Captan (pure grade) Boiling temperature. Huntingdon Life Sciences Ltd. Report number MAK854/052246. GLP, Unpublished.	Y	Makhteshim
IIA, 2.11.1/02	Turner, B.J.	2005b	Captan (technical grade) Flammability (solids) and relative self-ignition temperature for solids. Huntingdon Life Sciences Ltd. Report number MAK/853. GLP, Unpublished.	Y	Makhteshim
IIA, 2.11.2/02	Turner, B.J.	2005b	Captan (technical grade) Flammability (solids) and relative self-ignition temperature for solids. Huntingdon Life Sciences Ltd. Report number MAK/853. GLP, Unpublished.	Y	Makhteshim
IIA, 2.5.1/01	Comb, A.L.	2000	Folpet (pure grade) spectra. Huntingdon Life Sciences Ltd., Report No. MAK594/002162 (Company file: R-11510). GLP, Unpublished.	Y	Makhteshim
IIA, 4.2.1/07	Burden, A.N.	2004	Captan . Position paper on residue analytical methods. TSGE report April 2004. Not GLP, Unpublished.	N	Makhteshim/ Arysta Paris
IIA, 4.2.1/08	Faessel, V.	2004a	Validation study of the analytical method for the determination of captan and tetrahydrophthalimide (THPI) in tomato processed fractions. Anadiag report R A3153. GLP, Unpublished.	Y	Arysta Paris
IIA, 4.2.3/05	Burden, A.N.	2004	Captan . Position paper on residue analytical methods. TSGE report April 2004. Not GLP, Unpublished.	N	Makhteshim/ Arysta Paris
IIA, 4.2.4/02	Burden, A.N.	2004	Captan . Position paper on residue analytical methods. TSGE report April 2004. Not GLP, Unpublished.	N	Makhteshim/ Arysta Paris
IIIA, 2.7.3/01	Robaugh, D.A.	2005	Suspensibility determination, method validation and assay for the formulation Captan 80 WDG – 20 month report. Pyxant Labs, Report Arvesta-1446. GLP, Unpublished.	Y	Arysta Paris
IIIA, 2.8.3/01	Pollmann, B	2004	Sprayability test with Merpan 80 WDG in a commercial agricultural boom sprayer. GAB Biotechnologie GmbH report 20031377/G1-FPPT (Company file R-16560). GLP, Unpublished.	Y	Makhteshim

Annex point / reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**	**Data Protection Claimed** **Y/N**	**Owner**
IIIA 2.8.3/02	Robaugh, D.A.	2005	Suspensibility determination, method validation and assay for the formulation Captan 80 WDG – 20 month report. Pyxant Labs, Report Arvesta-1446. GLP, Unpublished.	Y	Arysta Paris
IIIA 2.8.6.3/01	Comb, A.L.	2001	Merpan 80 WDG attrition resistance, Huntingdon Life Sciences Ltd. Report number MAK651/004810. GLP, Unpublished.	Y	Makhteshim

Addendum
to the Draft Assessment Report

CAPTAN

Volume 4

ANNEX C

(Confidential information)

May 2005

Rapporteur Member State: Italy

CONFIDENTIAL BUSINESS INFORMATION:

available at RMS

European Commission

Peer Review Programme

ECCO-Meetings

Captan

Volume 3

Annex B
Addendum: definition of the residue

Rapporteur Member State: Italy

B.7.3 Definition of the residue (Annex IIA 6.7; Annex IIIA 8.6)

Captan: The residue definition for the fungicide captan should be captan only as the metabolites THPI, 3-OH-THPI and 5-OH-THPI are neither of toxicological significance nor pose a significant dose to humans,.

The collective data (toxicological data and residue data leading to estimated dose to humans) support the conclusion that the residue definition for captan should be **captan only**.

The DG SANCO Guideline notes (European Commission, 1997): Residue Definition – Of the three general considerations that are fundamental to the decision as to whether or not specific metabolites/degradation products should be included in the definition and expression of a residue, two are relevant to this discussion: (1) Their basic toxicology and (2) Their presence in significant amounts.

1) THPI basic toxicology

Three lines of evidence show that the metabolites of captan are not of toxicological significance:
a). Direct measurements of toxicity.
b). QSAR Analysis
c). Comparison of captan and its major metabolite in bioassays that are particularly sensitive to the toxicological properties of captan.

a). Direct measurements of toxicity

THPI is not acutely toxic. Its LD50 in rats is above 10 g/kg bw (Elsea, 1955).

THPI is not mutagenic. When tested in the multiple strains in the Ames Assay, it is negative (Carver, 1986).

THPI is not a developmental toxin. When tested at 75 mg/kg bw in Dutch Belted rabbits, developmental abnormalities were not seen (Kennedy *et al.,* 1968).

b). QSAR Analysis

THPI does not have structural alerts that indicate this metabolite poses a toxicological risk (Chaudry, 2005).

The hydroxylation of organic structures is considered a detoxification mechanism since hydroxylation makes a compound more polar which increases the potential for molecular conjugation and consequently facilitates excretion; thus, the hydroxylated metabolites of THPI are considered less toxic than THPI (*www.isu.edu/~watwmari/detox.doc*).

c). Comparison of captan and its major metabolite in fish bioassays that are particularly sensitive to the toxicological properties of captan.

The most sensitive bioassays for measuring toxicity of captan are those involving aquatic organisms. This follows from the mode of action of captan, which is irritation-based, due to its reactivity of the captan side chain with the thiol group. This reactive side chain is not present on the THPI metabolite. This high reactivity of the side chain of captan produces irritation to the tissues as well as to gill membranes in fish. THPI, has low reactivity and is not an irritant.

THPI was found to be non-toxic to fish species tested. The rainbow trout LC_{50} assay is able to distinguish the toxicity of captan and THPI in a dramatic way. The data for captan and THPI are noted below (Jenkins, 2002,Kent, 1994):

Rainbow trout 96 hour Static LC_{50}:
Captan 0.215 mg/L
THPI >120 mg/L

Ratio of THPI toxicity to captan toxicity is >500-fold. This decrease in toxicity attests to the relative innocuous character of THPI compared to the parent, captan.

In conclusion, THPI poses no significant toxicological risk for adverse effects.

2) Their presence in significant amounts

The following maximum residues have been found in milk and meat from dairy cows fed 10 ppm captan (the estimated maximum dose, based on captan use and cattle feed components) (Wiebe, 1991):

		Metabolite	
	THPI	**3-OH-THPI**	**5-OH-THPI**
Milk	**<0.01**	**0.02**	**<0.01 mg/kg**
Meat	**0.02**	**0.02**	**(0.003) mg/kg**

LOQ: 0.01 mg/kg

The less than Level of Quantification in the milk is consistent with an extensive market basket survey of milk sampled at the point of purchase from around the United States. There were no residues of THPI in all 224 milk samples analysed (Slesinski and Wilson, 1992).

Consumption of meat and milk calculated according to the worst case scenarios resulted with maximum possible daily intake of THPI in the most sensitive consumer groups of 0.00039 mg/kg bw/day (toddlers), 0.00053 mg/kg bw/day (infants).

The maximum possible daily intake of 3-OH-THPI are 0.00122 mg/kg bw/day (toddlers), 0.00203 mg/kg bw/day (infants).

The maximum possible daily intake of 5-OH-THPI are 0.00031 mg/kg bw/day (toddlers), 0.00051 mg/kg bw/day (infants).

The maximum possible daily intake of THPI, -3-OH-THPI and 5-OH-THPI (taking into consideration the most sensitive population group) are very low and significantly lower than the ADI for captan for the most sensitive consumer groups for animal products.
(Detailed calculations appear under point 2.c) below.)

Considering the low toxicity of captan metabolites and the low dose to humans that these metabolites represent, when calculated using conservative assumptions, there is no basis for rationally including these metabolites in the captan residue expression.

In conclusion, the residue expression for captan should be expressed as parent compound, captan, only.

The references submitted in support of the above position are summarised below.

---

1) THPI basic toxicology

a) Tetrahydrophthalimide: Acute oral administration - rats (Elsea, J.R., 1955; IIA 7.3/01).

The captan metabolite THPI, referred to in the report as phthalimide (N-trichloromethylthiophthalimide), purity 97%, in 0.5% aqueous methyl cellulose, was administered orally by gavage to groups of five fasted male rats as either a 10% or 40% w/v

suspension at dose levels of 1.00, 2.15, 4.64 or 10.00 g/kg bw. Animals were observed for signs of toxicity on the day of administration and for seven days thereafter. Animals were subject to gross necropsy.

The study pre-dated regulatory guidelines and GLP, but was performed at a reputable laboratory, and the result is considered valid.

There were no deaths. On the day of dosing, all animals appeared depressed and showed laboured respiration and diarrhoea. Animals at the 2.15 mg/kg bw and above also showed slight ataxia. From 24 hours post-dose, animals at 1.00 and 2.15 mg/kg bw appeared normal. Animals at 4.54 and 10.00 mg/kg bw appeared depressed and showed soft, light coloured faeces for one to three days following dosing. All groups gained weight during the study. Necropsy revealed mottled and granular livers in the majority of animals in all groups receiving the test material.

Conclusion: The acute oral LD_{50} of THPI in the male rat is greater than 10 g/kg bw. In accordance with 93/21/EEC classification is not required.

b) Microbial/Mammalian Microsome Mutagenicity Plate Incorporation Assay with Tetrahydrophthalimide (Carver, J.H., 1986; IIA 7.3/02)

NOTE: The summary below already appears in the DAR under B.6.8.1a Toxicity studies of metabolites as referred to in the introduction point (vii).

The mutagenicity of the captan metabolite THPI (purity 99.9%) in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 and in the tryptophan-deficient strain of *Escherichia coli* WP2 uvrA was investigated at concentrations of 0.1 to 10 mg/plate in the presence and absence of metabolic activation (S-9 mix). The test substance was dissolved in DMSO. S-9 mix was obtained from the liver of arochlor induced rats. The positive control substance with metabolic activation was 2-aminoanthracene (strains TA98, TA100, TA1537 and WP2 uvrA). Positive controls without metabolic activation were 2-nitrofluorene (strain TA98), sodium azide (strains TA100 and TA1535), ICR-191 (strain TA1537, WP2 uvrA), 2-aminoacridine (TA1537), danthron (TA102), mitomycin (TA102), 1-ethyl 2-nitroso-3-nitrosoguanidine (WP2 uvrA). All concentrations were run in triplicate and the results were confirmed by an independent experiment.
The study was conducted according to an in-house method basically in agreement with the OECD Guideline 471, and in compliance to Good Laboratory Practice.

results: there was no cytotoxicity at any of the concentrations tested. No reproducible increases in mutant frequency were observed with the *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 or the *E. coli* strain WP2 uvrA, with or without metabolic activation. The tester strains responded to the positive controls as expected.

Conclusion: Under the conditions of the test THPI was not mutagenic in the *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 or the *E. coli* strain WP2 uvrA in the presence or absence of metabolic activation.

c*) An investigation of the teratogenic potential of captan, folpet, and difolatan (Kennedy, G., Fancher, O. E., and Calandra, J. C., 1968; IIA 7.3/03).*

Study of effects of captan, folpet, the captan metabolite tetrahydrophthalimide (THPI), and the folpet metabolite phthalimide (PI) on the pregnant rabbit. Technical grade captan and folpet, and pure samples of THPI and PI were used. The related fungicide difoltan and the structurally similar drug thalidomide were also tested. The latter may be considered a positive control.

The study predated guidelines and was not to GLP. However, the study demonstrated that foetal malformations could be induced by a known positive control, and is considered valid.

Test materials were administered in gelatine capsules to groups of mated female Dutch Belted rabbits from day 6 to day 16 of pregnancy. Animals were weighed at three day intervals and killed on day 29, when uterine contents were examined, and foetuses examined. Live foetuses were placed in an incubator for 24 hours after which they were killed and dissected. The carcasses were cleared and the skeleton stained with alizarin and examined. THPI was administered at 75 mg/kg bw/day to a group of 9 females. The study also investigated possible strain effects, testing New Zealand White (NZW) rabbits and Dutch Belted rabbits with captan. Two control groups, one of each strain, received empty capsules only. Thalidomide was administered at 75.0 mg/kg bw/day to both strains of rabbit.

Maternal weight gains were not adversely affected by THPI at 75.0 mg/kg/day, and there were no deaths.

Incidence of foetal resorptions was marginally higher with THPI.

One control foetus (of 105, from 17 litters) showed shortening and flexure of the forelimb. There were no malformations in the 57 foetuses from 9 dams treated with THPI. Post-natal survival, crown-rump length, foetal weight and incidence of visceral and skeletal anomalies were not adversely affected by maternal treatment with THPI. Thalidomide induced typical 'clubbing' (phocomelia) in 38 of 100 foetuses from 17 litters.

The results are summarised below (Table B.7.3.1).

Table B.7.3.1: Summary of effects of captan, THPI and controls in rabbits

Compound	Oral dose (mg/kg)	No. of preg-nant females	Rabbit strain	No. of implants	No of resorp-tions	No of normal foetuses	No. (%) mal-formed foetuses	Mean litter size
Control	-	7	DB	52	0	51	1 (1.9)	7.4
	-	10	NZW	66	2	64	0 (0)	6.4
Thalidomide	75.0	7	BD	55	15	26	14 (35.0)	5.7
		10	NZW	74	10	40	24 (37.5)	6.4
Captan	75.0	6	DB	43	1	42	0 (0)	7.0
	18.75	6	NZW	46	11	35	0 (0)	5.8
	37.5	7	NZW	56	2	54	0 (0)	7.7
	75.0	5	NZW	39	33	6	0 (0)	1.2
THPI	75.0	9	DB	66	9	57	0 (0)	6.3

Conclusion: Tetrahydrophthalimide (THPI) showed no adverse effects on the developing rabbit foetus.

d) Assessment of the activity, toxicity and mutagenicity potential of THPI, using structure activity relationships (Chaudhry, Q., 2005; IIA 7.3/04). [This report was previously submitted with the toxicology addendum in March 2005.]

THPI was evaluated for their potential for activity, toxicity and mutagenicity using a Structure Activity Relationship (SAR) approach. The technique, referred to as Deduction of Risk from Existing Knowledge (DEREK), uses specialist software 'DEREK for Windows' (DfW) developed by Llhasa Ltd. The software works by matching structural entities in a query structure with structural alerts that are associated with different toxicity endpoints (toxicophores). A structural alert is the set of structural features in a molecule that makes a toxicologist suspect that the substance may show a particular toxic effect. DfW can predict alerts for carcinogenicity, irritation (e.g. of the skin, eye and gastrointestinal tract), genotoxicity, respiratory sensitisation, skin sensitisation, thyroid toxicity and a range of miscellaneous effects for bacteria and a range of mammalian species including man. The

programme used 482 structural alerts associated with the different endpoints.

DfW also predicts the likelihood of each effect using descriptive terms ranging from 'certain' to 'impossible' ('certain', 'probable', 'plausible', 'equivocal', 'doubted', 'improbable', 'impossible'), or 'open' or 'contradicted' in the case of findings where there is a prediction both that the proposition is true and that it is false.

There were no structural alerts in THPI.

In conclusion, computer predictions using DfW indicate that THPI is not expected to exhibit mutagenic activity, genotoxicity, irritation, sensitisation or thyroid toxicity.

2) Their presence in significant amounts

a) National Milk Survey (Slesinski, R., S. and Wilson, A. E., 1992; IIA 7.3/05).

Samples of whole milk were collected from 224 retail outlets of different sizes, including supermarkets and convenience stores (but not wholesale outlets nor roadside stalls), from 48 different states in the USA at various times over a 12-month period (January to December 1991). The stores selected for sampling were taken at random from a database of 95,000 outlets representing 83.8% of all grocery store sales in 1989. Two samples of 1.9 L (sample 'A' and a back-up sample 'B') were purchased from each store by shoppers. The samples were packed in dry ice and transferred to the analytical laboratory and stored frozen until analysis. Control samples were obtained by the laboratory from local stores.

Each sample was analysed for captan, THPI, trans-3-hydroxy THPI and trans-5-hydroxy THPI. Captan residues were extracted with benzene, filtered, subjected to partition and column clean-up and then quantified using a gas chromatograph equipped with a halogen-specific Coulson Electrolytic Conductivity detector; the GC column was packed with 10% SP 2100 on 80/100 mesh Supelcoport. THPI, trans-3-hydroxy THPI and trans-5-hydroxy THPI residues were extracted with acetone, filtered, subjected to partition clean-up. The residues were derivatised by trimethylsilylation and quantified by gas chromatography on a DB-17 capillary column and a mass selective detector (MSD) operating in the selective ion mode. The LOQ for all analytes was 0.005 mg/L.

Acceptable recoveries were obtained from samples fortified at 0.005 and 0.01 mg/L..

Conclusion: Residues of captan, THPI, trans-3-hydroxy THPI and trans-5-hydroxy THPI were below the LOQ in all 224 milk samples.

b) Captan: Magnitude of Residue of captan metabolites in bovine meat and milk (Wiebe, L. A., 1991; IIA 7.3/06).

Captan technical active substance (purity 89.3%; batch number PJB-1601 CTCS) was administered orally in gelatine capsules daily in the feed for 29 days to groups of four Holstein dairy cattle at dietary concentration of 0, 10, 30 and 100 mg/kg diet. Milk was collected twice daily before treatment, on selective days during treatment, and one, three and six days after treatment. Three cattle from each group were sacrificed three hours after treatment was complete and the remaining one after an additional seven days. Concentrations of THPI, 3-OH THPI (*cis* and *trans*) and 5-OH THPI (*cis* and *trans*) were determined in tissues and milk using gas liquid chromatography with mass-selective detection.

For milk, there were 48 determinations for each of the analytes and mean recoveries for each metabolite at all fortification levels were 93 - 98%. For tissues there were 11 or 12 determinations for each of the analytes and mean recoveries for all fortification levels were 95 - 106% (fat), 91 - 105% (kidney), 67 - 83% (liver) and 95 - 101% (muscle).

In the residue study milk samples were extracted within 159 days of collection and tissue samples within 317 days of collection. In the stability test, there was no reduction in levels of captan metabolites following storage at -20°C in the different commodities for up to six months (milk) or four months (tissues). The results of later samplings are reported by Meyers and Wiebe (1995 - see Point B.7.6.4.b) and the residues were found to be stable in milk and tissues following storage at -20°C for at least three years.

No residues of the metabolites *cis*-3-OH THPI or *cis*-5-OH THPI were detected in milk or tissues following administration of captan.

Residues in milk plateaued on day 1 of administration for all dosing levels. Within one day after the end of dosing, residues were not detected in the milk following 10 and 30 mg captan/kg and within three days after dosing there were no residues in the milk following 100 mg captan/kg. Residue levels in tissues were generally similar to those in the milk though residues in the fat were lower. THPI was the major metabolite in fat, liver and muscle and trans-3-OH THPI occurred at higher levels than trans-5-OH THPI.

Total residues were calculated by adding the individual values for the metabolites, corrected for the molecular mass. Thus, THPI (molecular mass 151.2) and 3-OH THPI/5-OH THPI (molecular mass 167.2) are multiplied by 2.0 and 1.8, respectively, to convert metabolite residues to captan (molecular mass 300.6). Residues below the limit of determination (< 0.01 mg/kg) are assumed to be zero for the purposes of the addition. Total residues were 0.04 mg captan equivalents in milk and < 0.01 - 0.08 mg captan equivalents/kg in tissues following administration of 10 mg captan/kg for 29 days. Following administration of 30 mg/kg, residues in milk and tissues were 0.17 and 0.06 - 0.38 mg captan equivalents/kg; following administration of 100 mg/kg, residues in milk and tissues were 0.89 and 0.21 - 1.11 mg captan equivalents/kg.

After the end of dosing, residues in the tissues dissipated within seven days.

Average residues of captan metabolites in milk during and after the dosing period are given in Table B.7.3.2

Average residues of captan metabolites in milk during the dosing period and residues in tissues at the end of the 29-day administration period are given in Table B.7.3.3.

Table B.7.3.2: Residues in milk following administration of captan to dairy cow for 29 days

Day	Dose rate (mg/kg diet)	Mean residue in milk (mg/kg)				
		THPI	*trans*-3-OH THPI	*trans*-5-OH THPI	*cis*-3-OH THPI	*cis*-5-OH THPI
1	10	< 0.01	0.023	< 0.01	< 0.01	< 0.01
	30	0.028	0.083	0.013	< 0.01	< 0.01
	100	0.153	0.310	0.060	< 0.01	< 0.01
4	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.020	0.063	< 0.01	< 0.01	< 0.01
	100	0.160	0.245	0.035	< 0.01	< 0.01
7	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.025	0.063	< 0.01	< 0.01	< 0.01
	100	0.298	0.265	0.035	< 0.01	< 0.01
10	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.016	0.060	< 0.01	< 0.01	< 0.01
	100	0.190	0.183	0.025	< 0.01	< 0.01
14	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.030	0.060	< 0.01	< 0.01	< 0.01
	100	0.173	0.200	0.030	< 0.01	< 0.01
21	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.030	0.060	< 0.01	< 0.01	< 0.01
	100	0.198	0.210	0.033	< 0.01	< 0.01
28	10	< 0.01	0.018	< 0.01	< 0.01	< 0.01
	30	0.030	0.063	< 0.01	< 0.01	< 0.01
	100	0.208	0.225	0.035	< 0.01	< 0.01
30*	10	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	30	0.01	< 0.01	< 0.01	< 0.01	< 0.01
	100	0.02	0.10	< 0.01	< 0.01	< 0.01
32*	10	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	30	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	100	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

Residues in milk and tissues from untreated controls were below the limit of determination except for one milk sample which contained 0.02 mg THPI/kg on Day 10.

Values of < 0.01 mg/kg are assumed to be 0.005 mg/kg for calculation of means (unless all replicate values are < 0.01 mg/kg in which case the mean is given as < 0.01 mg/kg).

*** After dosing; one animal only per dose (four animals per dose at other time points).**

Table B.7.3.3: Residues in tissues and milk following administration of captan to dairy cow for 29 days

Commodity	Dose rate (mg/kg diet)	Mean residue (mg/kg)				
		THPI	*trans*-3-OH THPI	*trans*-5-OH THPI	*cis*-3-OH THPI	*cis*-5-OH THPI
milk	10	< 0.01	0.02	< 0.01	< 0.01	< 0.01
	30	0.03	0.06	< 0.01	< 0.01	< 0.01
	100	0.20	0.23	0.04	< 0.01	< 0.01
fat	10	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	30	0.03	< 0.01	< 0.01	< 0.01	< 0.01
	100	0.08	0.03	< 0.01	< 0.01	< 0.01
kidney	10	0.02	0.02	< 0.01	< 0.01	< 0.01
	30	0.09	0.09	0.02	< 0.01	< 0.01
	100	0.25	0.27	0.07	< 0.01	< 0.01
liver	10	0.02	< 0.01	< 0.01	< 0.01	< 0.01
	30	0.12	0.04	< 0.01	< 0.01	< 0.01
	100	0.31	0.11	< 0.01	< 0.01	< 0.01
muscle	10	0.02	0.02	< 0.01	< 0.01	< 0.01
	30	0.07	0.06	0.01	< 0.01	< 0.01
	100	0.24	0.18	0.04	< 0.01	< 0.01

Residues in milk and tissues from untreated controls were below the limit of determination except for one milk sample which contained 0.02 mg THPI/kg.

Conclusion, following administration of captan to dairy cattle at a dietary concentration of 10, 30 and 100 mg/kg for 29 days, total residues in milk over the dosing period were 0.04, 0.17 and 0.89 mg captan equivalents/kg. In tissues, residues following the three doses were < 0.01 - 0.08, 0.06 - 0.38 and 0.21 - 1.11 mg captan equivalents/kg, respectively, with the highest levels found in the kidney and the lowest levels in the fat. THPI was the major metabolite in most tissues and no residues of *cis*-3-OH THPI or *cis*-5-OH THPI were found in milk or tissues above the limit of determination. Residue levels of all metabolites reduced during the withdrawal period and following all dose levels were below the limit of determination in milk and tissues after three days and seven days, respectively.

c) Dietary Risk assessment of Captan Metabolites: THPI, 3-hydroxy and 5-hydroxy THPI

The dietary risk assessment for THPI and the 3-OH and 5-OH THPI metabolites was calculated based on the residues found in milk and meat from dairy cows fed 10 ppm captan The rate of 10 mg/kg diet is greater than the worst-case intake of captan (based on residues in pomace calculated from the MRL in apple) for beef and dairy cattle as shown below:

Captan is recommended in pome fruit, tomatoes and peaches/nectarines. Fruit pomace (apple) can be used for cattle feed at a maximum of a 10% of the diet in dairy cattle and a 30% of the diet in beef cattle. Captan is not recommended on any crops which are fed to hens or pigs.

The potential dietary exposure of dairy and beef cattle to captan is calculated below based on a worst-case (using the MRL) and a more realistic case (using the STMR) according to Commission Working Document 7031/VI/95 rev 4 of 22 July 1996.

Worst-case calculation of captan intake in cattle (based on MRL values)

Based on a MRL of 5 mg/kg for apple and a mean transfer factor of 1.1 in apple pomace (residue in pomace = 5.5 mg/kg), the maximum residue concentration in feed of beef cattle is 107.8 mg captan/animal/day (Table B.7.3.4). This gives an estimated daily feeding rate of 7.2 mg captan/kg diet (107.8/15), assuming 15 kg as the daily intake of dry matter for cattle of

350 kg body weight, or 0.31 mg/kg bw /day (107.8/350). The maximum dietary concentration is 5.5 mg captan/kg fresh diet (107.8/19.6).

For dairy cattle, the maximum residue concentration in feed is 47.85 mg captan/animal/day (Table B.7.3.4). This gives an estimated daily feeding rate of 2.4 mg captan/kg diet (47.85/20), assuming 20 kg as the daily intake of dry matter for cattle of 550 kg body weight, or 0.09 mg/kg bw /day (47.85/550). The maximum dietary concentration is 5.5 mg captan/kg fresh diet (47.85/8.7).

Table B.7.3.4: Worst-case calculation of captan dietary exposure level in cattle (based on MRL values)

Animal/ Crop commodity consumed	% Diet contribution (dry weight)	Intake of dry matter (kg/animal /day)[1]	% Dry matter content	Intake of fresh material (kg/animal/ day)[2]	Captan residue in commodity (mg/kg)	Intake (mg captan / animal/ day)[3]
Beef cattle/ Apple pomace	30	4.5	23	19.6	5.5	107.8
Dairy cattle/ Apple pomace	10	2.0	23	8.7	5.5	47.85

[1] % diet contribution x total intake (15 kg for beef cattle; 20 kg for dairy cattle).
[2] Dry matter intake corrected for dry matter content (23%).
[3] Intake of fresh material x captan residue.

Realistic calculation of captan intake in cattle (based on STMR values)

Based on a STMR of 1.3 mg/kg for apple and a mean transfer factor of 1.1 in apple pomace (residue in pomace = 1.4 mg/kg), the maximum residue concentration in feed of beef cattle is 27.44 mg captan/animal/day (Table B.7.3.5). This gives an estimated daily feeding rate of 1.8 mg captan/kg diet (27.44/15), assuming 15 kg as the daily intake of dry matter for cattle of 350 kg body weight or 0.08 mg/kg bw /day (27.44/350). The maximum dietary concentration is 1.4 mg captan/kg fresh diet (27.44/19.6).

For dairy cattle, the maximum residue concentration in feed is 12.18 mg captan/animal/day (Table B.7.3.5). This gives an estimated daily feeding rate of 0.6 mg captan/kg diet (12.18/20), assuming 20 kg as the daily intake of dry matter for cattle of 550 kg body weight or 0.02 mg/kg bw /day (12.18/550). The maximum dietary concentration is 1.4 mg captan/kg fresh diet (12.18/8.7).

Table B.7.3.5: Realistic calculation of captan dietary exposure level in cattle (based on STMR values)

Animal/ Crop commodity consumed	% Diet contribution (dry weight)	Intake of dry matter (kg/animal /day)[1]	% Dry matter content	Intake of fresh material (kg/animal/ day)[2]	Captan residue in commodity (mg/kg)	Intake (mg captan / animal/ day)[3]
Beef cattle/ Apple pomace	30	4.5	23	19.6	1.4	27.44
Dairy cattle/ Apple pomace	10	2.0	23	8.7	1.4	12.18

[1] % diet contribution x total intake (15 kg for beef cattle; 20 kg for dairy cattle).
[2] Dry matter intake corrected for dry matter content (23%).
[3] Intake of fresh material x captan residue.

Based on the dietary burden calculations, the worst-case and realistic case intakes for captan are summarised in Table B.7.3.6. The rate of 10 mg/kg diet as used in the feeding study is

greater than the worst-case intake (and greater than the realistic intake) of captan for beef and dairy cattle.

Table B.7.3.6: Intake of captan in cattle

Animal	Calculated dietary intake (mg captan/kg diet)	
	Worst-case (based on MRL)	Realistic case (based on STMR)
Beef cattle	7.2	1.8
Dairy cattle	2.4	0.6

The following residues have been found in milk and meat from dairy cows fed 10 ppm captan (the estimated maximum dose, based on captan use and cattle feed components) (Wiebe, 1991):

Table B.7.3.7: Residues of THPI, 3-OH-THPI and 5-OH-THPI in meat and milk following administration of captan to dairy cow for 29 days

Commodity	Dose rate (mg/kg diet)	Mean residue (mg/kg)		
		THPI	3-OH THPI	5-OH THPI
milk	10	< 0.01 (0.005)*	0.02	< 0.01 (0.005)*
uscle	10	0.02	0.02	< 0.01 (0.005)*

Residues in milk and tissues from untreated controls were below the limit of determination except for one milk sample which contained 0.02 mg THPI/kg.

* Since the LOQ was 0.01 mg/kg, one half of the LOQ (i.e., 0.005 mg/kg) as worst case scenario was taken into consideration when residues were below the LOQ.

Estimation of the potential and actual exposure through diet and other means

Chronic exposure

Theoretical Maximum Daily Intake (TMDI)

The TMDI is calculated by multiplying the MRL/residues by the estimated average daily consumption for a given food commodity.

$TMDI = \sum MRL \times F$

where:
MRL = Maximum residue limit/residue for a given animal product
F = Consumption of that animal product.

This calculation is performed using:

1) An International diet (European Region) based on data from the World Health Organisation (WHO)[1].
2) The UK Dietary model (PSD, 1999[2])

WHO European diet

The TMDI calculation is presented in Table B.7.3.8

Table B.7.3.8: Consumption of milk and meat based on WHO diet

Commodity	Consumption (kg/person/day)
Total milk	0.3408
Cattle meat	0.0633

Table B.7.3.9: TMDI calculation for THPI, 3-OH-THPI and 5-OH-THPI based on WHO diet

Commodity	THPI (mg/kg)	TMDI for THPI (mg/person/ day)	3-OH-THPI (mg/kg)	TMDI for 3-OH-THPI (mg/person/ day	5-OH-THPI (mg/kg)	TMDI for 5-OH-THPI (mg/person/day
Total milk	0.005	0.0017	0.02	0.0068	0.005	0.0017
Cattle meat	0.02	0.0013	0.02	0.0013	0.005	0.0003
Total TMDI		**0.0030**		**0.0081**		**0.0020**

The total TMDI for **THPI in milk and meat** will be max 0.0030 mg/person/day or **0.0000** mg/kg bw/day for a 60 kg adult.
The total TMDI for **3-OH-THPI** is 0.0081 mg/person/day or **0.0001** mg/kg bw/day for a 60 kg adult.
The total TMDI for **5-OH-THPI** is 0.0020 mg/person/day or **0.0000** mg/kg bw/day for a 60 kg adult.

UK diet

UK consumption data of animal products for adults, children, toddlers and infants (mean consumers and high, i.e. 97.5th percentile, consumers) are presented in Table B.7.3.10.

[1] WHO (1989). Guidelines for predicting dietary intake of pesticide residues. Prepared by the joint UNEP/FAO/WHO Food Contamination Monitoring Programme in collaboration with the Codex Committee on Pesticide Residues. World Health Organisation, Geneva.

[2] PSD (1999). Guidance on the estimation of dietary intakes of pesticides residues. The Registration Handbook. Pesticides Safety Directorate, Ministry of Agriculture, Fisheries and Food.

Table B.7.3.10: UK consumption data for adults, children, toddlers and infants

Comm-odity	Consumption data (kg/day)							
	Adults (70.1 kg bw)		Children (43.6 kg bw)		Toddlers (14.5 kg bw)		Infants (8.7 kg bw)	
	Mean	High [1]	Mean	High	Mean	High	Mean	High
Milk	0.2573	0.6659	0.0304	0.6745	0.3064	0.8017	0.3377 5	0.8719
Meat	0.0841	0.2050	0.0641	0.1339	0.0276	0.0869	0.1339	0.0121

Since the milk and meat consumption (high levels) by toddlers and infants represents the worst case for risk assessments. The TMDI for THPI and hydroxylated THPI metabolites was calculated for these sub- populations.

Table B.7.3.11: TMDI calculation for THPI for toddlers and infants based on UK high consumption intakes

Commodity	THPI (mg/kg)	TMDI (mg/kg bw/day)	
		Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
Milk	0.005	0.0003	0.0005
Meat	0.02	0.0001	0.0000
Total exposure		**0.0004**	**0.0005**

The TMDIs of THPI are 0.0004 mg/kg bw/day (toddlers), 0.0005 mg/kg bw/day (infants).

Table B.7.3.12: TMDI calculation for 3- OH-THPI for toddlers and infants based on UK high consumption intakes

Commodity	3-OH-THPI (mg/kg)	TMDI (mg/kg bw/day) [1]	
		Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
milk	**0.02**	**0.0011**	**0.0020**
meat	**0.02**	**0.0001**	**0.0000**
Total exposure		0.0012	0.0020

The worst case for TMDIs for milk and meat of 3-OH-THPI are 0.0012 mg/kg bw/day (toddlers), 0.0020 mg/kg bw/day (infants).

Table B.7.3.13: TMDI calculation for 5-OH-THPI for toddlers and infants based on UK high consumption intakes

Commodity	5-OH-THPI (mg/kg)	TMDI (mg/kg bw/day) [1]	
		Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
milk	**0.005**	**0.0003**	**0.0005**
meat	**0.005**	**0.0000**	**0.0000**
Total exposure		0.0003	0.0005

The worst case TMDIs from milk and meat of 5-OH-THPI are 0.0003 mg/kg bw/day (toddlers), 0.0005 mg/kg bw/day (infants).

Comparison of TMDI with ADI

The worst case TMDI values of THPI, 3-OH-THPI and 5-OH-THPI for the most sensitive consumer groups and diets are summarised in table B.7.3.14.

Table B.7.3.14: TMDI values for different consumer groups and diets

Diet	Body weight (kg)	TMDI (mg/kg bw/day)		
		THPI (%ADI)	3-OH-THPI (%ADI)	5-OH-THPI (%ADI)
WHO adult	60	0.0000 (0)	0.0001 (0.1)	0.0000 (0)
UK toddler	14.5	0.0004 (0.4)	0.0012 (1.2)	0.0003 (0.3)
UK infant	8.7	0.0005 (0.5)	0.0020 (2.0)	0.0005 (0.5)

Based on the proposed ADI for captan of 0.1 mg/kg bw/day, the TMDI for THPI represents 0% to 0.5% of the ADI for the most sensitive consumer groups and different dietary intakes.

Based on the proposed ADI for captan of 0.1 mg/kg bw/day, the TMDI for 3-OH- THPI represents 0.1% to 2% of the ADI for the most sensitive consumer groups and different dietary intakes.

Based on the proposed ADI for captan of 0.1 mg/kg bw/day, the TMDI for 5-OH- THPI represents 0% to 0.5% of the ADI for the most sensitive consumer groups and different dietary intakes.

Conclusion

The maximum possible daily intake of THPI, -3-OH-THPI and 5-OH-THPI (taking into consideration the most sensitive population group) are very low and significantly lower than the ADI for captan for the most sensitive consumer groups for animal products.

There is therefore a large margin of safety for all consumer groups.

d) Toxicity of THPI to aquatic organisms

NOTE: The summaries below already appear in the DAR under B.9.2 Effects on aquatic organisms (Annex IIA 8.2; Annex IIIA 10.2), B.9.2.1 Acute toxicity to aquatic organisms

(i) THPI: acute toxicity to rainbow trout (Oncorhynchus mykiss) (Kent, S.J. et al. 1994a; IIA, 8.2.1/10; IIA 7.3/07)

The 96-hour acute toxicity of THPI (metabolite of captan; purity 96% w/w) to the rainbow trout (*Oncorhynchus mykiss*) was determined in a limit test with a static system with aeration. Groups of ten fish in 27.5 L glass tanks containing 20 L test solution (15°C, 16:8 hour light/dark regime) were exposed to a nominal concentration of THPI (dissolved in dimethylformamide) at 120 mg/L in comparison with a dilution water only (dechlorinated filtered tap water, total hardness approx. 27 mg $CaCO_3$/L) control and a solvent only (100 µL dimethylformamide/L) control for four days. The fish were not fed for 24 hours prior to, or during, exposure. The test solutions were not changed during the study. Samples of the test solutions were taken for analysis of the THPAM content (by HPLC) at the start of exposure and after 48 and 96 hours. Measurements of pH, dissolved oxygen and temperature were

taken daily. Mortality and behaviour were recorded at 24-hour intervals after the start of exposure.

The study met the essential criteria of OECD 203. One fish used in the water only control was slightly smaller than recommended (50 ± 10 mm) but this is not considered to have affected the validity of the study. It was conducted according to Good Laboratory Practice.

The mean measured concentration of THPI in the dosed medium was 100% of the nominal value and so the results are presented as nominal values. The physical and chemical parameters of the test solutions remained at expected values during the study (pH 7.3 to 7.8 for both treatments).

There were no symptoms of toxicity or mortalities during the study.

Conclusion: The 96-hour LC_{50} of THPI to the rainbow trout under static conditions was greater than 120 mg/L. The NOEC was equal to or greater than120 mg/L based on the absence of toxicological symptoms observed at the dose tested. The 24, 48 and 72-hour LC_{50} values were also greater than 120 mg/L.

(ii) Captan: acute toxicity to rainbow trout (Jenkins, C.A. 2002a; IIA, 8.2.1/03; IIA 7.3/08)

The 96-hour acute toxicity of captan technical (purity 95.2% w/w) to rainbow trout (*Oncorhynchus mykiss*, mean wet weight 1.9 g, mean fork length 5.3 cm) was determined in a static test system without replacement of the test medium. Groups of seven fish in glass aquaria containing 35 L of test medium (12 to 17°C, 16:8 hour light/dark regime) were exposed to nominal concentrations of captan (dissolved in dimethylformamide) at 30.1, 66.1, 145, 320 and 704 µg/L in comparison with a dilution water control treatment (dechlorinated, softened tap water, total hardness approximately 180 mg $CaCO_3$/L) and a solvent control treatment (100 µL dimethylformamide/L) for four days. The fish were not fed for 21 hours prior to, or during, exposure. Samples of the stock solutions (captan in dimethylformamide) were taken for analysis of captan by HPLC at the start of the test. Measurements of pH, dissolved oxygen and temperature were taken daily in all test vessels and hardness was measured at the start of the test. Temperature was monitored continuously in the control medium. Mortality and behaviour were recorded at 15 minutes, 2, 4, 24, 48, 72 and 96 hours after the start of exposure.

The study met the essential criteria of OECD 203 and EC Methods Part C 1. It was conducted according to Good Laboratory Practice.

Measured concentrations of captan in the stock solutions ranged from 91 to 102% of the nominal values. The results of the toxicity test are based on nominal concentrations of captan. The physical and chemical parameters of the test media remained at expected values during the study (pH 7.8 to 8.5, dissolved oxygen 88 to 106 % ASV, temperature 12.4 to 13.5°C and total hardness 178 to 180 mg $CaCO_3$/L).

At 320 and 704 µg/L, all fish exhibited hyperventilation within 15 minutes of exposure and were dead at 24 and four hours, respectively. At 66.1 and 145 µg/L, all fish were affected within 24 hours of exposure, exhibiting hyperventilation, darkened pigmentation and/or lethargy. Between 72 and 96 hours, some fish at 145 µg/L and six out of seven fish at 66.1 µg/L appeared to have recovered and were normal. At 30.1 µg/L, all fish appeared normal throughout the test. The darkened pigmentation in fish in the control treatments was ascribed to aggressive behaviour by one fish in each vessel. When the aggressive fish was screened from the other fish they appeared normal.

Conclusion: The 96-hour LC_{50} of captan technical to rainbow trout under static test conditions was 0.215 mg/L (with 95% confidence limits of 145 to 320 µg/L). Adjusting for the purity of captan in captan technical (95.2 %), the 96-hour LC_{50} was 0.205 mg/L

(with 95% confidence limits of 0.138 to 0.305 mg/L). The NOEC was 0.0301 mg/L based on reversible toxic symptoms at 0.0661 mg captan technical/L.

A comparison of the toxicity of captan and THPI to rainbow trout is given in Table B.7.3.15. **Captan is more toxic to fish than THPI with a ratio of >500-fold.**

Table B.7.3.15: Summary of acute toxicity of captan and THPI to rainbow trout

Compound	LC_{50} (mg/L)	Reference
captan	0.215	Jenkins, C.A. 2002a; IIA, 8.2.1/03; IIA 7.3/08
THPI	> 120	Kent, S.J. et al. 1994a; IIA, 8.2.1/10; IIA 7.3/07

B.7.17 References relied on

B.7.17.1 Active substance

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
IIA, 7.3/01	Elsea, J.R.	1955	Tetrahydrophthalimide: Acute oral administration - rats. [redacted] Not GLP; Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/02	Carver, J.H.	1986	Microbial/mammalian microsome mutagenicity plate incorporation assay with tetrahydrophthalimide. [redacted] 2618, 27 (Company file: R-4409/TMN-0863). GLP; Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/03	Kennedy, G., Fancher, O. E., Calandra, J. C.	1968	An investigation of the teratogenic potential of captan, folpet, and difolatan. *Toxicology and Applied Pharmacology* **13**, 420-430. (Company file R-169) Not GLP; Published.	N	-
IIA, 7.3/04	Chaudhry, Q.	2005	Assessment of the activity, toxicity and mutagenicity potential of THPI and THPAM, using structure activity relationships. Central Science Laboratory, report dated 4 February 2005. Not GLP, Unpublished	Y	Makhteshim
IIA, 7.3/05	Slesinski, R., S., Wilson, A. E	1992	National Milk Survey. Technical Assessment Systems, Inc., Washington, DC, Report 92-01. (Company file R-6147). GLP; Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/06	Wiebe, L.A.	1991	Captan: Magnitude of the residue of captan metabolites in bovine meat and milk. [redacted] unpublished report No. RR 91-033B (Company file: R-6370/TMN-0355). GLP; Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/07	Kent, S.J., Sankey, S.A., Caunter J.E., Magor, S.E.	1994a	THPI: acute toxicity to rainbow trout (*Oncorhynchus mykiss*). [redacted] Report BL5237/B. (Company file: R-8288/TMN-0025). GLP, Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/08	Jenkins, C.A,	2002a	Captan: acute toxicity to rainbow trout. [redacted] Report MAK660/013072. (Company file: R-12335/TMN-0020A). GLP, Unpublished.	Y	Makhteshim/ Arysta Paris

Captan

Addendum to Address Issues Raised at EPCO Meetings (11-14 April 2005)

Rapporteur Member State: Italy

EU review under Directive 91/414 EEC

Relating to Annex B (Volume 3) of the DAR

October 2005

Mammalian toxicology

‘Merpan’ 80 WDG/Malvin WG

Data on exposure

October 2005

1.1 Data on exposure

1.1.1 Operator exposure

Evaluation table number	Reporting table number	Open Point number
-	2(24), 2(27) should be 2(25)	2.11, 2.13

Conclusions of EPCO 23 (10-15.5.2005):
A new calculation on operator exposure has to be submitted (based on a dermal absorption value of 10%)

Amended calculations of operator exposure using the German BBA model are presented below in comparison with an AOEL of 0.1 mg/kg bw/day using a dermal absorption value of 10%. The AOEL value of 0.1 mg/kg bw/day has arisen following discussions between the RMS/EFSA/Member States on the DAR.

1.1.1.1 Estimation of operator exposure

For assessing operator exposure, the maximum rate, maximum concentration and the method of application for each crop type are given in **Error! Reference source not found.**.

Table 1 Summary of recommendations of 'Merpan' 80 WDG/'Malvin WG' for operator exposure assessment

Type of crop	Method of application	Maximum application rate (kg a.s./ha)	Minimum spray volume (L/ha)	Maximum in-use spray concentration (mg a.s./mL)
orchard (pome fruit, peaches/ nectarines)	orchard tractor-mounted/tractor drawn airblast	2.5	1,000	2.5*
field grown tomatoes	tractor-mounted/tractor-drawn field crop sprayer; hand held low-level knapsack	1.8	1,200	1.5

* Maximum rate recommended for peaches/nectarines. (Maxim rate for apples/pears is 2.4 kg a.s./ha)

Estimation of operator exposure using the German BBA Model

The German BBA model[3] uses standard figures for different parameters. Models are available for the estimation of exposure for liquid and solid (WP and WG) pesticide formulations using a tractor-mounted sprayer for application to field crops and 'high' crops (i.e. those such as orchards or vineyards where the product is applied sideways and/or upwards) and hand-held equipment for application to 'high' crops.

Percutaneous absorption through human skin is assumed to be 10%.

[3] Westphal, D., Zels, J., Hoernicke, E. and Lundehn, J-R. (1993). Instructions for the protection of operators and other persons in the directions for use. Braunschweig Federal Research Centre, Department for Plant Protection Products and Application Techniques. Guidelines for the examination of plant protection products in the authorisation procedure, Part I 3-3, Third Edition March, 1993.

Based on the GAP uses, operator exposure estimates were calculated for worst-case uses, i.e. using the highest application rates and the highest spray concentrations which will lead to highest exposure of the spray operator as presented in **Error! Reference source not found.**. The estimate for hand-held equipment for application to 'high' crops has been used for application to tomatoes by a knapsack sprayer and represents a worst-case for a low-level crop such as tomatoes. The individual estimates are presented in Appendix I.

Assessment

Table 2 Estimation of operator exposure to Captan using German BBA Model and the proportion of the AOEL accounted for

Type of application/crop	Systemic operator exposure (mg/kg bw/day); Proportion of AOEL	
	Without protective equipment	With protective equipment[1]
orchard tractor-mounted/tractor drawn airblast; peaches/nectarines	0.393 **393%**	0.056 **56%**
tractor-mounted/tractor-drawn field crop sprayer; tomatoes	0.212 **212%**	0.091 **91%**
hand held knapsack; tomatoes	0.1661 **166%**	0.086 **86%**

[1] For applications to peaches/nectarines: gloves during mixing/loading; gloves and protective garment and sturdy footwear during application.
For applications to tomato: gloves during mixing/loading, gloves during application.

The results of the BBA Model calculations demonstrate that for the different spray application techniques and different crops, 166 to 393% of the AOEL is accounted for by exposure when spray operators wear no protective clothing. When protective equipment is worn (gloves during mixing/loading and application for applications to tomato using tractor-mounted sprayer and hand-held knapsack sprayer; gloves during mixing/loading and gloves and protective garment/sturdy footwear during application to orchard crops using tractor mounted airblast sprayer) estimated exposure accounts for 56 to 91% of the AOEL.

The operator exposure study submitted was carried out with a WP and so exposure during mixing/loading is not relevant to a WG formulation such as 'Merpan' 80 WDG/ 'Malvin WG'. Due to the larger size and granular nature of the particles comprising 'Merpan' 80 WDG/ 'Malvin WG' there is likely to be less adhesion to clothing or skin and less inhalation exposure with this type of WG formulation compared to a WP, and so the operator exposure study will tend to over-predict exposure for a WG formulation.

Furthermore, in the operator exposure study the operators wore what are described in the report as 'overalls' but a full description of the overalls is not given in the report and their nature (i.e. whether they were chemical proof overalls) cannot be verified.

Using operator exposure modelling (BBA model), estimated exposure to captan when using 'Merpan 80 WDG'/ 'Malvin' WG is less than the AOEL for operators wearing gloves during mixing/loading and application for applications to tomato, and gloves plus a chemical proof garment/sturdy footwear during application to orchard crops.

Thus, the recommended protective requirements for operators are based on the results of the modelling rather than on the operator exposure study and these are given in Table 3 below.

Table 3 Proposed protective equipment for operators applying 'Merpan 80 WDG' / 'Malvin WG'

Use	Protective clothing required
Tomatoes (tractor-mounted sprayer)	Gloves during mixing/loading; gloves during application.
Tomatoes (hand-held knapsack sprayer)	Gloves during mixing/loading; gloves during application.
Peaches/nectarines (tractor-mounted airblast sprayer)	Gloves during mixing/loading; gloves and protective garment/sturdy footwear during application.
Apples/pears (tractor-mounted airblast sprayer)	Gloves during mixing/loading; gloves and protective garment/sturdy footwear during application.

1.1.2 Bystander exposure

Evaluation table number	Reporting table number	Open Point number
-	**2(26)**	**2.12**

Conclusions of EPCO 23 (10-15.5.2005):
A new calculation on bystander exposure has to be submitted (based on a dermal absorption value of 10%)

Amended calculations of bystander exposure are presented below in comparison with an AOEL of 0.1 mg/kg bw/day using a dermal absorption value of 10%.

The vapour pressure of captan is low 4.2 x 10^{-6} Pa at 20°C and so the inhalation risk to bystanders is considered to be negligible.

Bystanders could be exposed to spray if they were walking next to a field which was being treated. However, the bystander can always be expected to be several metres away from the spray boom. At 10 m from the spray application, BBA data (BBA, 2000[4]) estimates that for orchard crops, the maximum drift estimate (90th percentile data; early application) at 10 m is 11.81%. (Use on orchard crops will lead to the maximum drift value for captan; at 10 m from a spray application to a vegetable crop such as tomatoes, the maximum drift estimate (90th percentile data; crop greater than 50 cm in height) at 10 m is 1.23%.)

Based on the maximum application rate for captan of 2.5 kg/ha for peaches/nectarines this gives a deposition concentration of 250 mg/m^2. Assuming a bystander is located 10 m from the field, they could receive 11.81% drift, i.e. the deposition could reach 29.5 mg captan/m^2. Assuming that one-half the body surface (totalling approximately 1 m^2) is covered, the skin deposition could be 14.8 mg captan.

Using 10% skin absorption, the absorbed dose of captan would be 1.48 mg and assuming a 60 kg body weight, the systemic exposure would be 0.025 mg/kg.

[4] BBA, 2000: Bekanntmachung des Verzeichnisses risikomindernder Anwendungsbedingungen für Nichtzielorganismen. Bundesanzeiger Nr. 100, 9879-9880, May 26, 2000.

The exposure of bystanders can be compared with the AOEL for captan of 0.1 mg/kg bw/day, and such a comparison shows that exposure of bystanders is approximately 25% of the AOEL.
Therefore, the risk to bystanders following the use of 'Merpan' 80 WDG and 'Malvin' WG is acceptable.

1.1.3 Worker exposure

Evaluation table number	Reporting table number	Open Point number
-	**2(30)**	**2.14**
Conclusions of EPCO 23 (10-15.5.2005): ***A new calculation on worker exposure has to be submitted taking into account the new value for dermal absorption (10%) and foliar residues***		

Amended calculations of worker exposure are presented below in comparison with an AOEL of 0.1 mg/kg bw/day using a dermal absorption value of 10%.

1.1.4 Estimation of worker exposure

Workers could enter crops such as pome fruit, peaches/nectarines or tomatoes that had been treated with 'Merpan' 80 WDG and 'Malvin' WG soon after application to harvest the crop or to carry out maintenance pruning.

The risk assessment for spray operators based on worst-case model calculations indicates that the AOEL for captan will not be exceeded by exposure for operators wearing protective gloves during mixing/loading and application to tomatoes, and protective gloves during mixing/loading and application plus a protective garment for applications to orchard crops. The exposure of other workers is expected to be lower than the spray operators since the spray would have dispersed in the air and dried on the plants before they come into contact with the treated crop.

The vapour pressure of captan is low, 4.2 x 10^{-6} Pa at 20° and the tropospheric half-life of captan is estimated to be less than one hour. Consequently, captan will not persist in the atmosphere.

Studies to measure dislodgeable residues in foliage of peaches demonstrated that residues of captan in leaves declined with a half-life of 11.5 days. Crops recommended for treatment with 'Merpan' 80 WDG and 'Malvin' WG have a PHI of 7 days.

Two estimates of worker exposure to captan for workers harvesting peaches/nectarines with and without additional protective clothing (gloves) using the German Model[5] are presented below, the first one assuming re-entry of workers 7 days after application (equivalent to the PHI for peaches/nectarines according to the proposed GAP), the second one assuming re-entry at 14 days. 'Merpan' 80 WDG and 'Malvin' WG are also used on pome fruit and tomatoes but at lower rates of application (1.8 to 2.4 kg captan/ha) and so the calculations for peaches/nectarines represent the worst-case.

[5] Hoernicke, E. *et al*., 1998. Hinweise in der Gebrauchsanleitung zum Schutz von Personen bei Nachfolgearbeiten in mit Pflanzenschutzmitteln behandelten Kulturen. Nachrichtenbl.. Deut. Pflanzenschutzd. 50 (10) p. 267.

Dislodgeable residues of captan on peach foliage are derived from a study in California. In the study, mean residue values of 10.5 μg/cm^2 and of 3.2 μg/cm^2 were measured in peach foliage respectively at 7 and 14 days after three applications of a WP formulation at 4.48 kg captan/ha. These are equivalent to foliar residues of captan of respectively 2.3 μg/cm^2/kg a.s. and 0,71 μg/cm^2/kg a.s. applied. However, only part of the total foliar residues will be dislodgeable.

1st Estimate (PHI=7 days): Workers harvesting peaches/nectarines treated with 'Merpan' 80 WDG and 'Malvin' WG at 2.5 kg captan/ha.

Dermal exposure

D (without protective gloves) = FDR x TF x R x A
D (with protective gloves) = FDR x TF x R x P x A

where:
D = dermal exposure (mg/person/day)
FDR = foliar dislodgeable residues (2.3 μg/cm^2/kg a.s.)
TF = transfer factor (30,000 cm^2/person/hour)
R = working time (8 hours/day)
A = application rate (kg a.s./ha)
P = penetration through clothes and gloves (5%)

D (without protective gloves) = 2.3 x 30,000 x 8 x 2.5 ÷ 1000
= 1380 mg/person/day

D (with protective gloves) = 2.3 x 30,000 x 8 x 0.05 x 2.5 ÷ 1000
= 69 mg/person/day

Systemic exposure

S = D ÷ bw x AF

where:
S = systemic exposure (mg/kg bw/day)
bw = worker body weight (60 kg)
AF = dermal absorption (10%)

S (without protective gloves) = 1380 x 0.1 ÷ 60
= 2.3 mg/kg bw/day

S (with protective gloves) = 69 x 0.1 ÷ 60
= 0.115 mg/kg bw/day

The maximum systemic exposure of workers to captan in the worst-case calculation above in the absence of protective gloves is 2.3 mg/kg bw/day. This assumes that all of the foliar residues measured in the peach foliage 7 days after application will be dislodgeable. The exposure of workers harvesting peaches with protective gloves was 115% of the AOEL.

2nd Estimate (PHI=14 days): Workers harvesting peaches/nectarines treated with 'Merpan' 80 WDG and 'Malvin' WG at 2.5 kg captan/ha.

Estimates are presented below using the same model and assumptions, but the foliar residue value of 0,71 μg/cm^2/kg a.s. measured after 14 days.

Dermal exposure

D (without protective gloves) = 0.71 x 30,000 x 8 x 2.5 ÷ 1000
= 426 mg/person/day

D (with protective gloves) = 0.71 x 30,000 x 8 x 0.05 x 2.5 ÷ 1000
= 21.3 mg/person/day

Systemic exposure

S (without protective gloves) = 426 x 0.1 ÷ 60
= 0.71 mg/kg bw/day

S (with protective gloves) = 21.3 x 0.1 ÷ 60
= 0.0355 mg/kg bw/day

The maximum systemic exposure of workers to captan in the worst-case calculation above in the absence of protective gloves is 0.71 mg/kg bw/day. This assumes that all of the foliar residues measured in the peach foliage 14 days after application will be dislodgeable. The exposure of workers harvesting peaches with protective gloves was 35.5% of the AOEL.

1.1.4.1 Measurement of worker exposure

No amendments to text in DAR required.

1.1.4.2 Overall assessment of worker exposure

The values in Table B.6.14.3.2.3 in the DAR are derived by multiplying the values measured on the patches by body surface areas in the worker exposure study (Knarr, 1982; Annex IIIA, 7.2.3.2/01). The totals are derived from the addition of exposure of uncovered body parts (face, back of neck, chest 'v' and hands) plus covered body parts (head, trunk, arms, legs and feet).

Harvest workers may wear clothing which leaves the arms and legs uncovered and, in such situations, a risk assessment assuming a complete layer of clothing may not be appropriate. Therefore, exposure has been recalculated from the values in the original report for unprotected arms and legs.
The calculations are given in the Excel Spreadsheet in Appendix 2.

In the study, exposure was measured for harvesters picking apples treated with captan at 3.36 kg/ha for eight hours in a day. The rate applied was 1.34 times the maximum EU GAP rate of 2.5 kg captan/ha for tree fruit (as recommended rate for peaches). Therefore, the exposure values measured in the study can be corrected for the EU GAP rate, by dividing by 1.34.

To assess risk to harvesters, the exposure measured in the exposure study is compared with the proposed AOEL for captan of 0.1 mg/kg bw/day assuming harvesters have unprotected arms and legs.

A summary of the measured exposure values, the measured values corrected for the EU GAP rate, together with the proportion of the AOEL accounted for at each harvest date is given in **Error! Reference source not found.**.

Table 4 Harvester exposure to captan and the proportion of the AOEL accounted for workers with unprotected arms and legs

Days after application	Measured exposure (mg/kg bw/day)[1]		Systemic exposure[2] (mg/kg bw/day)		% of AOEL
	Dermal	Inhalation	Measured	Corrected for EU GAP[3]	
1	2.263	0.008	0.234	0.175	175
3	1.783	0.012	0.190	0.142	142
7	1.367	0.007	0.144	0.107	107
14	0.913	0.009	0.100	0.075	75

[1] Exposure recalculated from data in original report for unprotected arms and legs based on measured values for forearms and thighs without protection factor given by clothing (see Appendix 2). Assumes a body weight of 60 kg.
[2] Assumes 10% dermal exposure and 100% inhalation exposure is absorbed.
[3] Measured exposure divided by 1.34.

With a harvest interval of 14 days exposure for workers with uncovered arms and legs was only 75% of the AOEL. Thus, the exposure measured in the study was lower than estimated by the German model. The study was conducted with a WP formulation, but residues on treated crops have been shown to be similar with different formulations. Therefore, exposure during harvesting crops treated with a WG formulation will be similar to that from harvesting crops treated with a WP formulation.

According to results of the worker field study, exposure 7 days after application (equivalent to the PHI) is 107% of the proposed AOEL, while is only 75% of the AOEL with a harvest interval of 14 days exposure.

Exposure to captan for workers harvesting tomatoes is expected to be lower than for workers harvesting tree fruit as the maximum application rate for tomatoes (1.8 kg/ha) is lower than for peaches/nectarines (2.5 kg/ha).

In conclusion, both modelling and field exposure data indicate that the exposure of workers involved with the handling of crops treated with ‘Merpan’ 80 WDG/‘Malvin’ WDG is slightly higher than the AOEL 7 days after application, while risk is acceptable for re-entry at 14 days.

Section 2. Appendix I

BBA Model

Estimate Tractor-mounted application to peaches/nectarines: 2.5 kg captan/ha (3.125 kg product/ha).

Calculation of exposure during mixing/loading and application to 'high' crops using tractor-mounted equipment according to the BBA Model

Task	Type of exposure[1]	Specific Exposure (mg/person x kg a.s.)	Work rate (ha/day)	Application rate (kg a.s./ha)	Estimated Exposure	
					(mg/person/ day)	(mg/kg bw/day)
Mixing/loading	I_M	0.008	8	2.5	0.16	0.0023
	$D_{M(H)}$	2.0	8	2.5	40	0.5714
Application	I_A	0.018	8	2.5	0.36	0.0051
	$D_{A(H)}$	0.7	8	2.5	14	0.2000
	$D_{A(C)}$	1.2	8	2.5	24	0.3429
	$D_{A(B)}$	9.6	8	2.5	192	2.7429

[1] I_M Inhalation exposure during mixing/loading.
$D_{M(H)}$ Dermal hand exposure during mixing/loading.
I_A Inhalation exposure during application.
$D_{A(H)}$ Dermal hand exposure during application.
$D_{A(C}$ Dermal head (capita) exposure during application.
$D_{A(B)}$ Dermal body exposure during application.

Route of exposure	Exposure (mg/kg bw/day)		
	Without protective equipment	With protective equipment during mixing	
Inhalation			
Mixing/loading	0.0023	none	0.0023
Application	0.0051	none	0.0051
Total inhalation:	0.0074		0.0074
Dermal			
Mixing/loading			
- Hands	0.5714	gloves	0.0057
Application			
- Hands	0.2000	gloves	0.0020
- Head	0.3429	none	0.3429
- Body	2.7429	garment[2]	0.1371
Total dermal:	3.8571		0.4877
Total systemic[1]	0.3931		0.0562

[1] Assumes 10% dermal exposure and 100% inhalation exposure is absorbed.
[2] Standard protective garment and sturdy footwear

Estimate Tractor-mounted application to tomatoes: 1.8 kg captan/ha (2.25 kg product/ha).

Calculation of exposure during mixing/loading and application to field crops using tractor-mounted equipment according to the BBA Model

Task	Type of exposure[1]	Specific Exposure (mg/person x kg a.s.)	Work rate (ha/day)	Application rate (kg a.s./ha)	Estimated exposure	
					(mg/person/ day)	(mg/kg bw/day)
Mixing/loading	I_M	0.008	20	1.8	0.288	0.0041
	$D_{M(H)}$	2.0	20	1.8	72	1.0286
Application	I_A	0.001	20	1.8	0.036	0.0005
	$D_{A(H)}$	0.38	20	1.8	13.68	0.1954
	$D_{A(C)}$	0.06	20	1.8	2.16	0.0309
	$D_{A(B)}$	1.6	20	1.8	57.6	0.8229

[1] I_M Inhalation exposure during mixing/loading.
$D_{M(H)}$ Dermal hand exposure during mixing/loading.
I_A Inhalation exposure during application.
$D_{A(H)}$ Dermal hand exposure during application.
$D_{A(C}$ Dermal head (capita) exposure during application.
$D_{A(B)}$ Dermal body exposure during application.

Route of exposure	Exposure (mg/kg bw/day)		
	Without protective equipment	With protective equipment during mixing	
Inhalation			
Mixing/loading	0.0041	none	0.0041
Application	0.0005	none	0.0005
Total inhalation:	0.0046		0.0046
Dermal			
Mixing/loading			
- Hands	1.0286	gloves	0.0103
Application			
- Hands	0.1954	gloves	0.0020
- Head	0.0309	none	0.0309
- Body	0.8229	none	0.8229
Total dermal:	2.0777		0.8661
Total systemic[1]	0.2124		0.0912

[1] Assumes 10% dermal exposure and 100% inhalation exposure is absorbed.

Estimate Hand-held application to tomatoes: 1.8 kg captan/ha (2.25 kg product/ha).

Calculation of exposure during mixing/loading and application to 'high' crops using hand-held equipment according to the BBA Model

Task	Type of exposure[1]	Specific Exposure (mg/person x kg a.s.)	Work rate (ha/day)	Application rate (kg a.s./ha)	Estimated exposure	
					(mg/person/ day)	(mg/kg bw/day)
Mixing/loading	I_M	0.02	1	1.8	0.036	0.0005
	$D_{M(H)}$	21	1	1.8	37.8	0.5400
Application	I_A	0.3	1	1.8	0.54	0.0077
	$D_{A(H)}$	10.6	1	1.8	19.08	0.2726
	$D_{A(C)}$	4.8	1	1.8	8.64	0.1234
	$D_{A(B)}$	25	1	1.8	45	0.6429

[1] I_M Inhalation exposure during mixing/loading.
$D_{M(H)}$ Dermal hand exposure during mixing/loading.
I_A Inhalation exposure during application.
$D_{A(H)}$ Dermal hand exposure during application.
$D_{A(C}$ Dermal head (capita) exposure during application.
$D_{A(B)}$ Dermal body exposure during application.

Route of exposure	Exposure (mg/kg bw/day)		
	Without protective equipment	With protective equipment during mixing	
Inhalation			
Mixing/loading	0.0005	none	0.0005
Application	0.0077	none	0.0077
Total inhalation:	0.0082		0.0082
Dermal			
Mixing/loading			
- Hands	0.5400	gloves	0.0054
Application			
- Hands	0.2726	gloves	0.0027
- Head	0.1234	none	0.1234
- Body	0.6429	none	0.6429
Total dermal:	1.5789		0.7744
Total systemic[1]	0.1661		0.0856

[1] Assumes 10% dermal exposure and 100% inhalation exposure is absorbed.

Section 3. Appendix 2

Recalculations of worker exposure from worker exposure study (Knarr, 1982; Annex IIIA, 7.2.3.2/01) for workers with unprotected arms and legs

Original worked example	Uncovered		
Dermal exposure in ug	180	25	4500
	82	4.2	344.4
	180	5.8	1044
			5888.4
			5593.98
	4400	5300	9700
			12125
			17718.98
	Covered		
	610	4	2440
	872	47	40984
	610	35	21350
	1990	23	45770
	1070	86	92020
	1070	42	44940
	1070	25	26750
			274254
			104216.5
			99005.69
	Total		116724.7

Dermal Exposure in ug. Modified calculations based on worked example in Attachment 3 of original report.

		area ratio				area ratio	
Rep 1, 1	Uncovered	skin/pad	total	Rep 1, 2	Uncovered	skin/pad	total
face	180	25	4500		270	25	6750
back of neck	82	4.2	344.4		120	4.2	504
forearms	1990	23	45770		650	23	14950
legs	1070	42	44940		850	42	35700
front of neck	180	5.8	1044		270	5.8	1566
total			96598.4				59470
total x recovery			91768.48				56496.5
hands	4400	5300	9700		9500	8200	17700
hands x 1.25			12125				22125
total uncovered			103893.5				78621.5
	Covered				Covered		
head	610	4	2440		670	4	2680
trunk	872	47	40984		1060	47	49820
upper arms	610	35	21350		670	35	23450
			0				0
thighs	1070	86	92020		850	86	73100
			0				0
feet	1070	25	26750		850	25	21250
subtotal			183544				170300
subtotal x 0.38			69746.72				64714
total x 0.95			66259.38				61478.3
covered plus uncovered	Total		170152.9		Total		140099.8

Rep 1, 3	Uncovered	area ratio skin/pad	total
	340	25	8500
	120	4.2	504
	2210	23	50830
	740	42	31080
	340	5.8	1972
			92886
			88241.7
	5100	4800	9900
			12375
			100616.7
	Covered		
	600	4	2400
	1060	47	49820
	600	35	21000
			0
	740	86	63640
			0
	740	25	18500
			155360
			59036.8
			56084.96
	Total		156701.7

Rep 1, 4	Uncovered	area ratio skin/pad	total
	110	25	2750
	57	4.2	239.4
	740	23	17020
	910	42	38220
	110	5.8	638
			58867.4
			55924.03
	5000	5800	10800
			13500
			69424.03
	Covered		
	370	4	1480
	537	47	25239
	370	35	12950
			0
	910	86	78260
			0
	910	25	22750
			140679
			53458.02
			50785.12
	Total		120209.1

Rep 1, 5	Uncovered	area ratio skin/pad	total
	63	25	1575
	75	4.2	315
	910	23	20930
	490	42	20580
	63	5.8	365.4
			43765.4
			41577.13
	5700	4700	10400
			13000
			54577.13
	Covered		
	510	4	2040
	648	47	30456
	510	35	17850
			0
	490	86	42140
			0
	490	25	12250
			104736
			39799.68
			37809.7
	Total		92386.83

Rep 2, 1	Uncovered		
	65	25	1625
	34	4.2	142.8
	840	23	19320
	1010	42	42420
	65	5.8	377
			63884.8
			60690.56
	7700	6000	13700
			17125
			77815.56
	Covered		
	440	4	1760
	539	47	25333
	440	35	15400
			0
	1010	86	86860
			0
	1010	25	25250
			154603
			58749.14
			55811.68
	Total		133627.2

Rep 2, 2	Uncovered		
	110	25	2750
	110	4.2	462
	950	23	21850
	590	42	24780
	110	5.8	638
			50480
			47956
	13000	12000	25000
			31250
			79206
	Covered		
	910	4	3640
	1130	47	53110
	910	35	31850
			0
	590	86	50740
			0
	590	25	14750
			154090
			58554.2
			55626.49
	Total		134832.5

Rep 2, 3	Uncovered			Rep 2, 4	Uncovered			Rep 2, 5	Uncovered		
	280	25	7000		95	25	2375		38	25	950
	88	4.2	369.6		89	4.2	373.8		35	4.2	147
	730	23	16790		460	23	10580		470	23	10810
	400	42	16800		450	42	18900		510	42	21420
	280	5.8	1624		95	5.8	551		38	5.8	220.4
			42583.6				32779.8				33547.4
			40454.42				31140.81				31870.03
	7000	6800	13800		11000	11000	22000		6500	6700	13200
			17250				27500				16500
			57704.42				58640.81				48370.03
	Covered				Covered				Covered		
	556	4	2224		330	4	1320		290	4	1160
	924	47	43428		514	47	24158		363	47	17061
	556	35	19460		330	35	11550		290	35	10150
			0				0				0
	400	86	34400		450	86	38700		510	86	43860
			0				0				0
	400	25	10000		450	25	11250		510	25	12750
			109512				86978				84981
			41614.56				33051.64				32292.78
			39533.83				31399.06				30678.14
	Total		97238.25		Total		90039.87		Total		79048.17

Rep 2, 1	Uncovered			Rep 2, 2	Uncovered		
	65	25	1625		110	25	2750
	34	4.2	142.8		110	4.2	462
	840	23	19320		950	23	21850
	1010	42	42420		590	42	24780
	65	5.8	377		110	5.8	638
			63884.8				50480
			60690.56				47956
	7700	6000	13700		13000	12000	25000
			17125				31250
			77815.56				79206
	Covered				Covered		
	440	4	1760		910	4	3640
	539	47	25333		1130	47	53110
	440	35	15400		910	35	31850
			0				0
	1010	86	86860		590	86	50740
			0				0
	1010	25	25250		590	25	14750
			154603				154090
			58749.14				58554.2
			55811.68				55626.49
	Total		133627.2		Total		134832.5

Rep 3, 1	Uncovered		
	92	25	2300
	32	4.2	134.4
	420	23	9660
	1010	42	42420
	92	5.8	533.6
			55048
			52295.6
	5400	4700	10100
			12625
			64920.6
	Covered		
	300	4	1200
	424	47	19928
	300	35	10500
			0
	1010	86	86860
			0
	1010	25	25250
			143738
			54620.44
			51889.42
	Total		116810

Rep 3, 2	Uncovered		
	130	25	3250
	69	4.2	289.8
	350	23	8050
	560	42	23520
	130	5.8	754
			35863.8
			34070.61
	9000	7900	16900
			21125
			55195.61
	Covered		
	300	4	1200
	499	47	23453
	300	35	10500
			0
	560	86	48160
			0
	560	25	14000
			97313
			36978.94
			35129.99
	Total		90325.6

Rep 3, 3	Uncovered		
	190	25	4750
	30	4.2	126
	520	23	11960
	240	42	10080
	190	5.8	1102
			28018
			26617.1
	4000	3600	7600
			9500
			36117.1
	Covered		
	250	4	1000
	470	47	22090
	250	35	8750
			0
	240	86	20640
			0
	240	25	6000
			58480
			22222.4
			21111.28
	Total		57228.38

Rep 3, 4	Uncovered		
	110	25	2750
	56	4.2	235.2
	700	23	16100
	560	42	23520
	110	5.8	638
			43243.2
			41081.04
	3700	4100	7800
			9750
			50831.04
	Covered		
	270	4	1080
	436	47	20492
	270	35	9450
			0
	560	86	48160
			0
	560	25	14000
			93182
			35409.16
			33638.7
	Total		84469.74

Rep 3, 5	Uncovered		
	33	25	825
	29	4.2	121.8
	590	23	13570
	360	42	15120
	33	5.8	191.4
			29828.2
			28336.79
	4300	3900	8200
			10250
			38586.79
	Covered		
	240	4	960
	302	47	14194
	240	35	8400
			0
	360	86	30960
			0
	360	25	9000
			63514
			24135.32
			22928.55
	Total		61515.34

Rep 2, 1	Uncovered			Rep 2, 2	Uncovered		
	65	25	1625		110	25	2750
	34	4.2	142.8		110	4.2	462
	840	23	19320		950	23	21850
	1010	42	42420		590	42	24780
	65	5.8	377		110	5.8	638
			63884.8				50480
			60690.56				47956
	7700	6000	13700		13000	12000	25000
			17125				31250
			77815.56				79206
	Covered				Covered		
	440	4	1760		910	4	3640
	539	47	25333		1130	47	53110
	440	35	15400		910	35	31850
			0				0
	1010	86	86860		590	86	50740
			0				0
	1010	25	25250		590	25	14750
			154603				154090
			58749.14				58554.2
			55811.68				55626.49
	Total		133627.2		Total		134832.5

Rep 4, 1	Uncovered			Rep 4, 2	Uncovered		
	140	25	3500		90	25	2250
	28	4.2	117.6		24	4.2	100.8
	340	23	7820		256	23	5888
	620	42	26040		260	42	10920
	140	5.8	812		90	5.8	522
			38289.6				19680.8
			36375.12				18696.76
	4500	4600	9100		6100	4800	10900
			11375				13625
			47750.12				32321.76
	Covered				Covered		
	260	4	1040		192	4	768
	428	47	20116		306	47	14382
	260	35	9100		192	35	6720
			0				0
	620	86	53320		260	86	22360
			0				0
	620	25	15500		260	25	6500
			99076				50730
			37648.88				19277.4
			35766.44				18313.53
	Total		83516.56		Total		50635.29

Rep 4, 3	Uncovered			Rep 4, 4	Uncovered			Rep 4, 5	Uncovered		
	100	25	2500		52	25	1300		25	25	625
	21	4.2	88.2		34	4.2	142.8		28	4.2	117.6
	260	23	5980		406	23	9338		320	23	7360
	330	42	13860		220	42	9240		240	42	10080
	100	5.8	580		52	5.8	301.6		25	5.8	145
			23008.2				20322.4				18327.6
			21857.79				19306.28				17411.22
	3100	2500	5600		2900	3900	6800		3700	4000	7700
			7000				8500				9625
			28857.79				27806.28				27036.22
	Covered				Covered				Covered		
	224	4	896		199	4	796		198	4	792
	345	47	16215		285	47	13395		251	47	11797
	224	35	7840		199	35	6965		198	35	6930
			0				0				0
	330	86	28380		220	86	18920		240	86	20640
			0				0				0
	330	25	8250		220	25	5500		240	25	6000
			61581				45576				46159
			23400.78				17318.88				17540.42
			22230.74				16452.94				16663.4
	Total		51088.53		Total		44259.22		Total		43699.62

Dermal exposure in mg

	1	2	3	4	5	Total	Mean
PHI 1	170	140	157	120	92	679	135.8
PHI 3	134	135	97	90	79	535	107
PHI 7	117	90	57	84	62	410	82
PHI 14	84	51	51	44	44	274	54.8

Dermal exposure in mg

	1	2	3	4	5	Total	Mean
PHI 1	170	140	157	120	92	679	135.8
PHI 3	134	135	97	90	79	535	107
PHI 7	117	90	57	84	62	410	82
PHI 14	84	51	51	44	44	274	54.8

Residues

October 2005

Introduction

This document contains new calculations provided according to the evaluation table requirements.

New information is presented here cross-referencing the Open point numbers.

Document D1: Critical Good Agricultural Practice

Critical Good Agricultural Practice for captan in the EU

Crop	Member state or country	Product name	F, G or I	Pests or group of pests controlled	Formulation		Application			Application rate per treatment			PHI (days)	Remarks:
					Type	Conc. of a.s.	method kind	growth stage/ timing	number[b] (max.)	kg a.s./hL (max.)	water L/ha	kg a.s./ha (max.)		
Pome fruit	North EU	'Merpan' 80 WDG / 'Malvin' WDG	F[a]	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 53 / April	9 - 10	0.125	1000	1.25	14	
	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69 / April	9 + 3 [c]	0.125 0.24	1000 1000	1.25 2.4	14	
Tomatoes	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Foliar spray; down-wards	From BBCH 60 to 87	4	0.15	1200	1.8	14	
Peaches/ nectarines	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69: petal fall	4	0.25	1000	2.5	7	

[a] F = field.
[b] Applications at a minimum of 7 days for all crops.
[c] Nine applications at 1.25 kg a.s./ha (scab control) followed by three applications at 2.4 kg a.s/ha (*Nectria* control).

Evaluation table number	Reporting table number	Open Point number
-	**3(1)**	**3.1**

Conclusions of the EFSA Evaluation Meeting:
RMS to provide an addendum to be considered in expert meeting with the new MRL proposal for peaches and nectarines, new TMDI and I(N)EDI calculations, as well as new STMR calculations.

Peaches and nectarines

The relevant residue values according to the GAP (PHI 7 days) as given in Table B.7.6.3.1 in the DAR are underlined in Table 1 below.

Table 1 Residues of captan in peaches and nectarines following applications of WG and WP formulations of captan in southern EU

Location Year Trial	Application					Portion analysed	PHI (days)	Captan residue (mg/kg)	Ref.
	Formuln (type, content)	No.	Method	kg a.s./ ha	kg a.s./ hL				
Peaches									
S.France 2000 TL1 Grenade sur Garonne, (31330)	WG, 800 g/kg	4	foliar; knap-sack	3.06 - 3.52	0.25	whole fruit	7	3.5	TMN-0651A (IIA 6.3/17)
							13	1.3	
							21	0.56	
Spain 2000 PA1 Lora del Rio (41440)	WG, 800 g/kg	4	foliar; knap-sack	2.96 - 3.27	0.15	whole fruit	11	4.9	
							15	6.3	
							22	2.2	
Spain 2000 ES1 Gualta (17257)	WG, 800 g/kg	4	foliar; knap-sack	3.05 - 3.17	0.15	whole fruit	9	3.7	
							14	2.8	
							21	1.7	
S. France 2001 Vacquiers (31340)	WG, 800 g/kg	4	foliar; knap-sack	2.94 - 3.08	0.25	whole fruit	8	4.4	TMN-0652 (IIA 6.3/20)
							13	1.6	
							20	0.66	
Nectarines									
Greece 1999 GR1 Veria (59100)	WP, 830 g/kg	4	foliar; knap-sack	2.80 - 2.99	0.125	whole fruit	7	5.6	TMN-0643 (IIA 6.3/18)
							14	4.1	
							21	1.5	
Greece 1999 GR2 Naoussa (59100)	WP, 830 g/kg	4	foliar; knap-sack	2.85 - 3.00	0.125	whole fruit	7	3.1	
							14	2.3	
							21	0.90	
Spain 1999 ES1 Gualta (17257)	WP, 500 g/kg	4	foliar; knap-sack	2.84 - 3.03	0.15	whole fruit	7	2.1	
							11	1.8	
							21	0.62	
Spain 1999 ES2 Pals (Girona, 17256)	WP, 500 g/kg	4	foliar; knap-sack	2.98 - 3.02	0.15	whole fruit	7	2.5	
							11	1.3	
							21	0.43	

Calculations of MRL and STMR for peaches/nectarines

Calculations of the MRL, STMR and HR values for peaches and nectarines according to Commission Directive 7039/VI/95 EN are presented below.

The relevant residue results arranged in ascending order are presented in Table 2.

Table 2 Residues of captan in peaches and nectarines for calculating MRL, STMR and HR values

Location, Year, Trial	Application		PHI	Captan residue
	No.	kg a.s./ ha	(days)	(mg/kg)
Spain, 1999, ES1 Gualta	4	2.84 - 3.03	7	2.1
Spain 1999, ES2 Pals	4	2.98 - 3.02	7	2.5
Greece, 1999, GR2 Naoussa	4	2.85 - 3.00	7	3.1
S.France, 2000, TL1 Grenade sur Garonne	4	3.06 - 3.52	7	3.5
Spain, 2000, ES1 Gualta	4	3.05 - 3.27	9	3.7
S. France, 2001, Vacquiers	4	2.94 - 3.08	8	4.4
Spain , 2000, PA1 Lora del Rio	4	2.96 - 3.17	11	4.9
Greece, 1999, GR1 Veria	4	2.80 - 2.99	7	5.6

MRL calculation Method 1

$R(max) = R_{mean} + k \times s$
$= 3.73 + (3.188 \times 1.191)$

R(max) = 7.5 mg/kg.

k value from tables (according to Commission Working Document 7032, 1997)
s = standard deviation

MRL calculation Method 2

Number (n)	8
P = T/100	0.75
T = percentile value	75
J = integer of (n + 1) x P	6
G = modulus of (n + 1) x P	0.75
R(J) = residue value at point J	4.4
R(J + 1) = residue value at point J + 1	4.9

R(0.75) = (1 - G) x R(J) + G x R(J + 1)
= 1.1 + 3.7
= 4.8

R(calc) = 2 x R(0.75) in mg/kg = 9.6 mg/kg

Both methods of calculation indicate that a MRL of 10.0 mg/kg is appropriate for peaches and nectarines. A MRL of 10 mg/kg is proposed for peaches and nectarines.

STMR value = 3.5 + 3.7/2 = 3.6 mg/kg.

HR value = 5.6 mg/kg

Apple and pears

The value of 8.0 mg/kg recorded in apple following applications according to the GAP (PHI 14 days) at trial Brignano in Italy 2000 was not considered to be an outlier at the EPCO meeting.

Calculations of MRL and STMR for apples and pears

A MRL of 10 mg/kg has been agreed by EPCO for apple and pear.

STMR and HR values are calculated from the residue values below:

Table 3 Residues of captan in apples and pears in Southern EU for calculating STMR and HR

Location, Year, Trial	Application		PHI (days)	Captan residue (mg/kg)
	No.	kg a.s./ ha		
S.France, 2000	11	2.4-2.6	14	0.54
Spain, 2000	11	2.3-2.7	15	0.79
Italy, 1997	9	2.56	14	1.3
Spain, 2000	12	2.3-2.9	13	1.5
S.France, 2000	11	2.4-2.6	14	2.3
Portugal, 1991	10	2.4	14	2.9
Italy, 2000	12	2.3-2.5	14	4.2
Italy, 2000	11	2.3-2.5	14	8.0

STMR = 1.5 + 2.3/2 = 1.9 mg/kg.
HR = 8.0 mg/kg

Table 4 Residues of captan in apples and pears in Northern EU for calculating STMR and HR

Location, Year, Trial	Application		PHI (days)	Captan residue (mg/kg)
	No.	kg a.s./ ha		
Germany, 1993 RS-9312-K1 apple	10	1.494	13	0.71
Germany, 1994 4211 apple	10	1.245	14	0.76
Germany, 1993 RS-9312-G1 pear	10	1.494	14	1.2
Germany, 1993 RS-9312-G1 pear	10	1.494	14	1.3
Germany, 1993 RS-9312-K1 apple	10	1.494	13	1.3
Germany, 1994 4212 apple	10	1.245	14	1.3
Germany, 1993 RS-9312-B1 apple	10	1.494	14	2.1
Germany, 1993 RS-9312-B1 apple	10	1.494	14	2.5
Germany, 1993 RS-9312-B2 apple	10	1.494	13	2.7
Germany, 1993 RS-9312-B2 apple	10	1.494	13	3.5

STMR = 1.3 + 1.3/2 = 1.3 mg/kg.
HR = 3.5 mg/kg

Tomatoes

Relevant values proposed in the DAR are as follows:

MRL = 2 mg/kg
STMR = 0.28 mg/kg
HR = 1.1 mg/kg (from residue trial: Spain 2001 PA2 Lebrija 41740)

Consumer risk assessment

Chronic exposure

Theoretical Maximum Daily Intake (TMDI)

The TMDI is based on food consumption data and the existing or proposed MRLs for apples, pears, tomatoes, peaches and nectarines.

The TMDI assumes the following:

1) All the crop is treated and contains residues at the MRL.
2) Residues are not removed or reduced during storage, washing, processing or food preparation.

The TMDI is calculated by multiplying the MRL by the estimated average daily consumption for a given food commodity.

$TMDI = \sum MRL \times F$

where:
MRL = Maximum residue limit for a given food commodity
F = Consumption of that food commodity.

MRLs for captan are as follows:
Apples/pears – 10 mg/kg
Peaches/nectarines – 10 mg/kg
Tomatoes – 2 mg/kg

This calculation is performed using:

3) An International diet (European Region) based on data from the World Health Organisation (WHO)[6].
4) The UK Dietary model (PSD, 1999[7])
5) The German BBA average food consumption data (Federal Biological Office for Agriculture and Forestry, 1993[8])

WHO European diet

The TMDI calculation is presented in Table 5 below.

[6] WHO (1989). Guidelines for predicting dietary intake of pesticide residues. Prepared by the joint UNEP/FAO/WHO Food Contamination Monitoring Programme in collaboration with the Codex Committee on Pesticide Residues. World Health Organisation, Geneva.

[7] PSD (1999). Guidance on the estimation of dietary intakes of pesticides residues. The Registration Handbook. Pesticides Safety Directorate, Ministry of Agriculture, Fisheries and Food.

[8] Federal Biological Office for Agriculture and Forestry, (1993). Testing of the residue behaviour - Assessment of the intake of pesticide residues via food. Guidelines for pesticides testing in the registration procedure. Part IV 3 - 7.

Table 5 TMDI calculation for captan based on WHO diet

Commodity	MRL (mg/kg)	Consumption (kg/person/day)	TMDI (mg/person/day)
Apples	10	0.0400	0.4000
Pears	10	0.0113	0.1130
Tomatoes	2	0.0660	0.1320
Peaches and nectarines	10	0.0125	0.1250
Total			**0.7700**

The total TMDI is 0.7700 mg/person/day day or 0.013 mg/kg bw/day for a 60 kg adult.

UK diet

UK consumption data for adults, children, toddlers and infants (mean consumers and high, i.e. 97.5th percentile, consumers) are presented in Table 6.

The TMDI for adults, children, toddlers and infants based on the mean and 97.5th percentile consumption data for each commodity are presented in Table 7 and Table 8, respectively. Table 8 also includes the total TMDI calculated from the total of the two highest 97.5th percentile intakes plus the mean population intakes for the other crops.

Table 6 UK consumption data for adults, children, toddlers and infants

Commodity	Consumption data (kg/day)							
	Adults (70.1 kg bw)		Children (43.6 kg bw)		Toddlers (14.5 kg bw)		Infants (8.7 kg bw)	
	Mean	High [1]	Mean	High	Mean	High	Mean	High
Apples	0.0279	0.1566	0.0256	0.1328	0.0245	0.2186	0.0143	0.0751
Pears	0.0042	0.0988	0.0026	0.0634	0.0027	0.0974	0.0023	0.0254
Tomatoes	0.0228	0.0755	0.0086	0.0361	0.0061	0.0372	0.0013	0.0136
Peaches/ nectarines	0.0047	0.0958	0.0019	0.0478	0.0021	0.1074	0.0005	0.0194

[1] 97.5th percentile.

Table 7 TMDI calculation for captan for adults, children, toddlers and infants based on UK mean consumption intakes

Commodity	MRL (mg/kg)	TMDI (mg/kg bw/day) [1]			
		Adults (70.1 kg bw)	Children (43.6 kg bw)	Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
Apple	10	0.00398	0.00587	0.01690	0.01644
Pears	10	0.00060	0.00060	0.00186	0.00264
Tomatoes	2	0.00065	0.00039	0.00084	0.00030
Peaches/ nectarines	10	0.00067	0.00044	0.00145	0.00057

[1] Calculated for each crop from mean intakes.

Table 8 TMDI calculation for captan for adults, children, toddlers and infants based on UK high consumption intakes

Commodity	MRL (mg/kg)	TMDI (mg/kg bw/day) [1]			
		Adults (70.1 kg bw)	Children (43.6 kg bw)	Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
Apple	10	*0.02234*	*0.03046*	*0.15076*	*0.08632*
Pears	10	*0.01409*	*0.01454*	0.06717	*0.02920*
Tomatoes	2	0.00215	0.00166	0.00513	0.00313
Peaches/nectarines	10	0.01367	0.01096	*0.07407*	0.02230
Total exposure [2]		**0.03775**	**0.04583**	**0.22753**	**0.11639**

[1] Calculated for each crop from 97.5th percentile intakes.
[2] Calculated from total of the two highest 97.5th percentile intakes (*in italics*) plus mean population intakes for other crops (from Table 7).

The TMDIs are 0.038 mg/kg bw/day (adults), 0.046 mg/kg bw/day (children), 0.228 mg/kg bw/day (toddlers) and 0.117 mg/kg bw/day (infants).

German diet

The TMDI calculation for a 13.5 kg 4 to 6 year old girl is presented in Table 9.

Table 9 TMDI calculation for captan for a 4 to 6 year old girl based on German diet

Commodity	MRL (mg/kg)	Consumption (kg/person/day)	TMDI (mg/person/day)
Apples	10	0.0420	0.4200
Pears	10	0.0064	0.0640
Tomatoes	2	0.0151	0.0302
Peaches and nectarines	10	0.0079	0.0790
Total exposure	-	-	0.5932

The total TMDI is 0.593 mg/person/day day or 0.044 mg/kg bw/day for a 13.5 kg girl.

Comparison of TMDI with ADI

The TMDI values for different consumer groups and diets are summarised in Table 10.

Table 10 TMDI values for different consumer groups and diets

Diet	Body weight (kg)	TMDI (mg/kg bw/day)	TMDI as % of the ADI
WHO adult	60	0.013	13
UK adult	70.1	0.038	38
UK child	43.6	0.046	46
UK toddler	14.5	0.228	228
UK infant	8.7	0.117	117
German child	13.5	0.044	44

Based on the proposed ADI for captan of 0.1 mg/kg bw/day, the TMDI represents 13% to 228% of the ADI for the different consumer groups and different dietary intakes.

The TMDI is less than the ADI for captan for adults (WHO and UK diets) and children (UK and German diets). There is therefore a large margin of safety for these consumer groups and more refined calculations of intake are not required.

The TMDI for toddlers and infants using the UK dietary model exceeds the ADI and so it is necessary to carry out more refined calculations of intake for toddlers. These are presented below.

National Estimated Daily Intake (NEDI)

The NEDI is a more realistic estimate of pesticide residue intake. It takes into account distribution between edible and non-edible portions of crop, possible losses during processing or cooking and more realistic assessments of residue levels.

$NEDI = \sum F_i \times RL_i \times K$

where:
F_i = Consumption of that food commodity.
RL_i = Appropriate residue level for the food commodity (e.g. STMR).
K = Correction factor taking into account reduction or increase in residues during storage, processing, food preparation (washing, removing outer leaves), cooking.

The supervised trials median residue (STMR) is the residue value in the position of [0.5(n+1)], when residue values are placed in ascending order of magnitude, where n = number of residue values. STMR values for captan are as follows:

apples/pears – 1.9 mg/kg (worst-case STMR value calculated from Southern EU residue results)
tomatoes - 0.28 mg/kg
peaches/nectarines – 3.6 mg/kg

Since most of each of the commodities recommended for treatment with captan are consumed raw, no correction is made for loss of residues during processing for this calculation. No concentration of residues in human edible commodities occurred in processing studies. Therefore, in the above equation K = 1.

STMR values and NEDI calculations for a 14.5 kg toddler and 8.7 kg infant based on UK mean and high consumption intakes are presented in Tables 11 and 12, respectively. These tables also includes the total NEDI calculated from the total of the two highest 97.5th percentile intakes plus the mean population intakes for the other crops.

Table 11 NEDI calculation for captan for toddlers based on UK mean and high consumption intakes

Commodity	STMR (mg/kg)	NEDI (mg/kg bw/day) for toddlers (14.5 kg bw)	
		Mean consumption intakes[1]	High consumption intakes[2]
Apple	1.9	0.00321	*0.02864*
Pears	1.9	*0.00035*	0.01276
Tomatoes	0.28	*0.00012*	0.00072
Peaches/nectarines	3.6	0.00052	*0.02666*
Total exposure[3]		**0.05577**	

[1] Calculated for each crop from mean intakes.
[2] Calculated for each crop from 97.5th percentile intakes.
[3] Calculated from total of the two highest 97.5th percentile intakes (*in italics*) plus mean population intakes for other crops (*in italics*).

Table 12 NEDI calculation for captan for infants based on UK mean and high consumption intakes

Commodity	STMR (mg/kg)	NEDI (mg/kg bw/day) for infants (8.7 kg bw)	
		Mean consumption intakes[1]	High consumption intakes[2]
Apple	1.9	0.00312	*0.01640*
Pears	1.9	*0.00050*	0.00555
Tomatoes	0.28	*0.00004*	0.00044
Peaches/nectarines	0.78	0.00021	*0.00803*
Total exposure[3]		**0.02497**	

[1] Calculated for each crop from mean intakes.
[2] Calculated for each crop from 97.5th percentile intakes.
[3] Calculated from total of the two highest 97.5th percentile intakes (*in italics*) plus mean population intakes for other crops (*in italics*).

The NEDI values for toddlers and infants are 0.056 mg/kg bw/day and 0.025 mg/kg bw/day, respectively.

Comparison of NEDI with ADI

Table 13 NEDI values for different consumer groups based on UK diet

Diet	Body weight (kg)	NEDI (mg/kg bw/day)	NEDI as % of the ADI
UK toddler	14.5	0.056	56
UK infant	8.7	0.025	25

The NEDI value for toddlers and infants represents 56% and 25%, respectively, of the ADI for captan of 0.1 mg/kg bw/day. There is, therefore, a large margin of safety for toddler and infant consumers.

Evaluation table number	Reporting table number	Open Point number
-	-	**3.14**

Conclusions of the EFSA Evaluation Meeting:
RMS to include acute intake calculation in an addendum to be considered at an expert meeting.
Conclusions of the EPCO Expert Meeting:
Recalculations according to the latest formula is necessary

Acute exposure

National estimate of short-term intake (NESTI)

The NESTI is calculated by multiplying full portion consumption data by the highest residue level detected in trials (HR) corrected for processing, cooking, etc.

$$NESTI = \frac{(HR\text{-}P \times F)}{\text{mean body weight}}$$

where:
F = Full portion consumption data for the commodity unit.
HR-P = Highest residue level for a food commodity corrected for processing, etc.

Calculations of the NESTI for adults (16 to 64 years old) and toddlers (1½ to 4½ years old) according to the UK Dietary model and for children (2 to under 5 years old) according to the German model[9] are presented. The calculations use the highest residue levels arising from the use of captan found in trials conducted according to the GAP.

The HR values are as follows:
Apples/pears – 8.0 mg/kg (worst-case value recorded from trials in Southern EU).
Peaches/nectarines – 5.6 mg/kg
Tomatoes – 1.1 mg/kg

For certain crops, a variability factor (v) for residues in individual commodities is taken into account. This reflects the ratio of a high level residue in an individual commodity unit to the corresponding composite residue level.

Thus:

$$NESTI = \frac{\{U \times HR\text{-}P \times v\} + \{(F-U) \times HR\text{-}P\}}{\text{mean body weight}}$$

where:
U = Weight of the first commodity unit or if the full portion consumption data is less than one commodity unit then U is equal to the full portion consumption data and the second term of the equation drops out.

[9] Banasiak U, Heseker H, Sieke C, Sommerfeld C, Vohmann C (2005) Abschätzung der Aufnahme von Pflanzenschutzmitte-Rückständen in der Nahrung mit neuen Verzehrsmengen für Kinder. Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschutz 2005 48:84-98

HR-P = Highest residue level for a food commodity. Corrected for cooking/processing, etc., for commodities when none is consumed raw.
v = Variability factor
F = Full portion consumption data for the commodity unit.

Risk assessment (UK model)

UK portion consumption data, portion sizes, appropriate variability factors and HR values are shown in Table 15:

Table 15 UK portion consumption data, portion commodity sizes, appropriate variability factors and HR values

Commodity	UK 97.5th percentile portion consumption data (kg/day)		UK commodity size (kg)	Appropriate variability factor[a]	Highest captan residue (HR) values (mg/kg)
	Adults (70.1 kg bw)	Toddlers (14.5 kg bw)			
Tomatoes	0.157	0.093	0.085	7	1.1
Peaches	0.228	0.144	0.110	5	5.6
Apples	0.308	0.199	0.112	5	8.0
Pears	0.274	0.279	0.150	5	8.0

[a] See section 'Choice of Variability Factor' in text above.

Based on the portion data and variability factors in Table 15, NESTI values are presented in Table 16. The NESTI values are compared with the acute reference dose ARfD for captan of 0.1 mg/kg bw/day as proposed by RMS/EFSA/EPCO.

Table 16 NESTI calculation for captan based on UK consumption date and commodity size

Commodity	HR (mg/kg)	NESTI (mg/kg bw/day)		% of ARfD	
		Adults (70.1 kg bw)	Toddlers (14.5 kg bw)	Adults (70.1 kg bw)	Toddlers (14.5 kg bw)
Tomato	1.1	0.011[a]	0.046[b]	11%	46%
Peaches	5.6	0.053[c]	0.226[d]	53%	226%
Apple	8.0	0.086[e]	0.357[f]	86%	357%
Pear	8.0	0.100[g]	0.485[h]	100%	485%

[a] Adults: $NESTI = \frac{(0.085 \times 1.1 \times 7) + (0.157 - 0.085) \times 1.1}{70.1} = 0.011$

[b] Toddlers: $NESTI = \frac{(0.085 \times 1.1 \times 7) + (0.093 - 0.085) \times 1.1}{14.5} = 0.046$

[c] Adults: $NESTI = \frac{(0.110 \times 5.6 \times 5) + (0.228 - 0.110) \times 5.6}{70.1} = 0.053$

[d] Toddlers: $NESTI = \frac{(0.110 \times 5.6 \times 5) + (0.144 - 0.110) \times 5.6}{14.5} = 0.226$

[e] Adults: $NESTI = \frac{(0.112 \times 8.0 \times 5) + (0.308 - 0.112) \times 8.0}{70.1} = 0.086$

[f] Toddlers: NESTI = $\frac{(0.112 \times 8.0 \times 5) + (0.199 - 0.112) \times 8.0}{14.5} = 0.357$

[g] Adults: NESTI = $\frac{(0.150 \times 8.0 \times 5) + (0.274 - 0.150) \times 8.0}{70.1} = 0.100$

[h] Toddlers: NESTI = $\frac{(0.150 \times 8.0 \times 5) + (0.279 - 0.150) \times 8.0}{14.5} = 0.485$

The NESTI values for tomatoes represent 11 and 46% of the ARfD for captan of 0.1 mg/kg bw/day.

The NESTI values for peaches represent 53 and 226% of the ARfD for captan of 0.1 mg/kg bw/day.

The NESTI values for apples represent 86 and 357% of the ARfD for captan of 0.1 mg/kg bw/day.

The NESTI values for pears represent 100 and 485% of the ARfD for captan of 0.1 mg/kg bw/day.

Since the NESTI values for adults and toddlers consuming tomatoes, and adults consuming apples and peaches, are less than the ARfD, the acute risk to adults and toddlers is considered to be low.

Acute Risk Assessment (German model)

German portion consumption data, portion sizes, appropriate variability factors and HR values are shown in Table 21:

Table 21 German portion consumption data, portion commodity sizes, appropriate variability factors and HR values

Commodity	German 97.5th portion consumption data (kg/day) for children (16.15 kg bw)	German commodity size (kg)	Appropriate variability factor[a]	Highest captan residue (HR) values (mg/kg)
Tomatoes	0.1506	0.099	7	1.1
Peaches/ nectarines	0.1926	0.097	5	5.6
Apples	0.2348	0.182	5	8.0
Pears	0.2318	0.207	5	8.0

[a] See section 'Choice of Variability Factor' in text above.

Based on the portion data and variability factors in Table 19, NESTI values are presented in Table 22. The NESTI values are compared with the acute reference dose ARfD for captan of 0.1 mg/kg bw/day as proposed by RMS/EFSA/EPCO.

Table 22 NESTI calculation for captan based on German consumption date and commodity size

Commodity	HR (mg/kg)	Children (16.15 kg bw)	
		NESTI (mg/kg bw/day)	% of ARfD
Tomato	1.1	0.051[a]	51%
Peaches/ nectarines	5.6	0.201[b]	201%
Apple	8.0	0.477[c]	477%
Pear	8.0	0.525[d]	525%

[a] Children: NESTI = $\frac{(0.099 \times 1.1 \times 7) + (0.1506 - 0.099) \times 1.1}{16.15} = 0.051$

[b] Children: NESTI = $\frac{(0.097 \times 5.6 \times 5) + (0.1926 - 0.097) \times 5.6}{16.15} = 0.201$

[c] Children: NESTI = $\frac{(0.182 \times 8.0 \times 5) + (0.2348 - 0.182) \times 8.0}{16.15} = 0.477$

[d] Children: NESTI = $\frac{(0.207 \times 8.0 \times 5) + (0.2318 - 0.207) \times 8.0}{16.15} = 0.525$

The NESTI value for tomatoes represents 51% of the ARfD for captan of 0.1 mg/kg bw/day.

The NESTI value for peaches/nectarines represents 201% of the ARfD for captan of 0.1 mg/kg bw/day.

The NESTI value for apples represents 477% of the ARfD for captan of 0.1 mg/kg bw/day.

The NESTI value for pears represents 525% of the ARfD for captan of 0.1 mg/kg bw/day.

Since the NESTI values for children consuming tomatoes are less than the ARfD, the acute risk to children is considered to be low.

Makhteshim and Arysta have presented some alternative calculations based on different assumptions, as listed below

Refined calculations using UK model: Apples and pears
(Makhteshim and Arysta proposal)

The NESTI values for toddlers consuming apple and pear exceed the ARfD. However, it is noted that this risk assessment is based on a single extreme value of 8.0 mg/kg recorded in one supervised residue trial in apple, and consider by the Notifier to be a clear outlier. In 17 other supervised residue trials in apple/pear with applications according to the GAP (see Tables 3 and 4 in this document), residue levels ranged from 0.54 to 4.2 mg/kg. In survey data submitted by the notifier in March 2005[10], from a total of 3,083 samples of apples and pears 98.3% contained residues of captan of 1 mg/kg or less.

A NESTI calculation using a more realistic HR residue value of 1 mg/kg derived from the survey data is presented in Table 17 below:

Table 17 NESTI calculation for captan based on UK consumption data and commodity size plus a more realistic residue values for apple and pear

Commodity	*HR (mg/kg)*	*NESTI (mg/kg bw/day)*		*% of ARfD*	
		Adults (70.1 kg bw)	*Toddlers (14.5 kg bw)*	*Adults (70.1 kg bw)*	*Toddlers (14.5 kg bw)*
Apple	*1.0*	*0.011*[a]	*0.045*[b]	*11%*	*45%*
Pear	*1.0*	*0.013*[c]	*0.061*[d]	*13%*	*61%*

[a] *Adults: NESTI = $\frac{(0.112 \times 1.0 \times 5) + (0.308 - 0.112) \times 1.0}{70.1} = 0.011$*

[b] *Toddlers: NESTI = $\frac{(0.112 \times 1.0 \times 5) + (0.199 - 0.112) \times 1.0}{14.5} = 0.045$*

[c] *Adults: NESTI = $\frac{(0.150 \times 1.0 \times 5) + (0.274 - 0.150) \times 1.0}{70.1} = 0.013$*

[d] *Toddlers: NESTI = $\frac{(0.150 \times 1.0 \times 5) + (0.279 - 0.150) \times 1.0}{14.5} = 0.061$*

The NESTI values for apple and pear using the more realistic residue value of 1 mg/kg (taken from survey data in which 98.3% of 3,083 samples of apples and pears contained residues of captan of 1 mg/kg or less) represent 11 to 61% of the ARfD for captan of 0.1 mg/kg bw/day for adults and toddlers. Based on the refined calculation, the acute risk to adults and toddlers consuming apples and pears is considered to be low.

[10] Monitoring of pesticide residues in products of plant origin in the European Union, Norway, Iceland and Lichtenstein. 2001 report. European Commission, published report number Sanco/20/03. [Dossier reference number Annex Point IIA 6.3/24 – submitted March 2005.]
Monitoring of pesticide residues in products of plant origin in the European Union, Norway, Iceland and Lichtenstein. 2002 report. European Commission, published report number Sanco/17/04. [Dossier reference number Annex Point IIA 6.3/25 – submitted March 2005.]

In addition, the NESTI values for apple and pear based on the more realistic HR residue value of 1 mg/kg derived from the survey data together with the standard default variability value of 7 (consider to be inappropriate for captan in apples and pears), represents 14 to 81% of the ARfD for captan of 0.1 mg/kg bw/day as shown in Table 18 below.

Table 18 NESTI calculation for captan based on UK consumption data and commodity size plus a more realistic residue values for apple and pear with the standard default variability factor of 7

Commodity	*HR (mg/kg)*	*NESTI (mg/kg bw/day)*		*% of ARfD*	
		Adults (70.1 kg bw)	*Toddlers (14.5 kg bw)*	*Adults (70.1 kg bw)*	*Toddlers (14.5 kg bw)*
Apple	*1.0*	*0.014*[a]	*0.060*[b]	*14%*	*60%*
Pear	*1.0*	*0.017*[c]	*0.081*[d]	*17%*	*81%*

[a] *Adults: NESTI = $\frac{(0.112 \times 1.0 \times 7) + (0.308 - 0.112) \times 1.0}{70.1} = 0.014$*

[b] *Toddlers: NESTI = $\frac{(0.112 \times 1.0 \times 7) + (0.199 - 0.112) \times 1.0}{14.5} = 0.060$*

[c] *Adults: NESTI = $\frac{(0.150 \times 1.0 \times 7) + (0.274 - 0.150) \times 1.0}{70.1} = 0.017$*

[d] *Toddlers: NESTI = $\frac{(0.150 \times 1.0 \times 7) + (0.279 - 0.150) \times 1.0}{14.5} = 0.081$*

Refined calculations using UK model: Peaches
(Makhteshim and Arysta proposal)

The NESTI values for toddlers consuming peaches exceeds the ARfD. However, this risk assessment is based on the HR value of 5.6 mg/kg recorded in supervised residue trials at a PHI of 7 days. In March 2005, the Notifier requested a minor change to the GAP extending the PHI from 7 days to 21 days. The RMS, EFSA and EPCO are requested to accept this minor change to the GAP based on the following:

- *The change in PHI for peaches/nectarines has no affect on the existing assessments of risk of captan to operators or to the environment.*
- *No new data are submitted to support this change.*
- *The same residue trials as those summarised in Table B.7.6.3.1 of the current DAR are relevant to the amended GAP. All the relevant supervised residue trials were decline studies and results at the PHI of 21 days are already summarised in the DAR. The trials are listed in Table 1 above. No new evaluation of the residue data is required.*
- *The request for the amendment to the GAP to extend the PHI to 21 days for peaches and nectarines was submitted in March 2005 before the EPCO meetings and at the same time as new data in other areas were submitted and accepted for evaluation in response to requests by EFSA.*

With a PHI of 21 days, the HR value for peaches / nectarines is 2.2 mg/kg (Supervised trial: Spain 2000 PA1 Lora del Rio 41440) – see Table 1.

In addition, survey data were submitted by the notifier in March 2005[11] in which products were monitored in all countries of the European Union plus Norway, Iceland and Lichtenstein in 2002. The monitoring included a co-ordinated monitoring exercise on five commodities, which included peaches, following recommendations from the Commission via Commission recommendation 2001/42/EC and 2002/1/EC, respectively. Peaches were analysed for various pesticides including captan. Details of the sampling methods, sample numbers, statistical analysis, methods of analysis used in each country are given in the report. From a total of 952 samples of peaches monitored for captan, 916 (96%) contained no residues of captan. All the remaining 36 samples contained residues of captan of 1 mg/kg or less.

NESTI calculations using the more appropriate HR residue value of 2.2 mg/kg derived from extending the PHI to 21 days and using the more realistic value of 1 mg/kg derived from the survey data are presented in Table 19 below:

Table 19 NESTI calculation for captan based on UK consumption data and commodity size plus more appropriate/realistic residue values for peaches

Commodity	*HR (mg/kg)*	*NESTI (mg/kg bw/day)*		*% of ARfD*	
		Adults (70.1 kg bw)	*Toddlers (14.5 kg bw)*	*Adults (70.1 kg bw)*	*Toddlers (14.5 kg bw)*
Peaches	*2.2*	*0.021*[a]	*0.089*[b]	*21%*	*89%*
Peaches	*1.0*	*0.010*[c]	*0.040*[d]	*10%*	*40%*

[a] *Adults: NESTI = $\frac{(0.110 \times 2.2 \times 5) + (0.228 - 0.110) \times 2.2}{70.1} = 0.021$*

[b] *Toddlers: NESTI = $\frac{(0.110 \times 2.2 \times 5) + (0.144 - 0.110) \times 2.2}{14.5} = 0.089$*

[c] *Adults: NESTI = $\frac{(0.110 \times 1.0 \times 5) + (0.228 - 0.110) \times 1.0}{70.1} = 0.010$*

[d] *Toddlers: NESTI = $\frac{(0.110 \times 1.0 \times 5) + (0.144 - 0.110) \times 1.0}{14.5} = 0.040$*

The NESTI values for peaches using the more appropriate residue value of 2.2 mg/kg (based on a PHI of 21 days) and the more realistic residue value of 1 mg/kg (taken from survey data in which 100% of 952 samples of peaches contained residues of captan of 1 mg/kg or less) represent 10 to 89% of the ARfD for captan of 0.1 mg/kg bw/day for adults and toddlers. Based on the refined calculations, the acute risk to adults and toddlers consuming peaches is considered to be low.

In addition, the NESTI values for peaches based on the more realistic HR residue value of 1 mg/kg derived from the survey data together with the standard default variability value of 7 (consider to be inappropriate for captan in peaches), represents 13 to 55% of the ARfD for captan of 0.1 mg/kg bw/day as shown in Table 20 below.

[11] Monitoring of pesticide residues in products of plant origin in the European Union, Norway, Iceland and Lichtenstein. 2002 report. European Commission, published report number Sanco/17/04. [Dossier reference number Annex Point IIA 6.3/25 – submitted March 2005.]

Table 20 NESTI calculation for captan based on UK consumption data and commodity size plus more realistic residue values for peaches with the standard default variability factor of 7

Commodity	*HR (mg/kg)*	*NESTI (mg/kg bw/day)*		*% of ARfD*	
		Adults (70.1 kg bw)	*Toddlers (14.5 kg bw)*	*Adults (70.1 kg bw)*	*Toddlers (14.5 kg bw)*
Peaches	*1.0*	*0.013*[a]	*0.055*[b]	*13%*	*55%*

[a] *Adults: NESTI = $\frac{(0.110 \times 1.0 \times 7) + (0.228 - 0.110) \times 1.0}{70.1} = 0.013$*

[b] *Toddlers: NESTI = $\frac{(0.110 \times 1.0 \times 7) + (0.144 - 0.110) \times 1.0}{14.5} = 0.055$*

Refined calculations using German model: Apples and pears (Makhteshim and Arysta proposal)

The NESTI values for children consuming apple and pear exceed the ARfD. However, it is noted that this risk assessment is based on a single extreme value of 8.0 mg/kg recorded in one supervised residue trial in apple, and consider by the Notifier to be a clear outlier. In 17 other supervised residue trials in apple/pear with applications according to the GAP (see Tables 3 and 4 in this document), residue levels ranged from 0.54 to 4.2 mg/kg. As stated above, in survey data 98.3% of 3,083 samples of apples and pears contained residues of captan of 1 mg/kg or less.

A NESTI calculation using a more realistic HR residue value of 1 mg/kg (derived from the survey data) is presented in Table 23 below:

Table 23 NESTI calculation for captan based on German consumption data and commodity size plus a more realistic residue value for apple and pear

Commodity	*HR (mg/kg)*	*Children (16.15 kg bw)*	
		NESTI (mg/kg bw/day)	*% of ARfD*
Apple	*1.0*	*0.060*[a]	*60%*
Pear	*1.0*	*0.066*[b]	*66%*

[a] *Children: NESTI = $\frac{(0.182 \times 1.0 \times 5) + (0.2348 - 0.182) \times 1.0}{16.15} = 0.060$*

[b] *Children: NESTI = $\frac{(0.207 \times 1.0 \times 5) + (0.2318 - 0.207) \times 1.0}{16.15} = 0.066$*

The NESTI values for apple and pear using the more realistic residue value of 1 mg/kg (taken from survey data in which 98.3% of 3,083 samples of apples and pears contained residues of captan of 1 mg/kg or less) represent 60 to 66% of the ARfD for captan of 0.1 mg/kg bw/day for children. Based on the refined calculation, the acute risk to children consuming apples and pears is considered to be low.

In addition, the NESTI values for apple and pear based on the more realistic HR residue value of 1 mg/kg derived from the survey data together with the standard default variability value of 7 (consider to be inappropriate for captan in apples and pears), represents 82 to 91% of the ARfD for captan of 0.1 mg/kg bw/day as shown in Table 24 below.

Table 24 NESTI calculation for captan based on German consumption data and commodity size plus a more realistic residue value for apple and pear with the standard default variability factor of 7

Commodity	*HR (mg/kg)*	*Children (16.15 kg bw)*	
		NESTI (mg/kg bw/day)	*% of ARfD*
Apple	*1.0*	*0.082*[a]	*82%*
Pear	*1.0*	*0.091*[b]	*91%*

[a] *Children: NESTI = $\frac{(0.182 \times 1.0 \times 7) + (0.2348 - 0.182) \times 1.0}{16.15} = 0.082$*

[b] *Children: NESTI = $\frac{(0.207 \times 1.0 \times 7) + (0.2318 - 0.207) \times 1.0}{16.15} = 0.091$*

Refined calculations using German model: Peaches and nectarines (Makhteshim and Arysta proposal)

The NESTI values for children consuming peaches and nectarines exceed the ARfD. However, this risk assessment is based on the HR value of 5.6 mg/kg recorded in supervised residue trials at a PHI of 7 days. In March 2005, the Notifier requested a minor change to the GAP extending the PHI from 7 days to 21 days. With a PHI of 21 days, the HR value for peaches / nectarines is 2.2 mg/kg (Supervised trial: Spain 2000 PA1 Lora del Rio 41440) – see Table 1.

In addition, in survey data submitted by the notifier in March 2005[12], in which products were monitored in all countries of the European Union plus Norway, Iceland and Lichtenstein in 2002. The monitoring included a co-ordinated monitoring exercise on five commodities, which included peaches, following recommendations from the Commission via Commission recommendation 2001/42/EC and 2002/1/EC, respectively. Peaches were analysed for various pesticides including captan. Details of the sampling methods, sample numbers, statistical analysis, methods of analysis used in each country are given in the report. From a total of 952 samples of peaches monitored for captan, 916 (96%) contained no residues of captan. All the remaining 36 samples contained residues of captan of 1 mg/kg or less.

A NESTI calculation using the more appropriate HR residue value of 2.2 mg/kg derived from extending the PHI to 21 days and using the more realistic value of 1 mg/kg derived from the survey data is presented in Table 25 below:

[12] Monitoring of pesticide residues in products of plant origin in the European Union, Norway, Iceland and Lichtenstein. 2002 report. European Commission, published report number Sanco/17/04. [Dossier reference number Annex Point IIA 6.3/25 – submitted March 2005.]

Table 25 NESTI calculation for captan based on German consumption data and commodity size plus more appropriate/realistic residue values for peaches/nectarines

Commodity	***HR (mg/kg)***	***Children (16.15 kg bw)***	
		NESTI (mg/kg bw/day)	***% of ARfD***
Peaches/nectarines	*2.2*	*0.079*[a]	*79%*
Peaches/nectarines	*1.0*	*0.035*[b]	*35%*

[a] *Children: NESTI = $\frac{(0.097 \times 2.2 \times 5) + (0.1926 - 0.097) \times 2.2}{16.15} = 0.079$*

[b] *Children: NESTI = $\frac{(0.097 \times 1.0 \times 5) + (0.1926 - 0.097) \times 1.0}{16.15} = 0.035$*

The NESTI values for peaches/ nectarines using the more realistic residue value of 2.2 mg/kg (based on a PHI of 21 days) and 1 mg/kg (taken from survey data in which 100% of 952 samples of peaches contained residues of captan of 1 mg/kg or less) represent 35 and 79% of the ARfD for captan of 0.1 mg/kg bw/day for children. Based on the refined calculation, the acute risk to children consuming peaches is considered to be low.

In addition, the NESTI values for peaches/nectarines based on the more realistic HR residue value of 1 mg/kg derived from the survey data together with the standard default variability value of 7 (consider to be inappropriate for captan in peaches/nectarines), represents 48% of the ARfD for captan of 0.1 mg/kg bw/day as shown in Table 26 below.

Table 26 NESTI calculation for captan based on German consumption data and commodity size plus more appropriate/realistic residue values for peaches/nectarines with the standard default variability factor of 7

Commodity	***HR (mg/kg)***	***Children (16.15 kg bw)***	
		NESTI (mg/kg bw/day)	***% of ARfD***
Peaches/nectarines	*1.0*	*0.048*[a]	*48%*

[4] *Children: NESTI = $\frac{(0.097 \times 1.0 \times 7) + (0.1926 - 0.097) \times 1.0}{16.15} = 0.048$*

Choice of Variability Factor
(Makhteshim and Arysta proposal)

The UK model assumes a standard default variability factor of 7 for medium commodities (unit weights 25 to 250 g) treated using non-granular, non-soil applied pesticides. Thus, based on the UK assumptions, the default variability value for apple, pear, peaches, nectarines and tomatoes treated with captan would be 7. The UK model also uses a standard default variability factor of 5 for large commodities (unit weights greater than 250 g) treated using non-granular, non-soil applied pesticides. The German model also uses a standard default value of 7 for apple, pear, peaches/nectarines and tomatoes.

In contrast to the UK and German models, the JMPR use a default value of 3 for all commodities with unit weight exceeding 25 g (JMPR Report 2003).

According to the Opinion of the PPR Panel (2005)[13], the average variability factor measured in supervised residue trials for various crops (including crops recommended for treatment with captan) was 2.8 and the variability factors for market surveys (including crops recommended for treatment with captan) averaged 3.6. The PPR Panel concluded there was insufficient evidence to support a real difference between variability factors for medium and large sized commodities and indicated that a factor of 7 for medium sized commodities was very conservative.

The variability factors measured for crops recommended for treatment with captan extracted from Appendix I to the PPR Panel paper are presented in Table 14. (Only the individual market survey data selected for use by the PPR in their calculations of averages are included in Table 14. Appendix I to the PPR Panel report includes data on other crops not recommended for treatment with captan and these are not included in Table 14.)

The results in Table 14 can be summarised as follows:

For apple, the variability factors in supervised trials and market survey data considered together ranged from 2.0 to 5.7 (n = 20) with a mean variability factor of 3.3.

For peach, the variability factors in market survey data (there were no supervised trials in peach) ranged from 3.3 to 5.4 (n = 7) with a mean variability factor of 4.2.

For pear, the variability factors in market survey data (there were no supervised trials in pear) ranged from 2.5 to 4.0 (n = 4) with a mean variability factor of 3.5.

For tomato, the variability factors in market survey data (there were no supervised trials in tomato) ranged from 5.6 to 8.0 (n = 4) with a mean variability factor of 6.4.

Variability factors can also be calculated from the supervised trials with captan currently summarised in the DAR. The results in peaches/nectarines are summarised in Table 2 of this document. Residues in peaches/nectarines (PHI 7 days) ranged from 2.1 to 5.6 mg/kg and the mean value is 3.73 mg/kg. This gives a variability factor of 1.5 for peaches/nectarines (calculated from the maximum value of 5.6 mg/kg divided by the mean value of 3.73 mg/kg). The results in apples/pears are summarised in Table 3 and 4 of this document. Residues in apples/pears across both Southern and Northern EU regions ranged from 0.54 to 8.0 mg/kg and the overall mean value is 2.16 mg/kg. This gives a variability factor of 3.7 for apples/pears (calculated from the maximum value of 8.0 mg/kg divided by the mean value of 2.16 mg/kg).

[13] Opinion of the Scientific Panel on Plant health, Plant protection products and their Residues on a request from Commission related to the appropriate variability factor(s) to be used for acute dietary exposure assessment of pesticide residues in fruit and vegetables (Question N° EFSA-Q-2004-124) adopted on 16 February 2005. *The EFSA Journal* (2005) 177, 1-61.

Table 14 Variability factors measured in supervised trials and market surveys for crops recommended for treatment with captan (from Opinion of the PPR Panel (2005)

Commodity	***Variability factor***	***Origin of dataset***
Apple	*3.1*	*Supervised trial*
	2.9	*Supervised trial*
	3.2	*Supervised trial*
	2.2	*Market survey*
	2.9	*Market survey*
	2.6	*Market survey*
	3.4	*Market survey*
	3.5	*Market survey*
	3.2	*Market survey*
	2.4	*Market survey*
	4.8	*Market survey*
	3.5	*Market survey*
	5.7	*Market survey*
	3.1	*Market survey*
	4.2	*Market survey*
	2.0	*Market survey*
	2.7	*Market survey*
	4.7	*Market survey*
	2.3	*Market survey*
	4.2	*Market survey*
Peach	*3.9*	*Market survey*
	3.3	*Market survey*
	4.1	*Market survey*
	4.4	*Market survey*
	5.4	*Market survey*
	4.9	*Market survey*
	3.6	*Market survey*
Pear	*3.6*	*Market survey*
	2.5	*Market survey*
	4.0	*Market survey*
	3.8	*Market survey*
Tomato	*5.8*	*Market survey*
	5.6	*Market survey*
	8.0	*Market survey*
	6.3	*Market survey*
Apple	***Mean: 3.3***	
	Range: 2.0 – 5.7	
Peach	***Mean: 4.2***	
	Range: 3.3 - 5.4	
Pear	***Mean: 3.5***	
	Range: 2.5 – 4.0	
Tomato	***Mean: 6.4***	
	Range: 5.6 – 8.0	

In summary:

- *The average variability factor measured in supervised residue trials for all crops in the PPR Panel paper was 2.8.*

- *The average variability measured in market surveys factor for all crops in the PPR Panel paper was 3.6.*

- *The PPR Panel concluded there was insufficient evidence to support a real difference between variability factors for medium and large sized commodities and indicated that a factor of 7 for medium sized commodities was very conservative.*

- *For apple, pear and peaches, average variability factors from trials and market survey data presented in the PPR Panel document ranged from 3.3 to 4.2.*

- *The variability factors calculated from supervised residue trials with captan conducted according to the GAP (as summarised in the DAR) were 1.5 for peaches/nectarines and 3.7 for apples/pears.*

- *The JMPR assume a variability factor of 3 for commodities of 25 g or more (i.e. for all crops recommended for treatment with captan).*

Based on the conclusions of the PPR Panel and the data in Table 14, a variability factor of 7 for apple, pear and peach is therefore considered to be wholly inappropriate to use in acute risk assessment for all crops recommended for treatment with captan.

A variability factor of 5 is considered appropriate for use in risk assessment for apple, pear and peaches. This value is considered to still represent a conservative value as it exceeds the value of 3 as used by JMPR (and the average value in the PPR Panel document).

For tomato, it is acknowledged that variability factors measured in market surveys were higher than the other crops and there is therefore insufficient evidence to justify a lower factor than 7 for this crop. The variability factor of 7 as used by PSD, although considered to be conservative, is therefore considered appropriate to tomato.

Conclusions for Acute Risk Assessment
Makhteshim and Arysta have presented some alternative calculations based on different assumptions. Conclusions here listed are based on such calculations

Based on the UK and German models, the NESTI values for adults and toddlers/children consuming tomatoes, and adults consuming apples and peaches, are less than the ARfD of 0.1 mg/kg bw/day and so the acute risk to adults and toddlers/children is considered to be low.

Based on a refined calculation with the UK and German models using the more realistic residue value of 1 mg/kg in apples/pear (derived from survey data in which 98.3% of 3,083 samples of apples and pears contained residues of captan of 1 mg/kg or less), NESTI values for toddlers/children consuming apples and pears are less than the ARfD of 0.1 mg/kg bw/day. Therefore, the acute risk to toddlers/children consuming apples and pears is also considered to be low.

Based on a refined calculation with the UK and German models using the more appropriate residue value of 2.2 mg/kg in peaches/nectarines (based on extending the PHI to 21 days) and the more realistic value of 1 mg/kg in peaches/nectarines (derived from survey data in which 100% of 952 samples of peaches contained residues of captan of 1 mg/kg or less), NESTI values for toddlers/children consuming peaches/nectarines are less than the ARfD of

0.1 mg/kg bw/day. Therefore, the acute risk to toddlers/children consuming peaches/nectarines is also considered to be low.
In conclusion, safe uses of captan have been demonstrated for tomato, peaches/nectarines and apples/pears.

Evaluation table number	Reporting table number	Open Point number
-	-	**3.13**

Conclusions of the EFSA Evaluation Meeting:
RMS to include calculations of the potential exposure of animals by consumption of apple pomace in an addendum to be considered at an expert meeting.
Conclusions of the EPCO Expert Meeting:
Due to the new MRL of 10 mg/kg for apple this point remains open since the current calculations base on a MRL of 5 mg/kg for apple

Dietary Burden Calculation for Domestic Animals

Captan is recommended in pome fruit, tomatoes and peaches/nectarines. Fruit pomace (apple) can be used for cattle feed at a maximum of a 10% of the diet in dairy cattle and a 30% of the diet in beef cattle.

Captan is not recommended on any crops which are fed to hens or pigs and so feeding studies in hens or pigs are not required.

The potential dietary exposure of dairy and beef cattle to captan is calculated below based on a MRL of 10 mg/kg for apple).

Captan Dietary Exposure Level in Cattle
Based on a MRL of 10 mg/kg for apple and a mean transfer factor of 1.1 in apple pomace (= 11 mg/kg), the maximum residue concentration for captan in feed of beef cattle is 215.6 mg captan/animal/day (Table 27). This gives an estimated worst-case daily feeding rate of 14.4 mg captan/kg diet (215.6/15), assuming 15 kg as the daily intake of dry matter for cattle of 350 kg body weight, or 0.62 mg/kg bw /day (215.6/350). The maximum dietary concentration is 11 mg captan/kg fresh diet (215.6/19.6).

For dairy cattle, the maximum residue concentration for captan in feed is 95.7 mg captan/animal/day (Table 27). This gives an estimated worst-case daily feeding rate of 4.8 mg captan/kg diet (95.7/20), assuming 20 kg as the daily intake of dry matter for cattle of 550 kg body weight, or 0.18 mg/kg bw /day (95.7/550). The maximum dietary concentration is 11 mg captan/kg fresh diet (95.7/8.7).

Table 27 Captan Dietary Exposure Level in Cattle

Animal/Crop	% Dry Matter	% Diet Contribution (dry weight)	Intake of Dry Matter (kg/animal /day)	Intake of Fresh Material (kg/animal/ day)	Captan Residue (mg/kg)	Captan Intake (mg/animal/day)
Beef cattle/ Apple	23	30	4.5	19.6	11	215.6
Dairy cattle/ Apple	23	10	2.0	8.7	11	95.7

Makhteshim and Arysta have presented some alternative calculations based on different assumptions, as listed below

Realistic calculation according to <u>Makhteshim and Arysta proposal</u>

Based on a worst-case STMR of 1.9 mg/kg for apple and a mean transfer factor of 1.1 in apple pomace (= 2.1 mg/kg), the maximum residue concentration for captan in feed of beef cattle is 41.2 mg captan/animal/day (Table 28). This gives an estimated worst-case daily feeding rate of 2.7 mg captan/kg diet (41.2/15), assuming 15 kg as the daily intake of dry matter for cattle of 350 kg body weight or 0.12 mg/kg bw /day (41.2/350). The maximum dietary concentration is 2.1 mg captan/kg fresh diet (41.2/19.6).

For dairy cattle, the maximum residue concentration for captan in feed is 18.3 mg captan/animal/day (Table 28). This gives an estimated worst-case daily feeding rate of 0.92 mg captan/kg diet (18.3/20), assuming 20 kg as the daily intake of dry matter for cattle of 550 kg body weight or 0.03 mg/kg bw /day (18.3/550). The maximum dietary concentration is 2.1 mg captan/kg fresh diet (18.3/8.7).

Table 28 More Realistic Calculation of Captan Dietary Exposure Level in Cattle

Animal/Crop	***% Dry Matter***	***% Diet Contribution (dry weight)***	***Intake of Dry Matter (kg/animal /day)***	***Intake of Fresh Material (kg/animal/ day)***	***Captan Residue (mg/kg)***	***Captan Intake (mg/animal/day)***
Beef cattle/ Apple	*23*	*30*	*4.5*	*19.6*	*2.1*	*41.2*
Dairy cattle/ Apple	*23*	*10*	*2.0*	*8.7*	*2.1*	*18.3*

In metabolism studies in goats, captan was administered at a dietary concentration of 50 mg/kg for seven days and only 1-2% of the administered radioactivity was detected in animal tissues and milk; no parent captan was found in milk and tissues. The dietary concentration in the study was approximately 3.5 times the worst-case dietary burden (based on the MRL, i.e. 50 ÷ 14.4) and 19 times the realistic dietary burden (based on the STMR, i.e. 50 ÷ 2.7) for beef cattle, and approximately 10 times the worst-case dietary burden (based on the MRL, i.e. 50 ÷ 4.8) and 54 times the realistic dietary burden (based on the STMR, i.e. 50 ÷ 0.92) for dairy cattle.

Therefore, no residues in excess of the LOQ for captan in milk and bovine tissues are expected and a feeding study in ruminants is not required.

Environmental fate and behaviour

October 2005

B.8 Environmental fate and behaviour

Introduction

This document is an Addendum to the Draft Assessment Report (DAR) for the EU review of **captan** to address issues raised at the EPCO meeting held on 11-14 April 2005. The aim of this Addendum is to address 'Open points' and 'Data requirements' as raised in the official Evaluation Table (dated 11.08.05) in the area of **Environmental fate and behaviour**.

This Addendum includes summarisation and evaluation of new assessments submitted by Makhteshim Chemical Works Ltd and * Calliope SAS * (*formerly, Tomen France S.A.S.*).

Section numbering in this Addendum is in line with Annex B (Volume 3) of the DAR.

The Good Agricultural Practice (GAP) uses proposed by the Notifier for consideration under the review are specified in Table 1.

Table 1: Critical Good Agricultural Practice for captan in the EU review

Crop	Member state or country	Product name	F, G or I	Pests or group of pests controlled	Formulation		Application			Application rate per treatment			PHI (days)	Remarks:
					Type	Conc. of a.s.	method kind	growth stage/ timing	number [b] (max.)	kg a.s./hL (max.)	water L/ha	kg a.s./ha (max.)		
Pome fruit	North EU	'Merpan' 80 WDG / 'Malvin' WDG	F[a]	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 53 / April	9 - 10	0.125	1000	1.25	14	
	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69 / April	9 + 3 [c]	0.125 0.24	1000 1000	1.25 2.4	14	
Tomatoes	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Foliar spray; down-wards	From BBCH 60 to 87	4	0.15	1200	1.8	14	
Peaches/ nectarines	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69: petal fall	4	0.25	1000	2.5	7	

[a] F = field.
[b] Applications at a minimum of 7 days for all crops.
[c] Nine applications at 1.25 kg a.s./ha (scab control) followed by three applications at 2.4 kg a.s/ha (*Nectria* control).

Fate and behaviour in water (Annex IIA 7.2.1; Annex IIIA 9.2.1, 9.2.3)

Surface Water

Data requirement 4.14	PEC values for THPAI to be provided and PEC sediment to be recalculated with density of 1.3 g/mL.
Data requirement 4.16	For northern European use scenarios entry routes other than spray drift need to be addressed. RMS to include PEC_{SW} for northern European use scenarios in the list of endpoints.

The Notifier has submitted PEC_{sed} values for the metabolite THPI re-calculated using a sediment density of 1.3 g/mL. In addition, PEC_{sed} values for THPAI were also calculated and PEC_{sed} values were also reported for the North European use on pome fruit. All methods used and parameters selected have been previously evaluated and accepted (see Addendum to captan DAR, January 2005).

Report: *Terry, A. (2005) Captan: Responses to Environmental Fate and Behaviour data requirements and questions arising from EPCO meeting 21. CEA, unpublished report September 2005.*

PEC_{sed} values are calculated below for THPI and THPAI following use of captan in pome fruit in Southern Europe, pome fruit Northern Europe and for nectarine/peaches according to the methods reported previously in IIIA 9.2.3/01 (Terry, A (CEA.049)) as evaluated in previous DAR addendum. However, a sediment density value of 1.3 g/cm^3 is used rather than the previously used 1.5 g/cm^3. PEC_{sed} values are calculated for THPI and THPAI, simulating multiple applications of captan with resulting multiple drift into a water body.

THPAI was formed at a maximum level of 11.3% in sediment and a DT_{50} for degradation was not determined in the sediment/water study. However, following the approach previously used for captan metabolites, a worst case DT_{50} of 17.8 days was used in the calculations for THPAI.

The substance parameters selected for use in the calculations are summarised in Table B.8.6.31.

Table B.8.6.31: Summary of Parameters Selected for Use in the Calculation of PEC_{sed} values for THPI and THPAI

Compound:	Captan	THPI	THPAI
Molecular Weight (g/mol)	300.59	151.17	170.16
%-drift into water body	11.01	NR	NR
Sediment depth (cm)	NR	5	5
Sediment density (g/cm^3)	NR	1.3	1.3
Maximum % formed in sediment phase	NR	41.2	11.3
DT_{50} in sediment phase (days)	NR	4.8	17.8

NR: not relevant for these calculations

The calculated PEC_{sed} values are presented in Tables B.8.6.32-B.8.6.37.

Table B.8.6.32: Simulated PEC_{sed} for THPI following use on pome fruit in Southern Europe (9 x 1.25 kg a.s./ha + 3 x 2.4 kg a.s./ha)

Time (days)	Instantaneous PEC (µg/kg)	Maximum TWA PEC (µg/kg)	Day interval for TWA PEC calculation
app 1 (0)	43.87		
app 2 (7)	59.83		
app 3 (14)	65.64		
app 4 (21)	67.76		
app 5 (28)	68.53		
app 6 (35)	68.81		
app 7 (42)	68.91		
app 8 (49)	68.95		
app 9 (56)	68.96		
app 10 (63)	109.32		
app 11 (70)	124.01		
app 12 (77)	129.36		
1 (78)	111.96	120.66	77
2 (79)	96.91	112.55	77-78
4 (81)	72.60	98.43	77-80
7 (84)	47.07	81.54	77-83
14 (91)	17.13	79.86	70-83
21 (98)	6.23	76.21	63-83
28 (105)	2.27	68.02	56-83
42 (127)	0.30	59.83	42-83
100 (177)	0.00	44.59	0-99

Numbers in parentheses are days after first application

Table B.8.6.33: Simulated PEC_{sed} for THPAI following use on pome fruit in Southern Europe (9 x 1.25 kg a.s./ha + 3 x 2.4 kg a.s./ha)

Time (days)	Instantaneous PEC (µg/kg)	Maximum TWA PEC (µg/kg)	Day interval for TWA PEC calculation
app 1 (0)	13.54		
app 2 (7)	23.86		
app 3 (14)	31.71		
app 4 (21)	37.69		
app 5 (28)	42.24		
app 6 (35)	45.71		
app 7 (42)	48.34		
app 8 (49)	50.35		
app 9 (56)	51.88		
app 10 (63)	65.51		
app 11 (70)	75.88		
app 12 (77)	83.78		
1 (78)	80.58	82.18	77
2 (79)	77.51	80.61	77-79
4 (81)	71.70	77.59	77-80
7 (84)	63.79	73.34	77-83
14 (91)	48.57	69.89	70-83
21 (98)	36.98	65.71	63-83
28 (105)	28.16	63.24	63-90
42 (127)	16.33	57.08	49-90
100 (177)	1.71	43.96	14-113

Numbers in parentheses are days after first application

Table B.8.6.34: Simulated PEC_{sed} values for THPI following use on nectarines/peaches in Southern Europe (4 x 2.5 kg a.s./ha)

Time (days)	Instantaneous PEC (µg/kg)	Maximum TWA PEC (µg/kg)	day interval for TWA PEC calculation
app 1 (0)	87.74		
app 2 (7)	119.67		
app 3 (14)	131.29		
app 4 (21)	135.51		
1 (22)	117.29	126.40	21
2 (23)	101.52	117.90	21-22
4 (25)	76.05	103.12	21-24
7 (28)	49.32	85.42	21-27
14 (35)	17.95	84.09	14-27
21 (42)	6.53	81.20	7-27
28 (49)	2.38	74.73	0-27
42 (71)	0.31	56.89	0-41
100 (121)	0.00	24.35	0-99

Numbers in parentheses are days after first application

Table B.8.6.35: Simulated PEC_{sed} values for THPAI following use on nectarines/peaches in Southern Europe (4 x 2.5 kg a.s./ha)

Time (days)	Instantaneous PEC (µg/kg)	Maximum TWA PEC (µg/kg)	day interval for TWA PEC calculation
app 1 (0)	27.09		
app 2 (7)	47.71		
app 3 (14)	63.42		
app 4 (21)	75.38		
1 (22)	72.50	73.94	21
2 (23)	69.73	72.52	21-22
4 (25)	64.50	69.81	21-24
7 (28)	57.39	65.98	21-27
14 (35)	43.70	60.75	14-27
21 (42)	33.27	54.42	7-27
28 (49)	25.33	46.75	0-27
42 (71)	14.69	45.91	0-41
100 (121)	1.53	26.94	0-99

Numbers in parentheses are days after first application

Table B.8.6.36: Simulated PEC_{sed} values for THPI following use on pome fruit in Northern Europe (10 x 1.25 kg a.s./ha)

Time (days)	Instantaneous PEC (µg/kg)	Maximum TWA PEC (µg/kg)	Day interval for TWA PEC calculation
app 1 (0)	43.87		
app 2 (7)	59.83		
app 3 (14)	65.64		
app 4 (21)	67.76		
app 5 (28)	68.53		
app 6 (35)	68.81		
app 7 (42)	68.91		
app 8 (49)	68.95		
app 9 (56)	68.96		
app 10 (63)	68.96		
1 (64)	59.69	64.33	63
2 (65)	51.66	60.00	63-64
4 (67)	39.20	52.48	63-66
7 (70)	25.10	43.47	63-69
14 (77)	9.13	43.47	56-69
21 (84)	3.32	43.47	49-69
28 (91)	1.21	43.46	42-69
42 (105)	0.16	43.40	28-69
100 (163)	0.00	30.41	0-99

Numbers in parentheses are days after first application

Table B.8.6.37: Simulated PEC_{sed} values for THPAI following use on pome fruit in Northern Europe (10 x 1.25 kg a.s./ha)

Time (days)	Instantaneous PEC (µg/kg)	Maximum TWA PEC (µg/kg)	Day interval for TWA PEC calculation
app 1 (0)	13.54		
app 2 (7)	23.86		
app 3 (14)	31.71		
app 4 (21)	37.69		
app 5 (28)	42.24		
app 6 (35)	45.71		
app 7 (42)	48.34		
app 8 (49)	50.35		
app 9 (56)	51.88		
app 10 (63)	53.05		
1 (64)	51.02	52.04	63
2 (65)	49.07	51.04	63-64
4 (67)	45.40	49.13	63-66
7 (70)	40.39	46.44	63-69
14 (77)	30.75	45.93	56-69
21 (84)	23.42	45.31	49-69
28 (91)	17.83	44.57	42-69
42 (105)	10.34	42.54	28-69
100 (163)	1.08	31.56	0-99

Numbers in parentheses are days after first application

RMS comment: Notifier has used previously agreed parameters for deriving the PEC values. Hence, they are considered to be acceptable.

The Notifier has submitted the PEC_{SW} values for captan and the metabolites THPI and THPAM calculated for the North European use on pome fruit. All methods used and parameters selected have been previously evaluated and accepted (see Addendum to captan DAR, January 2005).

Report: *Terry, A. (2005) Captan: Responses to Environmental Fate and Behaviour data requirements and questions arising from EPCO meeting 21. CEA, unpublished report September 2005.*

The PEC_{SW} value for captan following spray drift for the North Europe use (pome fruit, 10 x 1.25 a.s./kg) has been calculated (see Table B.8.6.38). Captan has a water DT_{50} of less than a day and, therefore, a 90^{th}-percentile (according to Rautmann) worst case drift value (15.73%; drift from 3 m) was assumed as persistence of captan between spray events would not be expected.

PEC_{sw} values have been calculated previously for worst case exposure for the major metabolites of captan and reported (IIIA 9.2.3/01 Terry, A (CEA.049)) which were evaluated in previous DAR addendum. The PEC_{sw} values for the Northern Europe use in pome fruit have now also been calculated according to the method given in CEA.049 and are reported here in Tables B.8.6.39 and B.8.6.40.

Table B.8.6.38: Maximum PEC_{sw} for captan following use on pome fruit in Northern Europe (10 x 1.25 kg a.s./ha)

Pome fruit Northern Europe - captan	
PEC_{sw} Captan (µg/L)	Single application
Maximum	**65.54**

Table B.8.6.39: PEC_{sw} for THPI following use on pome fruit in Northern Europe (10 x 1.25 kg a.s./ha)

Time (days)	Instantaneous PEC (µg/L)
app 1	11.70
app 2	20.60
app 3	27.38
app 4	32.55
app 5	36.48
app 6	39.47
app 7	41.75
app 8	43.49
app 9	44.81
app 10	45.81
1 (64)	44.06
2 (65)	42.38
4 (67)	39.20
7 (70)	34.88
14 (77)	26.56
21 (84)	20.22
28 (91)	15.40
42 (105)	8.93
100 (163)	0.93

Numbers in parentheses are days after first application

Table B.8.6.40: PEC_{sw} for THPAM following use on pome fruit in Northern Europe (10 x 1.25 kg a.s./ha)

Time (days)	Instantaneous PEC (µg/L)
app 1	6.61
app 2	11.64
app 3	15.47
app 4	18.39
app 5	20.61
app 6	22.31
app 7	23.59
app 8	24.57
app 9	25.32
app 10	25.89
1 (64)	24.90
2 (65)	23.95
4 (67)	22.15
7 (70)	19.71
14 (77)	15.01
21 (84)	11.43
28 (91)	8.70
42 (105)	5.04
100 (163)	0.53

Numbers in parentheses are days after first application

RMS comment: Notifier has used previously agreed parameters for deriving the PEC values. Hence, they are considered to be acceptable.

The Notifier has also investigated the significance of non-spray drift exposure routes to surface water following use of captan on pome fruit in North Europe, using the FOCUS SW methodology which includes assessment of exposure from spray drift, drainage and runoff. All parameters selected have been previously evaluated and accepted (see Addendum to captan DAR, January 2005) or were recommended by EPCO 21.

Report: *Terry, A. (2005) Captan: Responses to Environmental Fate and Behaviour data requirements and questions arising from EPCO meeting 21. CEA, unpublished report September 2005.*

Surface water modelling for captan and its metabolites was undertaken to establish the relative significance of different exposure routes in Northern Europe based on the proposed relevant EU GAP for pome fruit. Substance parameters used in the modelling were as derived for previous PEC GW and SW calculations except for the following.

The K_{OC} value for captan was taken as 110.66 mL/g (as recommended by EPCO 21). In addition, the use of mean K_{OC} values was not appropriate for THPAM due to the pH-dependency of sorption (as previously taken into account in the GW modelling). There is significant variation in the sorption results for THPAM. In the tiered FOCUS SW approach, the Freundlich exponent (1/n) value is not required until step 3, therefore, selection of a value

for THPAM was postponed until after the outcome of step 2 was known. Further, the K_{OC} value is only used to determine the proportion of chemical partitioned into sediment at step 1 and 2. For THPAM, the variation in K_{OC} depending on pH presents difficulties with respect to selecting a representative value, but values were very low at alkaline pH values. Therefore, a surrogate zero value of 0.01 mL/g was selected for use at step 1 and 2. Substance parameters used in the modelling are given in Tables B.8.6.41 to B.8.6.44.

Table B.8.6.41: Summary of worst case sediment/water DT_{50} values for FOCUS modelling

Compound	$DT_{50,wat}$	$DT_{50,sed}$	$DT_{50,sys}$	Maximum % formed
Captan (DT_{50} days)	0.16	0.16	0.16	N.A.
THPI (DT_{50} days)	17.8	4.8	17.8	81.2
THPAM (DT_{50} days)	17.8	17.8	17.8	27.0

N.A.: Not Applicable

Table B.8.6.42: Soil degradation parameters for FOCUS modelling

Compound	Normalised soil DT_{50} (days)	Maximum % formed
Captan	1.10	N.A.
THPI	9.05	66.0
THPAM	7.80	16.8

N.A.: not applicable

Table B.8.6.43: Soil K_{OC} values used in surface water assessment

Compound	K_{OC} (mL/g)	1/n
Captan	110.66	0.90
THPI	9.34	NR
THPAM	0.01	NR

NR: not required at step 1 and 2; step 3 assessment not undertaken for these compounds

Table B.8.6.44: Other parameter values employed for the FOCUS simulations

Parameter	Captan	THPI	THPAM
Vapour Pressure (Pa) at 20°C	4.2×10^{-6}	0.3950×10^{-9}	0.1590×10^{-10}
Water Solubility (mg/L) at 20°C	5.2	42,778	53,720
Molecular Weight (g/mol)	300.59	151.17	169.18
Plant Uptake Factor	0.5	NR	NR
Crop Wash-off factor	0.030	NR	NR

NR: not required at step 1 and 2; step 3 assessment not undertaken for these compounds

FOCUS Step 1 inputs of runoff and erosion and/or drainage were evaluated as a single loading to the water body and worst case surface water and sediment concentrations were calculated. The crop types used were late application to pome fruit (Northern Europe).

The runoff/erosion/drainage loading to the water body is fixed at 10% of the application for all scenarios in the calculator at FOCUS Step 1. The runoff/erosion/drainage entry is distributed instantaneously between water and sediment at the time of loading according to the K_{OC} of the compound.

At Step 1, degradation in the water and sediment compartments is dependant on an overall dissipation rate, i.e. the total system DT_{50} (see Table B.8.6.41). Degradation is also assumed to follow 1st order kinetics. The Initial PEC_{SW} values for THPI and THPAM are summarised in Tables B.8.6.45 and B.8.6.46.

Table B.8.6.45: Calculated initial PEC_{SW} values for THPI (FOCUS Step 1)

Scenario		Max PEC in water (µg/L)
Pome fruit (late application)	NE	1.63×10^3

NE: Northern Europe

Table B.8.6.46: Calculated initial PEC_{SW} values for THPAM (FOCUS Step 1)

Scenario		Max PEC in water (µg/L)
Pome fruit (late application)	NE	493.54

NE: Northern Europe

The PEC_{SW} values obtained were compared to the worst-case runoff prediction made for THPI and THPAM (710 µg/L) given in the official list of endpoints. The toxicity of THPI and THPAM is such that it was previously established that this PEC value was of no concern. In the case of the FOCUS step 1 calculations reported, the PEC_{SW} for THPAM was below the worst-case PEC value, but the PEC_{SW} value for THPI was above the value. Therefore, no further assessment was required for THPAM, but FOCUS step 2 was required for THPI.

The Step 2 inputs are evaluated as a series of individual loadings comprising of drift events (number, interval between applications and rates of applications as defined in Step 1) followed by loadings from run-off, erosion and/or drainage 4 days after application. The GAP for captan recommends multiple applications. The assessment at Step 2 takes into account crop interception.

The run-off/erosion/drainage loading to the water body is simulated to occur 4 days after application. The amount is a function of the residue remaining in soil at this point and is also defined by the region and season of application. At step 2, quantities of pesticide available for runoff/erosion/drainage is dependant on the soil DT_{50}. In common with Step 1 the runoff/erosion/drainage entry is distributed between water and sediment at the time of loading according to the K_{OC} of the compound.

The calculated PEC values for THPI at Step 2 are given in Table B.8.6.47.

Table B.8.6.47: Calculated PEC values for THPI (FOCUS Step 2)

Scenario		Max PEC in water (µg/L)
Pome fruit (late application)	NE	62.62 (28.69)

NB. Number in brackets indicate single application;
NE: Northern Europe

The PEC_{SW} values for THPI were below the worst-case PEC value (710 µg/L) reported in the official list of endpoints and it was, therefore, established that non-spray drift exposure routes are of no concern for THPI.

FOCUS Step 3 calculations were carried out to assess the movement and fate of captan in surface waters. The relevant scenarios are summarised in Table B.8.6.48.

Table B.8.6.48: Scenarios used in FOCUS Step 3 assessments

Crop	Drainage Scenarios	Runoff Scenario
Pome fruit (NE)	D3, D4, D5	R1

NE: Northern Europe

Exposure following both multiple applications and single applications were investigated. The drift loadings to surface water expressed as percent areic mean are given in Table B.8.6.49. Percentage loadings were all higher for single applications.

Table B.8.6.49: Drift deposition into surface waters

Crop	Water body	Drift following Single Application (%)	Drift following Multiple Applications (%)
Pome Fruit (Late application) [#]	Ditch	11.1340	6.3372
	Stream	11.5484	6.6686
	Pond	1.6485	1.0264

[#]: 8 applications used for multiple applications

The method of application of captan is *via* foliar spray.

Multiple applications:

Application Rate: 10 x 1250 g a.s./ha (Annual total = 12500 g a.s./ha)
Crop: **Pome fruit (Northern Europe)**

FOCUS surface water models will only allow a maximum of eight applications. Therefore the GAP application rates detailed above for pome fruit were altered to accommodate the model in the following way:

Pome fruit (Northern Europe)
GAP: 10 x 1250 g a.s./ha
FOCUS model: (1250 x 10) / 8 = 1562.5 g a.s./ha x 8 applications

Application dates were generated using the scenario harvest date, pre-harvest interval (PHI; 14 days) and the minimal interval between applications (7 days). The last date of the application window was calculated by subtracting the PHI from the scenario harvest date (Equation 1). The first date of the application window was calculated using Equation 2.

Harvest date – PHI = last date of application window **Equation (1)**

Equation (1) – (30 + ((number of applications – 1) x minimal interval between applications)) = first date of application window **Equation (2)**

Single application:

The single application rates were a true representation of worst-case spray drift loadings. An application rate of 1 x 1.25 kg a.s./ha was used to simulate a worst-case single application according to the GAP for pome fruit in Northern Europe.

PEC_{SW} values generated for each scenario are reported in the following tables (Tables B.8.6.50 and B.8.6.51).

Table B.8.6.50: FOCUS Step 3 calculated PEC_{SW} values for captan applied to pome fruit in Northern Europe, multiple applications

Scenario	Max PEC_{sw} (µg/L)
D3-ditch	32.79
D4-pond	1.60
D4-stream	33.29
D5-pond	1.60
D5-stream	35.91
R1-pond	1.60
R1-stream	25.46

Table B.8.6.51: FOCUS Step 3 calculated PEC_{SW} values for captan applied to pome fruit in Northern Europe, single applications

Scenario	Max PEC_{sw} (µg/L)
D3-ditch	46.04
D4-pond	2.06
D4-stream	46.11
D5-pond	2.06
D5-stream	49.75
R1-pond	2.06
R1-stream	34.57

Given that in all cases the PEC values were worse for single applications compared to multiple applications, step 4 modelling was applied only to the single application scenarios.

The areic drift from 14 m was calculated in the SWASH drift calculator and, for streams following adjustment for spray drift input from upstream (x 1.2), the corresponding parameter in the TOXSWA 'txw' file (*mldsd*) was manually altered as appropriate. In effect, this resulted in a reduction of the spray drift associated with the application. If the resulting PEC_{SW} value was significantly lower than the corresponding PEC_{SW} value calculated at step 3, then this would indicate that spray drift was the dominant exposure route for that scenario.
PEC_{SW} values generated for each scenario are reported in the following table (Table B.8.6.52). Included in Table B.8.6.52 are the corresponding PEC_{SW} values obtained at step 3 (for comparison).

Table B.8.6.52: FOCUS Step 4 calculated PEC_{SW} values (14 m no-spray buffer zone) for captan applied to pome fruit in Northern Europe (single applications)

Scenario	Max PEC_{SW} (µg/L)	
	Step 4	Step 3
D3-ditch	7.88	46.04
D4-pond	0.90	2.06
D4-stream	9.13	46.11
D5-pond	0.90	2.06
D5-stream	9.85	49.75
R1-pond	0.90	2.06
R1-stream	6.84	34.57

Clearly, the PEC_{SW} values were all reduced significantly at step 4. This indicated that the PEC_{SW} values were dominated by the spray drift exposure route and that runoff and drainage are not predicted to be significant exposure routes for captan use on pome fruit in Northern Europe.

RMS comment: It is clear from this investigation that spray drift is the dominant exposure route to surface water for captan for North European uses.

Supplementary studies

Soil Photolysis

Data requirement 4.20	Notifier to assess soil photolysis metabolite THCY with regard to occurrence under field conditions and possibility of leaching into groundwater.

Notifier has presented an argument for why THCY should not be regarded as a soil photolysis metabolite:

Report: *Terry, A. (2005) Captan: Responses to Environmental Fate and Behaviour data requirements and questions arising from EPCO meeting 21. CEA, unpublished report September 2005.*

Two soil photolysis studies were conducted under natural sunlight with captan labelled in either the sidechain (IIA, 7.1.1.1.2/04) or the cyclohexene ring (IIA, 7.1.1.1.2/05). In the latter study, the metabolite THCY was found to reach a maximum of 15.3% of applied captan. However, THCY was also formed to the same extent under dark conditions (see Table B.8.1.2.19). As such, THCY cannot be regarded as a soil photolysis metabolite.

It is known that THCY is not formed in soil under aerobic conditions, but is formed under anaerobic conditions. Although it is not possible to determine what aspects of the incubations carried out in the soil photolysis study specifically led to the formation of THCY under both light and dark conditions, it is very clear that THCY was not formed in response to the presence of light, nor would it be expected to form in soil under aerobic conditions.

As such, it is not necessary to assess the possibility of THCY leaching into groundwater under field conditions because it would not be expected to form under field conditions.

Table B.8.1.2.19: THCY in soil following application of [cyclohexene 1,2 - ^{14}C] captan (mean of replicates)

Days after application	% of applied captan in the presence of light	% of applied captan in the dark
0	**ND**	**ND**
1	**4.4**	**10.2**
2	**6.2**	**7.2**
3	**4.9**	**3.0**
4	**15.3**	**13.3**
5	**9.5**	**6.0**

RMS comment: Agree.

B.8.11 References relied on

B.8.11.1Active ingredient

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
	Terry, A	2005	Captan: Responses to Environmental Fate and Behaviour data requirements and questions arising from EPCO meeting 21. Report dated 14 September 2005. CEA 099.	Y	Makhteshim/ Calliope SAS

Ecotoxicology

October 2005

B.9 Ecotoxicology

Introduction

This document is an Addendum to the Draft Assessment Report (DAR) for the EU review of captan to address issues raised at the EPCO meeting (no. 22) held on 11-15 April 2005. The aim of this Addendum is to address 'Open points' and 'Data requirements' as raised. in the official Evaluation Table (dated 11.08.05) in the area of Ecotoxicology.

This Addendum includes summarisation and evaluation of new data and risk assessments submitted by Makhteshim Chemical Works Ltd and *Calliope (*formerly, Tomen France S.A.S.).

Section numbering in this Addendum is in line with Annex B (Volume 3) of the DAR.

The Good Agricultural Practice (GAP) uses proposed by the Notifier for consideration under the review are specified in Table 1.

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Table 1: Critical Good Agricultural Practice for captan in the EU review

Crop	Member state or country	Product name	F, G or I	Pests or group of pests controlled	Formulation		Application			Application rate per treatment			PHI (days)	Remarks:
					Type	Conc. of a.s.	method kind	growth stage/ timing	number[b] (max.)	kg a.s./hL (max.)	water L/ha	kg a.s./ha (max.)		
Pome fruit	North EU	'Merpan' 80 WDG / 'Malvin' WDG	F[a]	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 53 / April	9 - 10	0.125	1000	1.25	14	
	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Scab and *Nectria*	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69 / April	9 + 3 [c]	0.125 0.24	1000 1000	1.25 2.4	14	
Tomatoes	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Foliar spray; down-wards	From BBCH 60 to 87	4	0.15	1200	1.8	14	
Peaches/ nectarines	South EU	'Merpan' 80 WDG / 'Malvin' WDG	F	Various diseases	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	From BBCH 69: petal fall	4	0.25	1000	2.5	7	

[a] F = field.
[b] Applications at a minimum of 7 days for all crops.
[c] Nine applications at 1.25 kg a.s./ha (scab control) followed by three applications at 2.4 kg a.s/ha (*Nectria* control).

B.9.1 Effects on birds (Annex IIA 8.1; Annex IIIA 10.1)
B.9.3 Effects on other terrestrial vertebrates (Annex IIIA 10.3)

As the issues are closely linked, the risk to birds and mammals is evaluated together in this Addendum.

Open point 5.5:
RMS to amend the list of endpoints regarding the LC50 and NOEC for birds. (see reporting table 5(7)).RMS should verify the recalculation to daily dose of the NOEC for bobwhite quail.

The conversion of the NOEC from the bobwhite quail reproduction study to daily dose has been checked. The mean food intake per day (quoted in Table 4 of the previous ecotoxicology addendum to the DAR) should be 17 g/bird/day (not 15.3 g/bird/day). Taking this into account the calculation of the daily dose is:

(mean food intake/mean bodyweight) x dietary concentration = daily dose

(17 g per day / 204.3 g) x 1000 ppm = 83.2 mg/kg bw/day

This does not affect the risk assessment as the lowest NOEL in terms of daily dose is for mallard (74.4 mg/kg bw/day). The list of endpoints will be amended to take account of the above. The 'LC50' as mentioned in the Open Point does not need to be changed.

New open point 5.20:
RMS to recalculate the long term risk to birds with the default RUD value.
See open point 5.6. This open point was proposed at EPCO 22.

The Notifier has provided the following response (Ref: Norman, 2005):

This request relates to the long term risk assessment for insectivorous birds. The toxicity exposure ratios (TER) using the default residue per unit dose (RUD) for 'small insects' of 29 (SANCO/4145/2000) are presented in Table 2.

Table 2: Long-term ETE and TER values for insectivorous birds using default RUD of 29.

Crop	Indicator species	App. rate, kg/ha	RUD mean[a]	FIR[b]	PT[c]	ETE, mg/kg bw/d[d]	NOEL, mg/kg bw/d	TER
Pome fruit North EU ('Orchard / vine / hops')	Insectivorous bird	1.25	29	1.04	0.61	23.0	74.4	3.2
Pome fruit South EU ('Orchard / vine / hops')	Insectivorous bird	2.4	29	1.04	0.61	44.2	74.4	1.7
Peaches/ nectarines ('Orchard / vine / hops')	Insectivorous bird	2.5	29	1.04	0.61	46.0	74.4	1.6
Tomatoes ('Leafy crops')	Insectivorous bird	1.8	29	1.04	1	54.3	74.4	1.4

[a] Residue per unit dose for small insects, quoted from SANCO/4145/2000.
[b] FIR: Food Intake Rate per day as a proportion of bodyweight, quoted from SANCO/4145/2000.
[c] PT is proportion of food obtained from the treated area. Informed that value of 0.61 was agreed by EPCO 22 for pome fruit and nectarines/peaches.
[d] ETE: Estimated theoretical Exposure (application rate x RUD x FIR x PT).

Long term TER values in Table 2 are lower than the Annex VI trigger of 5. Hence, the risk should be further assessed.

Long term risk assessment for birds including additional refinement:

Toxicity endpoint: It should be noted that there were no effects in the bird reproduction studies. Hence, the need for a refined assessment is not triggered by any adverse effect on reproduction. The TER values derived in Table 2 are simply a product of the highest concentration tested, i.e. 1000 ppm in the diet. Such a concentration is regarded as a reasonable upper limit for testing, and would have been high enough to justify low risk based on the previous commonly used risk assessment scheme (EPPO, 1992).

Residue per Unit Dose (RUD) of 29 for 'small insects': The default RUD value for 'small insects' quoted in the EU risk assessment guidance (SANCO/4145/2000) is extrapolated from residues on weed seeds (quoted from Hoerger and Kenaga, 1972). Hence, the values do not have a strong scientific basis. The EU guidance document states: *'The residue estimate for small insects appears unsatisfactory, and as soon as better information becomes available this surrogate should be replaced...'*. The available data on actual residues on insects suggests that the current default RUD values for small insects represent a significant overestimate. A research project (sponsored by ECPA) currently being undertaken by the contractor Rifcon is reviewing available insect residues trials. The project includes evaluation of modern insect residues trials conducted in the last few years. The project is well advanced, and the outcome is intended to be taken into account in a review of the existing default RUD values for insects. UK Central Science Laboratory is also undertaking research in this area. Following Annex I listing, risk assessments can be submitted at Member State level which include agreed *revised* RUD values for insects after these become available.

Refined risk assessment: As stated above the default RUD value for 'small insects' appears unsatisfactory (albeit precautionary). As there is currently no agreed alternative value, this value can be incorporated into a refined risk assessment for insectivorous birds. Under the

EU guidance document on risk assessment for birds and mammals (SANCO/4145/2000) a refined assessment can be conducted by defining appropriate key (focal) species for the crop use scenario under discussion. This has now been conducted for the use of captan in pome fruit, nectarines/peaches and tomatoes (Ref: Gerlach, 2005). A summary of this risk assessment is provided below. The refinements in this assessment are based on ecological information from the published literature on energy requirements, dietary composition and foraging behaviour of relevant insectivorous bird species:

Gerlach, J (2005): Captan: Long term risk assessment for insectivorous birds. Rifcon GmbH report no. RC05-016. September 2005:

[The full text of this assessment is provided in Appendix 1 of this Addendum]

Species of concern:

Tomato: **Yellow wagtail** (*Motacilla flava*) is frequently observed in tomato fields and is known to nest within the crop. As a small insect-eating bird, is has been selected as a key species on which to base the refined risk assessment.

Pome fruit, peaches/nectarines: **Great tit** (*Parus major*) has been identified as key foliage foraging insectivorous species in modern orchards in central Europe. No published data regarding species composition is available for south EU orchards. However, great tits do occur throughout the Mediterranean region. As a small insect-eating bird, great tit has been selected as a key species on which to base the refined risk assessment.

Refinement of food intake rate (FIR):

Based on bodyweights, energetic requirement and energy value of relevant feed items, the food intake per day in terms of fresh weight can be estimated for a species. For **yellow wagtail** (approximate weight 17 g) this has been calculated to be 15 g of arthropods, giving as **FIR** of **0.88**. For **great tit** (approximate weight 17.4 g) this has been calculated to be 15.2 g of arthropods, giving as **FIR** of **0.88**, or 22.1 g of caterpillars giving as **FIR** of **1.27**.

Refinement of proportion of diet obtained from the treated area:

Yellow wagtail: For nesting, yellow wagtails require sufficient vegetation to cover the nest (which is why they have been observed to nest in tomato and potato fields). However, for feeding they prefer areas with no vegetation or short vegetation (short grazed pasture, mown meadow). Hence, they feed mainly outside the treated area. For a long term risk assessment, it is conservatively assumed that yellow wagtails will obtain at least half of they food from the treated area (i.e. **PT = 0.5**). This is supported by the EFSA PPR opinion (2004) on an avian risk assessment (on methamidophos) for yellow wagtails in potato fields (a similar crop to tomato in structure and taxonomy) which also used a PT of 0.5.

Great tit: From a study on foraging behaviour of great its in orchards in Germany, it is clear that a PT of <1 is justified. In commercially managed orchards a shortage of potential prey items can force great tits to forage outside the treated area. Based on radio-tracking data on blue tit (a closely related species to great tit) in orchards a **PT** of **0.61** is derived (agreed to be appropriate PT by EPCO 22).

Refinement of portion of diet (PD):

Yellow wagtail: Information is available in the literature regarding size preference for insect food items for yellow wagtail. Based on this information it can be concluded that in terms of *number* of insects around 76.4% (**PD: 0.764**) are '**large insects'** and 23.6% (**PD: 0.236**) '**small insects'**. Data on mass of insects in relation to bodylength indicate that in terms of *mass* the PD for large insects would be higher than 0.764. Hence, the use of this value is conservative.

Great tit, north EU: Available information indicates that around 50% of the diet of a great tit is caterpillars, with the remainder comprising spiders and dipterans. Hence, **PD** of **0.5** can be used for **caterpillars** (using 'large insects' RUD of 5.1); **PD** of **0.125** each for **small and large insects** either *in* of *below* the canopy (the latter taking account of some foliar interception), i.e. the total PD for large and small insects is 0.5 (0.125 x 4).

Great tit, south EU: Information on great tits foraging in modern citrus orchards indicate that 44% (**PD: 0.44**) of diet consists of **large insects** (mainly Lepidoptera) and 44% (**PD: 0.44**) of **caterpillars** ('large insects' RUD). The remainder are likely to be **small insects** (**PD: 0.06**) and **insect eggs** (**PD: 0.06**; using 'small insects' RUD).

Exposure and risk assessment:

Yellow wagtail: The exposure assessment for yellow wagtails potentially foraging in tomato fields treated with captan at a rate of 1.8 kg a.s./ha is depicted in Table 3.

Table 3: Exposure assessment for yellow wagtails in tomato fields

Diet proportions	large insects	small insects	Whole diet
Application rate [kg a.s./ha]	1.8	1.8	
RUD [mg/kg a.s./ha]	5.1	29	
Maximum initial concentration after last application [mg a.s./kg]	9.18	52.2	
Relative daily food intake (FIR/b.w.) [g fresh weight/g b.w./day]	0.88	0.88	
Portion of diet obtained in-crop (PT)	0.5	0.5	
Portion of diet (PD)	0.764	0.236	
Estimated theoretical exposure (ETE) [mg a.s./kg b.w./day]	3.09	5.42	**8.51**

<u>Great tit:</u> The exposure assessments for great tits foraging in north EU pome fruit orchards (Table 4), south EU pome fruit orchards (Table 5) and south EU peaches/ nectarines orchards (Table 6) treated with captan are depicted below.

Table 4: Exposure assessment for the great tit in pome fruit in Northern Europe

Diet proportions	Large arthropods		Small arthropods		Caterpillars	
	soil	foliage	soil	foliage	foliage	
Application rate [kg a.s./ha]	1.25					
RUD [mg/kg a.s./ha]	5.1	5.1	29	29	5.1	
Maximum initial concentration after last application [mg a.s./kg]	6.375	6.375	36.25	36.25	6.375	
Relative daily food intake (FIR/b.w.) [g fresh weight/g b.w./day]	0.88	0.88	0.88	0.88	1.27	
Portion of diet obtained in-crop (PT)	0.61					
Portion of diet (PD)	0.125	0.125	0.125	0.125	0.50	
Deposition factor	0.6	1	0.6	1	1	
Estimated theoretical exposure (ETE) [mg a.s./kg b.w./day]	0.26	0.43	1.46	2.43	2.47	**7.05**

Table 5: Exposure assessment for the great tit in pome fruit in Southern Europe

Diet proportions	Large arthropods		Small arthropods		Cater-pillars	
	soil	foliage	soil	foliage	foliage	
Application rate [kg a.s./ha]	2.4					
RUD [mg/kg a.s./ha]	5.1	5.1	29	29	5.1	
Maximum initial concentration after last application [mg a.s./kg]	12.24	12.24	69.6	69.6	12.24	
Relative daily food intake (FIR/b.w.) [g fresh weight/g b.w./day]	0.88	0.88	0.88	0.88	1.27	
Portion of diet obtained in-crop (PT)	0.61					
Portion of diet (PD)	0.22	0.22	0.06	0.06	0.44	
Deposition factor	0.6	1	0.6	1	1	
Estimated theoretical exposure (ETE) [mg a.s./kg b.w./day]	0.87	1.45	1.35	2.24	4.17	**10.08**

Table 6: Exposure assessment for the great tit in peaches / nectarines in Southern Europe

Diet proportions	Large arthropods		Small arthropods		Cater-pillars	
	soil	foliage	soil	foliage	foliage	
Application rate [kg a.s./ha]	2.5					
RUD [mg/kg a.s./ha]	5.1	5.1	29	29	5.1	
Maximum initial concentration after last application [mg a.s./kg]	12.75	12.75	72.5	72.5	12.75	
Relative daily food intake (FIR/b.w.) [g fresh weight/g b.w./day]	0.88	0.88	0.88	0.88	1.27	
Portion of diet obtained in-crop (PT)	0.61					
Portion of diet (PD)	0.22	0.22	0.06	0.06	0.44	
Deposition factor	0.6	1	0.6	1	1	
Estimated theoretical exposure (ETE) [mg a.s./kg b.w./day]	0.90	1.51	1.40	2.34	4.35	**10.50**

Toxicity Exposure ratios are calculated and presented in Table 7 below.

Table 7: Refined long-term TER calculation for insectivorous birds

Species	**Scenario**	**Toxicity mg/kg b.w./day**	**ETE mg/ kg b.w.**	**TER_{lt}**
Yellow wagtail	Tomatoes	**74.4**	8.51	**8.74**
Great tit	Pome fruit, North EU		7.05	**10.6**
	Pome fruit, South EU		10.07	**7.38**
	Peaches / nectarines		10.50	**7.09**

TER values are greater than the Annex VI trigger of 5, indicating low risk.

Comment from RMS on the above:

The RMS has considered the refined risk assessment report (Gerlach, 2005) and other argumentation provided above. The major point is that existing bird reproduction studies show no effects at the highest treatment level of 1000 ppm. Hence, there is no inherent concern over the potential for captan to affect reproduction in birds. The refined risk assessment based on information from the published literature includes more realistic assumptions in terms of dietary composition (PD) and proportion of food taken from the treated area (PT). It is reasonable, especially over the long term, to assume that an individual insectivorous bird would consume a mixed diet including both small and large insects. Birds are obviously highly mobile, so modifications to PT over the long term are also justified (as agreed at EPCO 22). The choice of key species and refinement of parameters for these species in the higher tier assessment (Gerlach, 2005), are considered to be reasonable.

Considering the refined risk assessment, together with the fact that there were no effects in reproduction studies, a low risk can be concluded.

Data requirement 5.3:
Notifier to present an argumentation on the residue decline in insects. See open point 5.6. This data gap was identified at EPCO 22.

The Notifier provided the following statement (Ref: Norman, 2005):

No decline in insect residues is assumed in the long term risk assessment for insectivorous birds, which is the default approach according to EU guidance document on birds and mammals. An insect residues study for captan is not available in order to quantify the decline in residues. This type of study is only triggered where there is a significant concern over risk to birds, which is not the case for captan (low acute and short term risk; no effects in bird reproduction studies). From the generally rapid degradation of captan in the environment (i.e. in soil and water by hydrolysis) it is predicted that residues in insects would also decline relatively quickly. Immigration of insects from untreated areas would also dilute any residue.

Comment from RMS on the above:

The RMS agrees with the above statement from the Notifier.

New open point 5.21:
Open point pending on the outcome of the relevance of insectivorous mammals in southern European orchards a risk has to be calculated. See open point 5.6. This open point was proposed at EPCO 22.

The Notifier has submitted the following statement (Ref: Norman, 2005):

The EU guidance document on risk assessment for birds and mammals (SANCO/4145/200) does not include a scenario for an insectivorous mammal in an orchard. As such, consideration of this scenario would be outside the current agreed guidance. Clearly, the relevance of insectivorous mammals in south European orchards is a generic question, not only relating to captan. For illustration, the insectivorous mammal scenario identified in the EU guidance (SANCO 4145/2000) as relevant to late season cereals can be used (the shrew). The highest application rate proposed in South EU orchards is 2.5 kg a.s./ha in peaches/nectarines. The estimated theoretical exposure (ETE) for the long term assessment would be 2.5 kg/ha x 5.1 (RUD) x 0.63 (food intake rate, FIR) = 8.0 mg/kg bw/day. Compared with a long term NOEL of 250 mg/kg bw/d the TER is 31.3. This value is greater than the Annex VI long term trigger of 5, indicating low risk.

Comment from the RMS on the above:

A low risk can be concluded.

Data requirement 5.4:
Notifier to submit an argumentation on the PT assumption of 0.5 for the use in orchards. See open point 5.6. This data gap was identified at EPCO 22.

The Notifier provided the following statement (Ref: Norman, 2005):

This requirement relates to the long term risk assessment for herbivorous mammals. The tier 1 risk assessment is based on the worst case of a field vole. The field vole occurs typically in ungrazed grassland or in the early stages of forestry plantations but may also live in woodland, hedgerows, dunes or moorland, wherever grass is available (ref: website of The Mammal Society). The grass growth under trees in a modern commercial orchard is likely to be managed in some way, and in any case its growth will be restricted by shading from the trees. It is unlikely that a field vole would obtain its entire diet of grass from the treated area over an extended period (i.e. 21 days, which is the assumed exposure window in the EU guidance document SANCO 4145/2000). It is more likely that feeding in field margins and ungrazed grassland would make up a significant portion of the diet. A more reasonable generic assumption (still worst case) is that 50% of the diet is obtained from the treated area over the long term. A PT value of 0.5 has therefore been used in the previously submitted risk assessment (ref: Norman and Wyness, 2003).

It should be noted that in a large proportion of south European pome fruit orchards and peach/nectarine orchards there is no vegetation on the ground, in order to minimise competition for water. In such cases, there is no potential for exposure of herbivorous mammals (i.e. PT of 0). In addition, mammals will not graze on tomato plants (Solanaceae) as they are unpalatable. Hence, PT is effectively zero for this use as well.

Long-term endpoint for mammals: It is understood that there was discussion on this issue at EPCO 22. The Notifier continues to support the endpoint of 250 mg/kg bw/day as proposed in a previously submitted risk assessment (ref: Norman and Wyness, 2003) as the endpoint should be relevant at the population level.

RMS comment on the above statement:

Considering that this is a long term assessment the assumption of some refinement of PT is considered acceptable. The justification provided for the PT of 0.5 is qualitative. However, the value appears to be reasonable. It was commented at EPCO 22 that in southern Europe the soil is vegetation-free in orchards (pome fruit, nectarines/peaches) due to competition for water, and the risk to herbivorous mammals could be regarded as addressed. Southern Member States were asked to confirm this after the meeting. Participant from Spain confirmed this is common practice. Participant from Greece indicated that all ground vegetation is removed either by herbicide, or by combination of herbicide followed by mechanical methods. Hence, it can be concluded that there is unlikely to be exposure of herbivorous mammals in south EU orchards. Therefore, for south EU uses (pome fruit, nectarines/peaches and also tomatoes) there is a low risk to herbivorous mammals.

For long term risk to mammals in north EU orchards the discussion at EPCO on the long term endpoint for mammals is relevant. It needs to be decided whether the appropriate endpoint is 250 mg/kg bw/d or 100 mg/kg bw/d. RMS supports 250 mg/kg bw/d as a reasonable endpoint. Using both these values, the TER for the use in north EU pome fruit (for south EU uses exposure would not be significant, as stated above) is as follows:

ETE = 1.25 kg/ha x 76 (RUD) x 1.39 (FIR)x 0.25 (deposition) x 2.5 (MAF) x 0.79* (ftwa) x 0.5 (PT)

*taking account spray interval of 7 days, as stated in previous ecotoxicology addendum

ETE = 32.6 mg/kg bw/day TER = 250 / 32.6 = 7.7 or TER = 100 / 32.6 = 3.1

The TER using the endpoint of 250 mg/kg bw/d is greater than the Annex VI trigger of 5, indicating low risk. The TER using the endpoint of 100 mg/kg bw/d is 3.1 and is below the Annex VI trigger of 5. If 100 mg/kg bw/d is used, considering the conservative nature of the risk assessment in terms of the choice of long term endpoint, RUD, and daily intake of the model herbivorous mammal, the risk is considered to be acceptable.

New open point 5.22:
RMS to conduct the long-term risk assessment for aquatic organisms with proposal made by EFSA. See open point 5.10. This open point was proposed at EPCO 22.

EFSA proposed that long term risk assessment could be conducted based on the NOEC from the 28 day semi-static study on rainbow trout, compared with the initial PEC value. The NOEC from this study (ref: Schanne, 1999) is 199.2 µg a.s./L. The endpoint is compared with initial PECsw values in Table 8:

Table 8: Fish: TER for pome fruit, peaches/nectarines and tomato using NOEC of 199.2 µg/L

Dist. (m)	**Late season Drift (%)**	**Pome fruit**				**Peaches, nectarines**	
		1.25 kg as/ha		**2.4 kg a.s./ha**		**2.5 kg a.s./ha**	
		PEC_i µg a.s./L	**TER***	**PEC_i µg a.s./L**	**TER***	**PEC_i µg a.s./L**	**TER***
3	15.73	65.54	3.04	125.84	1.58	131.08	1.52
5	8.41	35.04	5.68	67.28	2.96	70.08	2.84
10	3.60	15.00	**13.3***	28.80	6.92	30.00	6.64
15	1.81	7.54	-	14.48	**13.8***	15.08	**13.2***
20	1.09	4.54	-	8.72	-	9.08	-
30	0.54	2.25	-	4.32	-	4.50	-
40	0.32	1.33	-	2.56	-	2.67	-
50	0.22	0.92	-	1.76	-	1.83	-

Distance (m)	**Drift (%)**	**Tomatoes 1.8 kg a.s./ha**	
		PEC_i (µg a.s./L)	**TER**
1	2.77	16.62	**12.0***
5	0.57	3.42	-
10	0.29	1.74	-

*TER is greater than the relevant trigger of 10 at a distance of 10 m (North EU pome fruit), 15 m (South EU pome fruit, and peaches/nectarines) and 1 m (tomato). Hence, there is a low chronic risk to fish at these distances.

The above does not affect the overall outcome of the risk assessment, which is based on the *acute* risk to fish (six species tested, lowest LD50 98 µg/L, with a reduced TER trigger of 10).

Data requirement 5.2:
Notifier to address the risk to other non-target fauna and flora. (see reporting table 5(54))

The Notifier has submitted the following statement (Ref: Norman, 2005), together with a study on effects of captan (and folpet) on non-target plants (Ref: Kay, 2000):

A study on the effects of captan and folpet on non-target terrestrial plants is available, and is now submitted (ref: Kay, 2000). The following summarises the part of the study relevant to captan. Merpan 80 WDG (80% captan w/w) was applied as a foliar spray to 10 different crop plants (including both mono-cot and di-cot plants). These were: winter wheat, spring barley, winter oats, spring oats, rye, winter oilseed rape, linseed, peas, winter beans, and sugar beet. The study was conducted on plants growing in the field and was undertaken in the south of England (Oxfordshire). Each plot consisted of a 12 m length of 2 rows of the crop. There were two replicate plots for each crop / treatment rate variant. Merpan 80 WDG was applied once at rates of 5.4 and 9 kg a.s./ha. Plants were at the 3-4 leaf stage at the time of treatment. Observations for phytotoxicity and effects on plant vigour were 7, 14 and 28 days after application. The results of the study showed no phytotoxicity and no effects on vigour.

The highest application rate in the study, 9 kg a.s./ha, is 3.6 to 7.2 times higher than the proposed rates in the EU GAP (and is obviously many times higher than any off field exposure that could occur from drift). Hence, it can be concluded that there is a low risk to non-target flora.

Comment from the RMS on the above statement (and study):

The RMS considers the submitted study to be acceptable. There is a low risk to non-target plants.

New references, by Annex point

Annex point / reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**	**Data Protection Claimed** **Y/N**	**Owner**
Annex IIA 10.6	Kay, C. N.	2000	A evaluation of the effects of Folpan WDG and Merpan applied to a wide number of crops. Oxford Agricultural Trials Project No. 677-99-MAK-PAN (R-11417) non-GLP, unpublished	Y	Makhteshim/ Calliope* (*formerly Tomen)
Annex IIIA 11.1	Gerlach, J	2005	Captan: Long-term risk assessment for insectivorous birds. September, 2005 Rifcon Report No. RC05-016 GLP not applicable, unpublished.	Y	Makhteshim/ Calliope* (*formerly Tomen)

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
	Norman, S	2005	Captan: Responses to questions raised at EPCO 22 on ecotoxicology. September 2005.	Y	Makhteshim/ Calliope* (*formerly Tomen)

Appendix:1

Gerlach, 2005: Captan: Long term risk assessment for insectivorous birds (Rificon study report, September 2005):

Background information

3.1 Use pattern of Captan

The use pattern of Captan on which the refined risk assessment is based is shown in Table 1.

Table 1 Crops and application rates for Captan

Crop	Northern Europe (NE)/ Southern Europe (SE)	Max. application rate kg a.s./ha	Max. no. of applications
Pome fruit	NE	1.25	9-10
Pome fruit	SE	1.25 2.4	9 and 3
Tomatoes	SE	1.8	4
Peaches / nectarines	SE	2.5	4

3.2 Effects on birds

The long-term toxicological endpoint for birds used in this refined risk assessment is presented in Table 2

Table 2 Toxicological endpoint for birds for Captan

Organism	Duration	Test-substance	Ecotoxicological endpoint
Mallard	chronic, dietary	a.s.	NOEC = 1000 ppm equivalent to NOEC = 74.4 mg a.s./kg b.w./day

Section 4. Refinement of factors

4.1 Species of concern

4.1.1 Tomatoes (leafy crops)

According to SANCO/4145/2000 the risk for an insectivorous bird as a recommended indicator species has to be evaluated in the leafy crop category, i.e. in tomatoes.
The yellow wagtail (*Motacilla flava*) was frequently observed in tomato fields and was confirmed to be nesting inside the crop (Anonymous 2004).
Based on these data yellow wagtails are deemed to be a characteristic species to be encountered in tomato fields in Southern Europe. This species will be used in the risk assessment for Southern European tomato fields.

4.1.2 Pome fruit / peaches / nectarines (orchards)

The great tit (*Parus major*) has been identified as a foliage-foraging key species in modern orchards in Central Europe.
This was confirmed by a PhD in the Netherlands where the majority of insectivorous birds in modern spindle bush orchards were great tits (Mols 2003). The tits were attracted to the orchards by providing nest boxes which is a widespread practice among apple growers. The great tit is a common species that readily breeds in nest boxes and hence the local density of great tits can be increased by putting up nest boxes in orchards. The modern growing type of orchard trees, i.e. spindle bush trees, does not hinder great tits to breed in these surroundings as far as sufficient nest boxes are available (Mols 2003). The great tit has been likewise selected as key bird species in a study on the impact of pesticide treatments on the reproduction of great tits inhabiting modern orchards in southern Germany (Mattes et al. 1980).
There are no published generic data regarding the species composition of the avian community potentially foraging in southern European orchards. However, great tits also occur throughout the Mediterranean and are therefore included in the risk assessment on southern European orchards.

4.2 Refinement of the food intake rate (FIR)

Yellow wagtails have a body weight of about 17 g (Dittberner & Dittberner 1984). The average daily food intake was estimated to amount 73.7 kJ/day according to (Crocker et al. 2002a) based on a body weight of 17.0 g (Dittberner and Dittberner 1984). Arthropods contain on the average 21.9 kJ/g dry weight and consist of 70.5% water. Therefore arthropods contain 6.5 kJ/g fresh weight. A yellow wagtail using 73.7 kJ/day will eat 11.4 g arthropods per day. Adjusting this figure for assimilation efficiency (76% for a passerine bird) this results in an average daily food intake of a yellow wagtail of 15 g arthropods per day. Related to the average body weight the FIR/bw will be **0.88**.

Great tits have a body weight of about 17.4 g (females) and 19.2 g (males) (Perrins 1998). The average daily food intake was estimated to amount 74.9 kJ/day according to (Crocker et al. 2002a) based on a body weight of 17.4 g.
Arthropods on the average contain 21.9 kJ/g dry weight and consist of 70.5% water. Therefore arthropods contain 6.5 kJ/g fresh weight. A great tit using 74.9 kJ/day will eat 11.6 g arthropods per day. Adjusting this figure for assimilation efficiency (76% for a passerine

bird) this results in an average daily food intake of a great tit of 15.2 g arthropods per day. Related to the average body weight the FIR/bw of great tits feeding on arthropods will be **0.88**.

Caterpillars on the average contain 21.7 kJ/g dry weight and consist of 79.5% water (Crocker et al. 2002a). Therefore caterpillars contain 4.4 kJ/g fresh weight. A great tit using 74.9 kJ/day will have to eat 16.8 g caterpillars per day. Adjusting this figure for assimilation efficiency (76% for a passerine bird) this results in an average daily food intake of a great tit of 22.1 g caterpillars per day. Related to the average body weight the FIR/bw of great tits feeding on caterpillars will be **1.27**.

4.3 Refinement of the proportion of diet obtained in the treated area (PT)

Yellow wagtail

The proportion of diet obtained within the tomato field is set at **0.5**. This is explained by the peculiar biology of the yellow wagtail since for the yellow wagtail a distinction between nesting habitat and foraging habitat is obvious and reported from several studies.

For nesting, yellow wagtails require sufficient vegetation to cover the nest. However, for foraging, the species prefers areas devoid of vegetation or characterized by short vegetation such as lawns, short-grazed pastures or mown meadows (Dittberner & Dittberner 1984). For example, optimum nesting habitats for yellow wagtails in Russia were characterized by a vegetation height of 40 – 60 cm and a coverage of 90% (Dittberner & Dittberner 1984). The preference for yellow wagtails to feed in areas of short vegetation (e.g. pasture) or bare soil is in accordance with the main foraging behaviour of the species, i.e. picking arthropods from the ground or fly-catching arthropods (Davies 1977, Dittberner and Dittberner 1984). Thus, a pronounced distinction between foraging habitat and nesting habitat is obvious. Commonly parent wagtails have to cover a distance of several hundreds of meters between nesting and foraging habitat (Dittberner & Dittberner 1984).
For a long-term risk assessment it is therefore assumed that yellow wagtails will obtain at least 50% of their diet outside the treated areas. This PT of 0.5 is still considered to be a conservative estimate.

This was corroborated by the EFSA PPR Panel that concluded, considering long-term exposure, that PT for yellow wagtails in potato fields would be less than 0.5 (Anonymous 2004). As observations of yellow wagtails in tomatoes showed similar numbers compared to potatoes (Anonymous 2004), the results are assumed to hold also true for tomato fields.

Great tit
There is no published data on the time great tits spent foraging in an orchard. However, based on a study conducted in Germany on the foraging behaviour and the reproductive performance of great tits breeding in intensively managed orchards (Mattes et al. 1980), it is obvious that a PT smaller than 1 is justified.
In the treated orchards the impoverishment of potential prey forced the tits to forage in more distant habitats such as woodland edges and groves. The maximum distances covered were 220 m from the nest. Within the orchard the great tits predominantly foraged on the ground, particularly after mowing and mulching. This resulted in a higher amount of arachnida compared to non-treated orchards. The average feeding rate was significantly reduced in the treated orchards and the foraging distances were enlarged, reflecting the reduced prey potential of treated orchards.

Based on the radio-tracking data of (Crocker et al. 2002b) on the blue tit, a closely related

species, it was suggested that 95% of the local tit population spent less than 61% of potential foraging time among the orchard trees. This figure (PT = **0.61**) is assumed to hold true for great tits as well, given the results of the German study cited above, particularly when referring to long-term exposure.

2.4 Refinement of the portion of diet (PD)

Yellow wagtail

In a study on the foraging behaviour of yellow wagtails in the UK the diet of solitary foraging yellow wagtails was examined on non-flooded areas of a meadow (Davies 1977). The predominant prey types of foraging yellow wagtails were flies around dung pats. The availability of the individual prey types was estimated by counting the number of prey individuals per 100 dung pats transect. The size distribution of available insects and ingested insects (from assessment of faecal material) was ascertained (Table 3). This research is valuable to the risk assessment. In effect, the yellow wagtails are presented with insects in a range of sizes (dung flies in a meadow in this case), from which their size preference is determined.

Table 3 The prey types eaten by solitary foraging yellow wagtails (adopted from Davies 1977)

Prey type	Body length	Availability	remains in droppings
	[mm]	[%]	[%]
Scatophagidae	5-10	77.1	35.1
Sphaeroceridae	1-2	6.9	2.3
Sphaeroceridae	3-4	10.1	41.3
Sepsidae	3-4	0.7	0.0
Coleoptera	2-3	5.1	6.4
others	--	0.1	14.9

Scatophagidae vary from 5 mm to 10 mm in body length with females being smaller. On the dung pats males outnumbered females by 3.7 to 1.0. Yellow wagtails preferred flies having about 7 mm in length. Prey up to this size is swallowed immediately in a very short period of time (< 1 sec). Larger prey, 10 mm in length, is bashed against a perch, sometimes dropped and took 5 – 10 sec to handle (Davies 1977).

From caloric specific values and the handling times for each size of prey, the energy intake per unit handling time was calculated and it could be seen that the size of the prey selected by wild wagtails corresponds to the optimum prey size they can handle. Thus small prey items (1-2 mm) were ignored because although quick to handle the ratio between energy used for foraging and energy gained from successful prey was too unfavorable for the bird. On the other end of the scale the largest Scatophagidae were rejected because although worth very much energy they took too long to handle (Davies 1977).

Based on the data presented by Davies (1977) which is the most comprehensive study on yellow wagtail diet available, the majority of prey items collected by yellow wagtails are 3 - 4 mm and greater.

The size definition of ‘small’ and ‘large’ insects is not stated in the EU guidance document on risk assessment for birds and mammals. The residue estimate for ‘small’ insects in the guidance document is derived from Kenaga (1973) on the basis of residues in weed seeds. Such seeds would typically be 1-2mm. The residues estimate for ‘large’ insects, which was previously quoted in the EPPO 1992 vertebrate scheme, came from the same published paper. This value was based on residues on wheat seeds. Wheat seeds are typically 4-5 mm in

length. Hence, a working definition of 'large' (≥ 3 mm) and 'small' (<3mm) can be determined.

By summing the percentages for flies from the 3-4 mm and 5-10 mm categories (please see table 3), a total of 76.4% is derived (**PD** of **0.764**). PD for small insects is conservatively set at **0.236** (remaining groups).

These percentages are based on numbers of insects, *not* mass of insects. Clearly, the proportion of large insects based on *mass*, would be much more than 76.4%. In order to give an indication of the proportion according to mass, data are needed on the corresponding mass for a fly of known length. Makhteshim asked a contract laboratory (Huntingdon Life Sciences) to measure and weigh dung flies, and winged aphids (as surrogate for small dung flies). The data are presented below:

Table 4 Winged aphid wet weight and body length (weighed on 13 September 2004)[1]

Insect no.	*Rhopalosiphum padi* (Cereal aphid)		*Acyrthosiphon pisum* (Pea aphid)	
	Body length (mm)	Wet weight (mg)	Body length (mm)	Wet weight (mg)
1	1.41	N/A	2.98	2.1
2	1.66	N/A	2.83	1.8
3	1.72	N/A	3.41	2.1
4	1.28	N/A	3.07	2.1
5	1.74	N/A	3.00	1.8
6	1.38	N/A	3.14	1.9
7	1.68	N/A	2.53	1.4
8	1.66	N/A	2.77	1.7
9	-	-	2.69	1.4
10	-	-	2.44	1.1
11	-	-	2.58	1.8
12	-	-	2.94	1.5
13	-	-	2.46	1.4
14	-	-	2.59	1.5
15	-	-	3.12	1.9
16	-	-	3.33	1.7
17	-	-	2.96	1.2
18	-	-	3.08	1.5
19	-	-	2.67	1.2
20	-	-	2.50	1.0
21	-	-	3.01	1.7
Total	-	1.5	-	-
Mean	**1.5663**	**0.1875**	**2.8619**	**1.6095**

N/A = Not Applicable; insects were weighed together to arrive at mean body mass.
1: Alan Lawrence, HLS, personal communication, 13 Sept 2004.

Table 5 Winged aphid wet weight and body length (weighed on 13 September 2004)[1]

Fly number	*Scathophaga stercoraria*	
	Body length (mm)	Wet weight (mg)
1	7.62	25.6
2	5.99	19.3
3	6.89	24.9
4	7.04	26.3
5	7.62	31.2
6	7.19	22.0
7	7.70	30.3
8	7.12	23.6
9	5.87	13.8
10	6.15	17.7
11	8.58	45.9
12	7.72	23.2
13	9.56	41.2
Mean	**7.31**	**26.54**

1: Alan Lawrence, HLS, personal communication, 13 Sept 2004
Based on the above a fly of body length 7.3 mm, is around 17 times heavier than an aphid of 2.9 mm body length, which in turn is around 15 times heavier than an aphid of 1.6 mm bodyweight.

Hence, it can be determined that using a **PD** of **0.764** for large insects, based on information of number of insects, rather than mass, is particularly conservative.

Great tit

The diet of the great tit includes a wide variety of insects, especially Lepidoptera and Coleoptera but also spiders and a significant amount of seeds and fruit is taken during winter (Perrins 1998). The majority of published data available relates to nestlings diet which is obviously due to methodical reasons (neck-collar sampling). For the long-term risk assessment presented here it is assumed that the diet of adult great tits is similar to that of great tit nestlings.

The nestlings diet is less diverse compared to that of the great tit adults and is dominated by lepidopteran larvae (Perrins 1998). Great tits provisioning nestlings in apple orchards predominantly prey on caterpillars. Table 6 summarizes the results of studies on the diet of great tit nestlings in orchards.

Table 6 Nestlings diet of great tits in various habitats in various parts of the species´ range

Country	Habitat	Lepidopteran larvae	Spiders	Dipterans	Reference
Germany	apple orchard	62%	12%	9%	(Görnandt 1959)
Germany	apple orchard	51%	31%	10%	(Hölzinger 1997)
Germany	treated modern orchard	47-85%	7-29%	3-13% [2)]	(Mattes et al. 1980)
Germany	treated modern orchard	58-71%	9-14%	14% [2)]	
Germany	traditional orchard [1)]	53-59%	5-7%	10-25% [2)]	
Germany	traditional orchard [1)]	42-58%	5-12%	32-39% [2)]	

1) non-treated with chemical crop protection products
2) Hymenopterans and Dipterans

As can be seen from the data presented in Table 6 caterpillars comprise about half of the prey items of great tits foraging in Central European orchards. The remainder is made up of other arthropods with spiders predominating. The portion of diet for great tits foraging in orchards is roughly estimated to consist of 50% caterpillars and 50% of other arthropods.

There are no published generic data on the size of prey items collected by great tits in orchards. However, based on the results of several studies throughout the species´ range in various habitats, it is obvious that the bulk of the great tits prey items comprises large insects.

The size of 2,553 insects from 150 great tits collected throughout the year in British oak woods was for 26.5 % 0-2 mm, 19.6 % 3-4 mm, 21.9 % 5-6 mm and for 32 % greater than 6 mm (Betts 1955). The smallest insect items eaten by the great tit were aphids and the eggs of the vapourer moth and both items have been found in clusters (Betts 1955).

In the analysis of 132 stomach contents of great tits which lived in the Ukraine a total of 881 insects was found, of which 27.5 % were less than 5 mm, 65.5 % were 5-10 mm, 4.3 % were 10-15 mm and 2.9 % were of greater size than 15 mm (Perrins 1998).

Therefore as a conservative approach it is estimated that in Central European orchards about 25% of the great tits prey items comprise large insects and 50% large caterpillars. The remainder is made up of small insects or insect eggs.
A study on the diet composition of great tits foraging in modern citrus orchards in Spain revealed that great tit nestlings in a modern orange grove near Sagunto, East Spain, from April to August 1988 were predominantly fed with Lepidoptera to about 87.8 % in numbers of 526 prey items (Barba and Gil-Delgado 1990). Among the lepidopterans 49.8 % were imagines, almost exclusively Noctuidae (*Peridroma saucia* to about 45.4 %, but also *Agrotis segetum, Agrotis exclamationis, Agrotis ipsilon, Noctua pronuba, Xestia c-nigrum, Mythimna unipunctata, Mythimna loreyi, Spodoptera littoralis, Athetis hospes, Autotrapha gamma* and *Hoplodrina ambigua*), 23.6 % were lepidopteran caterpillars, 14.3 % lepidopteran pupae (Barba & Gil-Delgado 1990). Furthermore the nestlings obtained 5.7 % spiders and 6.5 % other prey items including Hymenoptera, Coleoptera (Curculionidae), Orthoptera (grass-hoppers), egg cocoons and orange pieces (Barba & Gil-Delgado 1990). Caterpillars were the most abundant prey delivered to the young only during 6-15 May, while Lepidoptera imagines were more abundant during the rest of the season and thus were considered as an important resource for the great tits breeding in orange groves (Barba & Gil-Delgado 1990). The mean size of the prey items brought to great tit nestlings in Spanish pine forests was 15.5 mm on the average (Monros et al. 1997).

Therefore as a conservative approach it is estimated that in Southern European orchards about 44% of the great tits prey items comprise large insects (Lepidopterans) and 44% large caterpillars. The remainder is assumed to be made up of small insects or insect eggs.

2.5 Refinement of foraging strata

Great tit

In a comprehensive field study on the impact of insecticides on vitality and reproduction of great tits in southern Germany five orchards were supplied with nest boxes to enlarge or to establish populations of great tits. The orchards differed significantly by the amount of insecticides applied. Three study sites (2 traditional orchards, 1 modern spindle bush orchard) received no application and two study sites (modern spindle bush orchards) were regularly treated with up to 18 annual treatments with fungicides and insecticides. The populations were monitored for 3 years to gather data on breeding biology (Mattes et al. 1980).

In the treated orchards the impoverishment of potential prey forced the tits to forage in off-crop habitats such as hedges and woodland edges. The maximum distances covered were 220 m from the nest. Within the orchard the great tits predominantly foraged on the ground, particularly after mowing and mulching. This resulted in a higher amount of arachnida compared to non-treated orchards (Mattes et al. 1980).
For the risk assessment of captan it is assumed that great tits forage for caterpillars in the canopy of the orchard trees while for the remaining diet components it is assumed that the birds obtain 50% of each group on the ground. Based on these considerations for the latter diet components a deposition factor of 0.6 according to the guidance document SANCO/4145/2000 (Anonymous 2002) is incorporated in the exposure assessment.

Section 5. Exposure assessment

5.1 Yellow wagtail

The exposure assessment for yellow wagtails potentially foraging in tomato fields treated with Captan at a rate of 1.8 kg a.s./ha is depicted in Table 7.

Table 7 Exposure assessment for yellow wagtails in tomato fields

Diet proportions	large insects	small insects	Whole diet
Application rate [kg a.s./ha]	1.8	1.8	
RUD [mg/kg a.s./ha]	5.1	29	
Maximum initial concentration after last application [mg a.s./kg]	9.18	52.2	
Relative daily food intake (FIR/b.w.) [g fresh weight/g b.w./day]	0.88	0.88	
Portion of diet obtained in-crop (PT)	0.5	0.5	
Portion of diet (PD)	0.764	0.236	
Estimated theoretical exposure (ETE) [mg a.s./kg b.w./day]	3.09	5.42	**8.51**

5.2 Great tit

The exposure assessments for great tits foraging in Northern European pome fruit orchards (Table 8), Southern European pome fruit orchards and Southern European peaches / nectarines orchards (Table 9 and 10) treated with Captan are depicted below.

Table 8 Exposure assessment for the great tit in pome fruit in Northern Europe

Diet proportions	Large arthropods		Small arthropods		Caterpillars	
	soil	foliage	soil	foliage	foliage	
Application rate [kg a.s./ha]	1.25					
RUD [mg/kg a.s./ha]	5.1	5.1	29	29	5.1	
Maximum initial concentration after last application [mg a.s./kg]	6.375	6.375	36.25	36.25	6.375	
Relative daily food intake (FIR/b.w.) [g fresh weight/g b.w./day]	0.88	0.88	0.88	0.88	1.27	
Portion of diet obtained in-crop (PT)	0.61					
Portion of diet (PD)	0.125	0.125	0.125	0.125	0.50	
Deposition factor	0.6	1	0.6	1	1	
Estimated theoretical exposure (ETE) [mg a.s./kg b.w./day]	0.26	0.43	1.46	2.43	2.47	**7.05**

Table 9 Exposure assessment for the great tit in pome fruit in Southern Europe

Diet proportions	Large arthropods		Small arthropods		Cater-pillars	
	soil	foliage	soil	foliage	foliage	
Application rate [kg a.s./ha]	2.4					
RUD [mg/kg a.s./ha]	5.1	5.1	29	29	5.1	
Maximum initial concentration after last application [mg a.s./kg]	12.24	12.24	69.6	69.6	12.24	
Relative daily food intake (FIR/b.w.) [g fresh weight/g b.w./day]	0.88	0.88	0.88	0.88	1.27	
Portion of diet obtained in-crop (PT)	0.61					
Portion of diet (PD)	0.22	0.22	0.06	0.06	0.44	
Deposition factor	0.6	1	0.6	1	1	
Estimated theoretical exposure (ETE) [mg a.s./kg b.w./day]	0.87	1.45	1.35	2.24	4.17	**10.08**

Table 10 Exposure assessment for the great tit in peaches / nectarines in Southern Europe

Diet proportions	Large arthropods		Small arthropods		Cater-pillars	
	soil	foliage	soil	foliage	foliage	
Application rate [kg a.s./ha]	2.5					
RUD [mg/kg a.s./ha]	5.1	5.1	29	29	5.1	
Maximum initial concentration after last application [mg a.s./kg]	12.75	12.75	72.5	72.5	12.75	
Relative daily food intake (FIR/b.w.) [g fresh weight/g b.w./day]	0.88	0.88	0.88	0.88	1.27	
Portion of diet obtained in-crop (PT)	0.61					
Portion of diet (PD)	0.22	0.22	0.06	0.06	0.44	
Deposition factor	0.6	1	0.6	1	1	
Estimated theoretical exposure (ETE) [mg a.s./kg b.w./day]	0.90	1.51	1.40	2.34	4.35	**10.50**

Section 6. Risk assessment

The risk assessment of Captan for insectivorous birds in tomato fields, pome fruit and peaches / nectarines is depicted in Table.

Table 11 Refined long-term TER calculation for insectivorous birds

Species	Scenario	Toxicity mg/kg b.w./day	ETE mg/ kg b.w.	TER_{lt}
Yellow wagtail	Tomatoes	**74.4**	8.51	**8.74**
Great tit	Pome fruit (Northern Europe)		7.05	**10.6**
	Pome fruit (Southern Europe)		10.07	**7.38**
	Peaches / nectarines		10.50	**7.09**

A further refinement of the long-term risk assessment for insectivorous birds potentially foraging in tomato fields, pome fruit orchards and peaches / nectarines orchards is not necessary. The TER-values derived from the application scenarios are above the Annex VI trigger of concern of 5 for long-term exposure, indicating a considerable margin of safety for wild birds from the use of Captan in tomato fields, pome fruit orchards and peaches / nectarines orchards under practical conditions.

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Addendum
to the Draft Assessment Report

CAPTAN

Volume 4

ANNEX C

(Confidential information)

October 2005

Rapporteur Member State: Italy

CONFIDENTIAL BUSINESS INFORMATION:

available at RMS

Captan

Addendum

Prepared by EFSA on 05. 12. 2005

Section Ecotoxicology

In the DAR no risk assessment was conducted for the risk to birds and mammals from the uptake of contaminated drinking water. It is not clear whether exposure to contaminated drinking water in puddles/leaf axils can be excluded for the representative uses of captan. Therefore EFSA calculated the TER values according to the "Guidance Document on Risk Assessment for Birds and Mammals Under Council Directive 91/414/EEC" (Sanco/4145/2000 of 25. September 2002). The exposure concentration was calculated from the sprayed solution with a dilution factor of 5.

The endpoints from the list of endpoints (September 2005) were used for the TER calculations. the NOEC of 100 mg captan/kg bw/d was used instead of 250 mg captan/kg bw/d for the long-term risk assessment for mammals. The NOEC of 100 mg captan/kg bw/d was agreed on by most experts in the EPCO experts' meeting for ecotoxicology (EPCO 22) in April 2005 because effects on pup body weight were observed at the dose of 250 mg captan/kg bw/d.

Table 1: Acute, short-term and long-term risk for birds and mammals from consumption of contaminated drinking water for the intended use in pome fruit (Northern EU) for a sprayed solution of 1250 mg captan/L.

Organisms	Risk	PEC* mg a.s./L	Body weigh t in kg	Total water ingestion . rate	Daily dose (mg a.s./kg bw/d)	LC50/NOE C (mg a.s./ kg bw/d	TER	AnnexV I trigger
Birds	Acute	250	0.01	0.002697	67.42050797	> 2000	> 29.66	10
	Short -term	250	0.01	0.002697	67.42050797	> 800	> 11.9	10
	Long- term	250	0.01	0.002697	67.42050797	74.4	1.1	5
Mammals	Acute	250	0.01	0.001569	39.22610651	> 2000	> 51	10
	Long- term	250	0.01	0.001569	39.22610651	100	2.55	5

* The PEC drinking water (= 20 % of the sprayed concentration) was calculated according to SANCO/4145/2000 (25. Sep. 2002).

Table 2: Acute, short-term and long-term risk for birds and mammals from consumption of contaminated drinking water for the intended use in pome fruit (South EU) for a sprayed solution of 2400 mg captan/L.

Organisms	Risk	PEC* mg a.s./L	Body weigh t in kg	Total water ingestion . rate	Daily dose (mg a.s./kg bw/d)	LC50/NOE C (mg a.s./ kg bw/d	TER	AnnexV I trigger
Birds	Acute	480	0.01	0.002697	129.4473753	> 2000	> 15.45	10
	Short -term	480	0.01	0.002697	129.4473753	> 800	> 6.18	10
	Long- term	480	0.01	0.002697	129.4473753	74.4	0.57	5
Mammals	Acute	480	0.01	0.001569	75.31412451	> 2000	> 26.56	10
	Long- term	480	0.01	0.001569	75.31412451	100	1.33	5

* The PEC drinking water (= 20 % of the sprayed concentration) was calculated according to SANCO/4145/2000 (25. Sep. 2002).

Table 3: Acute, short-term and long-term risk for birds and mammals from consumption of contaminated drinking water for the intended use in tomatoes for a sprayed solution of 1500 mg captan/L.

Organisms	Risk	PEC* mg a.s./L	Body weigh t in kg	Total water ingestion . rate	Daily dose (mg a.s./kg bw/d)	LC50/NOE C (mg a.s./ kg bw/d	TER	AnnexV I trigger
Birds	Acute	300	0.01	0.002697	80.90460956	> 2000	> 24.72	10
	Short -term	300	0.01	0.002697	80.90460956	> 800	> 9.89	10
	Long- term	300	0.01	0.002697	80.90460956	74.4	0.92	5
Mammals	Acute	300	0.01	0.001569	47.07132782	> 2000	> 42.49	10
	Long- term	300	0.01	0.001569	47.07132782	100	2.12	5

* The PEC drinking water (= 20 % of the sprayed concentration) was calculated according to SANCO/4145/2000 (25. Sep. 2002).

Table 4: Acute, short-term and long-term risk for birds and mammals from consumption of contaminated drinking water for the intended use in peaches/nectarines for a sprayed solution of 2500 mg captan/L.

Organisms	Risk	PEC* mg a.s./L	Body weigh t in kg	Total water ingestion . rate	Daily dose (mg a.s./kg bw/d)	LC50/NOEC (mg a.s./ kg bw/d	TER	AnnexVI trigger
Birds	Acute	500	0.01	0.002697	134.8410159	> 2000	> 14.83	10
	Short-term	500	0.01	0.002697	134.8410159	> 800	> 5.93	10
	Long-term	500	0.01	0.002697	134.8410159	74.4	0.55	5
Mammals	Acute	500	0.01	0.001569	78.45221303	> 2000	> 25.49	10
	Long-term	500	0.01	0.001569	78.45221303	100	1.27	5

* The PEC drinking water (= 20 % of the sprayed concentration) was calculated according to SANCO/4145/2000 (25. Sep. 2002).

The acute TER values for birds and mammals exceeded the relevant Annex VI trigger values. The short-term TER values for birds were below the Annex VI trigger of 10 for the use in pome fruit (South EU) and peaches/nectarines. The TER value of > 9.89 was very close to the trigger and it is based on a NOEC from a study where no effects were observed at the highest tested concentration. Therefore the short term risk for birds from uptake of contaminated drinking water is considered to be low for the representative use in tomatoes. The long-term TER values for birds and mammals were below the Annex VI trigger value of 5.

The acute risk to birds and mammals from uptake of contaminated drinking water is low for all representative uses. A high short-term risk to birds is indicated for the representative uses in pome fruit (South EU) and peaches/nectarines. The long-term risk to birds and mammals from uptake of contaminated drinking water is assumed to be high.

A refined risk assessment for the uptake of contaminated drinking water is required for the intended uses in pome fruit (South EU) and in peaches/nectarines to address the short-term risk to birds and the long-term risk to mammals. For the representative uses in pome fruit (North EU) and in tomatoes a refined risk assessment is required to address the high long-term risk posed to birds and mammals.

CAPTAN

Addendum on Section Residues

Prepared by EFSA on 30 Januanry 2006

This addendum is prepared in order to provide Member states with all the needed details to understand the intake calculations carried out according to the residue definition (sum of captan and THPI expressed as captan) proposed by the expert meeting (EPCO 24). The data reported in the DAR and intake calculations conducted by the RMS considered only captan in the residue definition.

1. Residues of captan and its metabolite THPI resulting from the use of captan.

Supervised residue trials carried out according to the use of captan are available with analysis of both captan and its metabolite THPI. These trials are reported in the DAR but with results for captan only. In the tables here below the mentioned trial codes allow the reader to refer to the DAR in order to obtain all information about the trial conditions.

Residues of captan and THPI in apples and pears following application of WG and WP formulations in Northern Europa.

Location Year Trial	**PHI (days)**	**Captan residues (mg/kg)**	**THPI residue (mg/kg, expressed as captan)**	**Sum of captan and THPI residues (mg/kg, expressed as captan)**
Germany, 1993 (Apple) RS-9312-B1	14	2.1	0.78	2.88
Germany, 1993 (Apple) RS-9312-B1	14	2.5	0.86	3.36
Germany, 1993 (Apple) RS-9312-B2	13	2.7	0.54	3.24
Germany, 1993 (Apple) RS-9312-B2	13	3.5	0.68	4.18
Germany, 1993 (Pear) RS-9312-G1	14	1.3	<0.1	1.4
Germany, 1993 (Pear) RS-9312-G1	14	1.2	<0.1	1.3
Germany, 1993 (Apple) RS-9312-k1	13	0.71	0.1	0.81

Germany, 1993 (Apple) RS-9312-k1	13	1.3	0.18	1.48
Germany, 1994 (Apple) N° 4211	14	0.76	0.72	1.48
Germany, 1994 (Apple) N° 4212	14	1.3	0.86	2.16
STMR = 1.86 mg/kg; R max = 5.84 mg/kg; R ber = 6.54 mg/kg				

Residues of captan and THPI in apples following application of WG and WP formulations in Southern Europa.

Location Year Trial	**PHI (days)**	**Captan residues (mg/kg)**	**THPI residue (mg/kg, expressed as captan)**	**Sum of captan and THPI residues (mg/kg, expressed as captan)**
Portugal 1991 (Apple) Turcifal	14	2.9	<0.2	3.1
S. France 2000 (Apple) Grenade sur Garonne	14	2.3	1.42	3.72
Spain 2000 (Apple) Gualta	13	1.5	0.94	2.44
Italy 2000 (Apple) Brignano	14	4.2	1.8	6.0
Italy 2000 (Apple) Brignano	14	8.0	1.6	9.6
S. France 2000 (Apple) Grenade sur Garonne	14	0.54	0.96	1.50
Spain 2000 (Apple) Gualta	15	0.79	0.76	1.55
STMR = 3.1 mg/kg; R max = 13.9 mg/kg; R ber = 12.0 mg/kg				

Residues of captan and THPI in field tomatoes following application of WG formulation in Southern Europa.

Location Year Trial	**PHI (days)**	**Captan residues (mg/kg)**	**THPI residue (mg/kg, expressed as captan)**	**Sum of captan and THPI residues (mg/kg, expressed as captan)**
Spain 2000 PA1 Lebrija	14	0.06	0.20	0.26
Spain 2000	14	0.09	0.34	0.43

PA2 Lebrija				
Greece 2000 GR1 Xechasmeni	15	0.03	0.20	0.23
Greece 2000 GR2 Xechasmeni	14	0.33	0.72	1.05
Spain 2001 PA1 Peñaflor	14	0.56	0.26	0.82
Spain 2001 PA2 Lebrija	14	1.1	0.42	1.52
Greece 2001 GR1 Kavasila	14	0.28	0.42	0.70
Greece 2001 GR2 Skilitsi	13	0.15	0.26	0.41
STMR = 0.57 mg/kg; R max = 2.1 mg/kg; R ber = 2.0 mg/kg				

Residues of captan and THPI in peaches and nectarines following application of WG formulation in Southern Europa.

Location Year Trial	**PHI (days)**	**Captan residues (mg/kg)**	**THPI residue (mg/kg, expressed as captan)**	**Sum of captan and THPI residues (mg/kg, expressed as captan)**
S. France 2000 (Peaches) TL1 Grenade sur Garonne	7	3.5	2.0	5.5
Spain 2000 (Peaches) PA1 Lora Del Rio	15	6.3	3.14	9.44
Spain 2000 (Peaches) ES1 Gualta	9	3.7	2.78	6.48
France 2001 (Peaches) Vacquiers	8	4.4	0.14	4.54
Greece 1999 (Nectarine) GR1 Veria	7	5.6	1.32	6.92
Greece 1999 (Nectarine) GR2 Naoussa	7	3.1	0.52	3.62
Spain 1999 (Nectarine) ES1 Gualta	7	2.1	0.72	2.82
Spain 1999 (Nectarine) ES2 Pals	7	2.5	0.60	3.10
STMR = 5.02 mg/kg; R max = 12.5 mg/kg; R ber = 13.6 mg/kg				

2. Transfer factors from raw to processed commodities for human consumption.

Several processing studies were submitted by the notifier with analysis of both captan and THPI in raw and processed commodities. In the DAR, transfer factors were calculated for captan only. Considering the residue definition proposed by the expert meeting, transfer factors should be calculated for the sum of the 2 compounds of the residue definition.

Apples

Location Year trial	Residue in raw commodity (mg/kg)			Residues in pasteurised juice* (mg/kg)	Residues in puree* (mg/kg)	Transfer factor in pasteurised juice	Transfer factor in puree
	Captan	THPI (expressed as captan)	Total (expressed as captan)	THPI (expressed as captan)	THPI (expressed as captan)		
Germany 1994 U94 RUF 06	2.3	2.2	4.5	5.6	3.4	1.2	2.3
Germany 1994 U94 RUF 07	2.2	1.7	3.9	4.4	2.8	1.1	2.2
Germany 1994 No 4211	0.76	0.72	1.48	0.60	0.66	0.4	0.8
Germany 1994 No 4212	1.3	0.86	2.16	1.16	1.02	0.5	1.3
Germany 1991 91JH045B1	2.2	0.28	2.48	2.52	1.84	1.0	2.2
Germany 1991 91JH045B1	1.8	0.36	2.16	2.26	2.36	1.0	1.8
Germany 1991 91JH045Ext2	1.1	0.42	1.52	1.76	2.00	1.2	1.1
Germany 1991 91JH045Ext2	1.8	0.72	2.52	2.24	1.34	0.9	1.8
Average transfer factors						**0.9**	**0.8**
*: residues of captan in pasteurised juice and puree are below the Limit of Quantification							

Tomatoes

Location Year trial	Residue in raw commodity (mg/kg)			Residues in tomato juice*	Residues in tomato puree*	Residues in tomato ketchup*	Residues in canned tomatoes*	Transfer factor in tomato juice	Transfer factor in tomato puree	Transfer factor in tomato ketchup	Transfer factor in canned tomatoes
	Captan	THPI (expressed as captan)	Total (expressed as captan)	THPI (expressed as captan)	THPI (expressed as captan)	THPI (expressed as captan)	THPI (expressed as captan)				
USA 1986 TMN-0691	0.52	0.20	0.72	0.18	0.46	0.92	-	0.3	0.6	1.3	-
USA 1986 TMN-0691	1.2	0.26	1.46	0.24	0.76	1.46	-	0.2	0.5	1.0	-
France 2003 FRC0301arc	<0.02	<0.04	<0.06	0.06	0.12	<0.04	<0.04	Transfer factors not calculated due to the very low residue levels			
France 2003 FRC0301arc	0.16	0.08	0.24	0.26	0.58	0.62	0.12	1.1	2.4	2.6	0.5
Average transfer factors								**0.5**	**1.2**	**1.6**	**0.5**
*: residues of captan in juice, puree, ketchup and canned tomatoes are below the Limit of Quantification											

3. Transfer factor to apple pomace (Feed item).

These calculations are carried out considering as residue definition for raw and processed commodities the sum of captan and THPI expressed as captane, as proposed by the expert meeting.
In some trials, information is available on residues of captan and THPI in both wet and dry pomace. As the guideline for determining the potential exposure of livestock considers as feed item 23% dry matter pomace, it seems more appropriate to use the values on wet pomace for the calculation of transfer factors.

Location Year trial	**Residue in raw commodity (mg/kg)**			**Residue in wet pomace (mg/kg)**			**Transfer factor in wet pomace**
	Captan	**THPI (expressed as captan)**	**Total (expressed as captan)**	**Captan**	**THPI (expressed as captan)**	**Total (expressed as captan)**	
Germany 1991 91JH045B1	2.2	0.28	2.48	3.8	1.98	5.78	2.3
Germany 1991 91JH045B1	1.8	0.36	2.16	5.2	1.68	6.88	3.1
USA 1986 TMN-0567	5.3	0.44	5.74	2.1	3.80	5.90	1.0
Michigan 1990 RR 92-023B	0.17	<0.10	0.27	0.07	0.42	0.49	1.8
Virginia 1990 RR 92-023B	1.5	0.14	1.64	0.72	1.70	2.42	1.5
Average transfer factor							**2.0**

4. Estimation of potential livestock exposure.

This estimation is carried out considering the residue definition for plant products as the sum of captan and THPI, as recommended by the expert meeting (EPCO 24).
In addition, the following specific criteria were used:

- The residue level in raw apples considered as representative of the highest residue likely to occur in practice is the STMR as apple pomace is a processed product resulting from a mixture of raw material originating from a number of producers.
- The STMR for apples was found to be 3.1 mg/kg for the Southern region of EU.
- The transfer factor from raw apples to apple wet pomace is 2 as calculated here above. This results in an expected residue level of 6.2 mg/kg in apple wet pomace.
- The body weights of beef and diary cattle are respectively 350 and 550 kg.

Calculation of captan dietary exposure level for cattle.

Animal/feed item	% dry matter feed item	% of contribution to the diet of the feed item	Intake of dry matter from the feed item (kg/animal/d)	Intake of 'fresh' feed item (kg/animal/d)	Sum of captan and THPI residue in feed item (mg captan eq/kg)	Animal intake (mg captan eq/animal/d)
Beef cattle/apple pomace	23	30	4.5	19.6	6.2	121
Diary cattle/apple pomace	23	10	2.0	8.7	6.2	54
The dietary exposure level of beef and diary cattle to the sum of captan and THPI is therefore 0.35 and 0.10 mg/kg bw/d, respectively						

Considering the potential livestock exposure calculated here above, it can be established that the metabolism studies reported in the DAR were carried out with large overdosing factors, as illustrated here below

Metabolism study	Administered dose (mg/kg bw/d)	Overdosing factor dairy cattle	Overdosing factor beef cattle
Daun, 1988, reported under point B.7.2.c of the DAR	1.4	14	4
Cheng, 1980, reported under point B.7.2.d of the DAR	4.2	43	12

Considering the results of these metabolism studies, it can be extrapolated that residues of THPI, 3-OH THPI and 5-OH THPI will likely not exceed 0.05 mg/kg in animal commodities. A feeding study carried out at appropriate exposure level should be submitted to confirm this.

5. MRL Proposals.

Considering the outcome of the residue trials reported here above, The MRL proposals for the sum of captan and THPI (expressed as captan) are:

Apples and pears	10 mg/kg
Peaches and nectarines	10 mg/kg
Tomatoes	2 mg/kg
Animal products	Data insufficient at this stage

6. Estimation of the potential and actual exposure through diet and other means.

The calculations presented here below are made taking into account the contribution of representative uses only. They were performed using the relevant WHO guidelines and according to the residue definition for risk assessment (sum of captan and THPI expressed as captan) recommended by the expert meeting. No exposure resulting from the consumption of animal commodities was considered as available data are not sufficient to set MRLs. It is however expected that animal commodities do not contribute significantly to the global intake.

6.1 Chronic intake calculation according to the WHO typical diet.

These calculations are TMDI calculations according to the diet of an average European adult consumer of 60 kg.

Commodity	**Consumption (kg/d)**	**MRL (mg/kg)**	**Intake (mg/kg bw/d)**
Apples	0.040	10	0.0067
Pears	0.0113	10	0.0018
Peaches and nectarines	0.0125	10	0.0021
Tomatoes	0.066	2	0.0022
Total			**0.0128**
Considering the ADI of 0.1 mg/kg, the exposure level of the European adult consumer is **13 % of the ADI.**			

6.2 Chronic intake calculations according to the diet of adults, children, toddlers and infants in UK.

TMDI calculations.

These calculations are TMDI calculations according to the diet of infants (6-12 months), toddlers ($1^{1/2}$-$4^{1/2}$ years), children and adults of UK, using high consumptions values (97.5^{th} percentile of the distribution of consumption in their specific population) for the 2 commodities which represent the most important contribution to the total intake and mean consumption values for the other commodities. Their body weights are 8.7, 14.5, 43.6 and 70.1 kg respectively.

Commodity	MRL (mg/kg)	Infants				Toddlers			
		Consumption (kg/d)		Intake (mg/kg bw/d)		Consumption (kg/d)		Intake (mg/kg bw/d)	
		Mean	97th perc.	Mean	97th perc.	Mean	97th perc.	Mean	97th perc.
Apples	10	0.0143	0.0751	0.01644	*0.08632*	0.0245	0.2186	0.01690	*0.15076*
Pears	10	0.0023	0.0254	0.00264	*0.02920*	0.0027	0.0974	0.00186	0.06717
Peaches and nectarines	10	0.0013	0.0136	0.00030	0.00313	0.0061	0.0372	0.00084	0.00513
Tomatoes	2	0.0005	0.0194	0.00057	0.02230	0.0021	0.1074	0.00145	*0.07407*
Total*		**0.11639**				**0.22753**			
Considering the ADI of 0.1 mg/kg, the exposure level of the British infants and toddlers are 120 and 230 % of the ADI respectively.									

* Calculated from total of the two highest 97.5th percentile intakes (*in italics*) plus mean population intakes for other crops

Commodity	MRL (mg/kg)	Children				Adults			
		Consumption (kg/d)		Intake (mg/kg bw/d)		Consumption (kg/d)		Intake (mg/kg bw/d)	
		Mean	97th perc.	Mean	97th perc.	Mean	97th perc.	Mean	97th perc.
Apples	10	0.0256	0.1328	0.00587	*0.03046*	0.0279	0.1566	0.00398	*0.02234*
Pears	10	0.0026	0.0634	0.00060	*0.01454*	0.0042	0.0988	0.00060	*0.01409*
Peaches and nectarines	10	0.0086	0.0361	0.00039	0.00166	0.0228	0.0755	0.00065	0.00215
Tomatoes	2	0.0019	0.0478	0.00044	0.01096	0.0047	0.0958	0.00067	0.01367
Total*		**0.04583**				**0.03775**			
Considering the ADI of 0.1 mg/kg, the exposure level of the British children and adults are about 50 and 40% of the ADI respectively.									

* Calculated from total of the two highest 97.5th percentile intakes (*in italics*) plus mean population intakes for other crops

NEDI calculations

These NEDI calculations were performed for infants and toddlers as the TMDI calculations lead to values exceeding the ADI. STMRs from supervised residue trials were used as more representative levels of the chronic exposure. No transfer factor was used as it is not known which amount of each commodity is consumed after processing;

Commodity	STMR (mg/kg)	Infants				Toddlers			
		Consumption (kg/d)		Intake (mg/kg bw/d)		Consumption (kg/d)		Intake (mg/kg bw/d)	
		Mean	97th perc.	Mean	97th perc.	Mean	97th perc.	Mean	97th perc.
Apples	3.1	0.0143	0.0751	0.00510	*0.02676*	0.0245	0.2186	0.00524	*0.04674*
Pears	3.1	0.0023	0.0254	0.00082	*0.00905*	0.0027	0.0974	0.00058	*0.02082*

Peaches and nectarines	5.0	0.0013	0.0136	0.00075	0.00781	0.0061	0.0372	0.00209	0.01282
Tomatoes	0.57	0.0005	0.0194	0.00003	0.00127	0.0021	0.1074	0.00008	0.00422
Total*		**0. 03659**				**0.06973**			
Considering the ADI of 0.1 mg/kg, the exposure level of the British infants and toddlers are about 40 and 70 % of the ADI respectively.									

* Calculated from total of the two highest 97.5th percentile intakes (*in italics*) plus mean population intakes for other crops

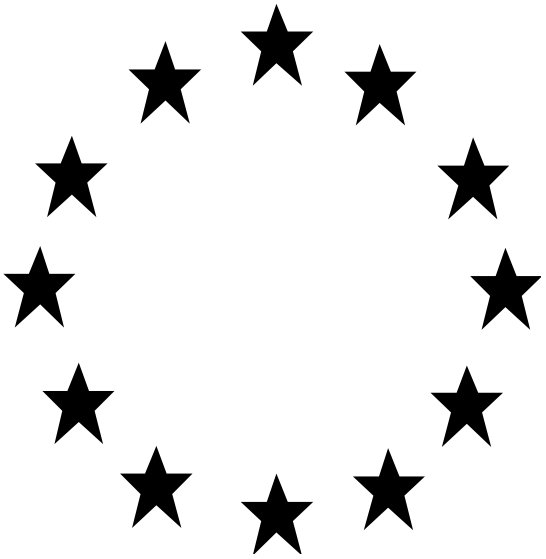
6.3 Acute intake calculations.

These calculations were performed considering:

- a variability factor of 7 for all commodities examined
- The proposed MRL instead of the highest residue from the supervised trials

Large portion consumption data from UK were used for adult (70.1 kg), toddlers (14.5 kg) and infants (8.7 kg)

Consumer group	**NESTI (% of the ARfD)**			
	Apples	**Pears**	**Peaches**	**Tomatoes**
Adults	150	161	123	21
Infants	980	724	344	97
Toddlers	720	766	550	82



Final addendum to the

Draft Assessment Report (DAR)

- public version -

Initial risk assessment provided by the rapporteur Member State Italy for the existing active substance

CAPTAN

of the second stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC

January 2009

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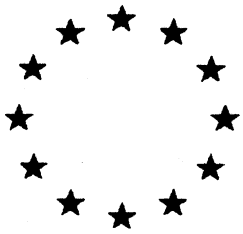


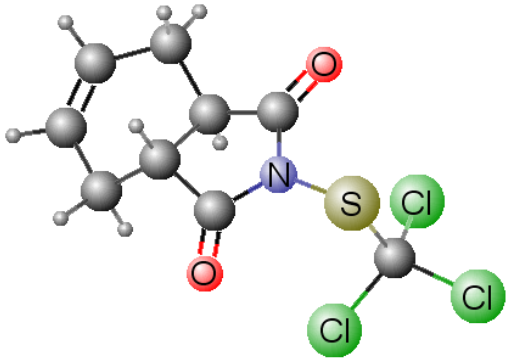
Captan

Volume 3

Annex B
Addendum: Position paper relating to non-setting of Acute Reference Dose (ARfD)

Rapporteur Member State: Italy

B.6.10.2 Acute Reference Dose (Annex IIA 5.10)



Captan

Captan: The 2004 JMPR set an ARfD of 0.3 mg/kg bw/day for women of child-bearing age only for Captan based on foetal data from a rabbit developmental toxicity study, stating it was an ARfD that was not appropriate for the general population. Whilst in the EU an ARfD of 0.1 mg/kg bw has been proposed.

Both ARfDs are derived largely from the same toxicology database using rabbit prenatal development studies in their assessments. The foundation for the JMPR and the EU evaluation in selecting the prenatal development studies was based essentially on JMPR criteria used for assessing toxicological alerts when considering whether setting an ARfD is appropriate. Overall the evidence for Captan suggests that there are no toxicologically alerts as a consequence of acute exposure. There are also no teratogenic effects and only slight embryo-foetal effects at 30 mg/kg bw/day (which were within the historical control database range). The embryo-foetal effects were associated with maternal toxicity and most probably are secondary to this (reduced food intake and body weight) caused by high, local concentrations of Captan produced by administration by gavage which are not considered to be relevant to dietary exposure. Such effects (on the GI-tract) appear more pronounced in the rabbit than in the rat. This questions the value of the rabbit model with compounds known to induce local GI-tract irritancy or capable of affecting the status of the gut micro-flora upon which the rabbit is dependant. Data from a new rabbit developmental toxicity study on THPI strengthens the suggestion that Captan exerts its effects on maternal food intake by inducing local GI-tract irritation with concomitant inappetance. Moreover, MIC studies with Captan and THPI clearly show that Captan, but not THPI, has significant antimicrobial activity. Taken together these data indicate that impaired maternal nutrition in the rabbit can impact on foetal development. Therefore the strength and weight of evidence suggest that setting an acute reference dose for Captan is unnecessary.

Captan has a robust toxicological database and been evaluated by several international regulatory authorities. There have been a number of JMPR Monographs and WHO Evaluations for Captan (e.g. JMPR 1995, 2004) and it has also been evaluated by the US EPA (1999). In the EU Captan has been assessed under the EC Directive 91/414/EEC and has been included in Annex 1 of that directive for continued use in the EU.

For the JMPR evaluation of a plant protection product the setting of an appropriate acute reference dose (ARfD) for dietary risk assessment may be considered if the toxicological database (toxicological alerts) for a molecule is considered to warrant it. In 2004 the JMPR considered Captan as part of their evaluation for dietary risk assessment. In their judgement:

"…the establishment of ARfDs for (Captan and) Folpet was considered necessary only for women of child-bearing age."

The basis for this was that in their judgement Captan produced no toxicological effects that might be considered to be a consequence of acute exposure (other than supposed developmental effects). In setting their ARfD they stated that an ARfD for the general population (including children aged 1-6 years) was unnecessary. Furthermore they suggested that:

"...it might be necessary to establish an ARfD to protect the embryo or foetus from possible effects in utero. Such an ARfD would apply to women of childbearing age."

It is clear that the database for this fungicide suggests that setting an ARfD of 0.3 mg/kg bw/day, as the 2004 JMPR did, may be considered a cautious approach for dietary risk assessment. There is no need to set an ARfD for the general population as the toxicology results suggest that there is a negligible human health risk from acute dietary exposure. However, the 2004 JMPR concluded:

"... that the database was insufficient (in particular, with regard to the absence of studies on the developmental effects of THPI) to establish the mode of action by which the increased incidence of intrauterine deaths and of foetuses with malformations, observed at 100 mg/kg bw per day (NOAEL, 30 mg/kg bw per day) in rabbits, were induced. As a consequence, their relevance for deriving an ARfD could not be dismissed."

Considering the 2004 JMPR's view a new developmental toxicity study (Blee, 2006) has been conducted and is reviewed in the position paper prepared by the Notifier and presented in this addendum. Additionally in order to shed some light on one possible cause of maternal toxicity, and foetal effects, after Captan exposure, two new studies are presented that investigated the effects of Captan and THPI on micro-organisms selected as representative of those found in the rabbit gut. The dependence of the rabbit on its gut micro-flora is of paramount importance in ensuring normal gut function and nutrition (the rabbit is coprophagous and depends on its caecotrophs and gut micro-flora for normal nutrition). Any perturbation in the gut micro-flora may lead to nutritional deficits in the dam which may impact on the outcome of her pregnancy.

The Notifier's position paper briefly reviews the relevant endpoints used for the ARfD assessment of Captan, a new developmental toxicity study, two new MIC assays (Captan and THPI) and suggests that an ARfD for Captan is not required.

1) Review of prenatal developmental toxicity studies for Captan

The database contains four established studies, one in the rat and three in the rabbit. The references submitted in support of the above position are summarised below.

a) Prenatal development toxicity study in the rat.

b) Prenatal development toxicity studies in the rabbit.

a). Prenatal development toxicity study in the rat.

a) Captan: teratology study in the rat. (Rubin, Y. 1987b; IIA, 5.6.2.2/01)

The study was a US EPA 83.3 and OECD 415 guideline compliant study. Pregnant CD strain rats (Sprague-Dawley origin) were administered Captan (purity 91%) in the vehicle [redacted] at dose levels of 0, 18, 90 and 450 mg/kg bw/day (22 dams/dose) on days 6 to 15 of gestation. Dams were sacrificed on day 20 of gestation and a full in utero macroscopic examination performed followed by a detailed examination of the foetal pathology.

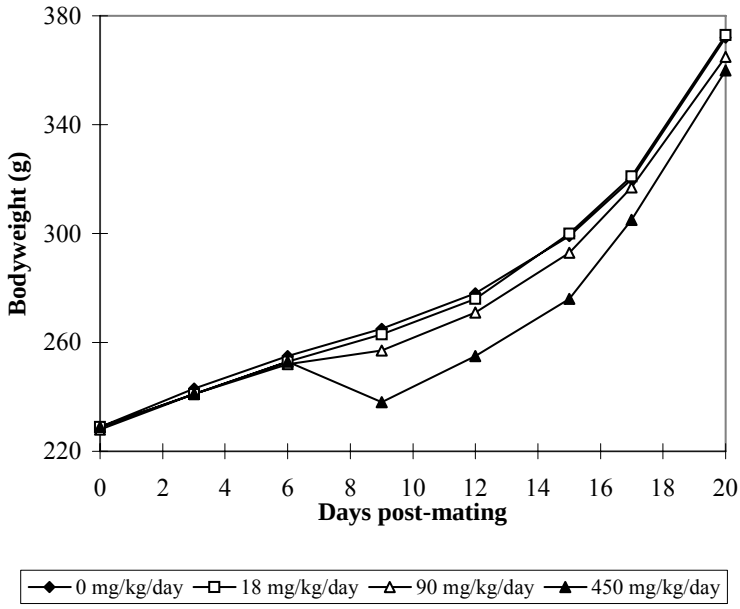
Maternal food consumption was reduced at 450 mg/kg bw/day during the dosing period and also on days 7 to 9 in the 90 mg/kg bw/day dams. A compensatory increase in food consumption in the 450 mg/kg bw/day dams was observed post-dosing (Table B.6.10.2.1). Maternal body weight was reduced over the dosing period in the 450 mg/kg bw/day dams (Fig. 1). By day 20 no treatment-related differences from the control were apparent in any dose group.

Table B.6.10.2.1: Group mean (± SD) food consumption by dams

Gestation day	Food consumption (g/animal/day)			
	Dose group (mg/kg bw/day)			
	0	**18**	**90**	**450**
1 - 3	26.0 ± 2.6	25.1 ± 2.1	25.3 ± 2.2	25.3 ± 2.2
4 - 6	25.0 ± 3.6	24.5 ± 2.0	24.3 ± 2.5	25.2 ± 2.4
7 - 9	25.1 ± 3.3	24.4 ± 3.0	20.7 ± 2.6***	13.4 ± 3.6***
10 - 13	25.9 ± 2.7	25.4 ± 2.6	24.7 ± 2.1	21.4 ± 2.8***
14 - 16	26.7 ± 2.9	26.3 ± 2.6	25.7 ± 2.3	22.2 ± 3.9***
17 - 20	27.7 ± 2.7	28.6 ± 2.7	28.4 ± 2.7	32.4 ± 3.8***

*** significantly different from the control ($p < 0.001$)

Figure 1Developmental toxicity study in the rat: body weight of dams (mean)



Foetal viability as measured by post-implantation loss was not adversely affected by treatment. Although pre-implantation loss was elevated in the 90 mg/kg/day treatment group, the incidence in the 450 mg/kg/day group was not affected and therefore was considered to be incidental. Mean foetal weight was reduced in the 450 mg/kg bw/day dose group (mean foetal weights of 3.49 and 3.27 g in the control and 450 mg/kg bw/day dose groups, respectively).

No treatment-related foetal malformations were observed in any treated group. The incidence of small foetuses was increased in the 450 mg/kg bw/day dose group corresponding with lower foetal weights. Observations at free-hand foetal sectioning did not reveal any treatment-related major abnormalities. A number of minor skeletal variants were observed in the 450 mg/kg bw/day dose group which may have been treatment-related. The number of foetuses with a 14th (lumbar) rib unilaterally or bilaterally was slightly elevated in this dose group as was the incidence of foetuses with one or two vertebral hemicentra incompletely fused (on a litter basis). The incidence of reduced ossification of the pubic bone was more frequent in the 450 mg/kg bw/day dose group. An increased incidence of rudimentary 13th ribs in the 18

mg/kg bw/day dose group foetuses was not considered to be treatment-related. A summary of the significant skeletal variations is presented in Table B.6.10.2.2.

Table B.6.10.2.2 Developmental toxicity study in the rat: incidence of skeletal variations

Incidence of foetal skeletal variations	Dose group (mg/kg bw/day)			
	0	**18**	**90**	**450**
Number of foetuses affected				
Number foetuses examined	169	163	157	164
14th lumbar rib (unilaterally)	2 (1.18)	0 (0.00)	1 (0.64)	8 (4.88)*
14th lumbar rib (bilaterally)	0 (0.00)	0 (0.00)	1 (0.64)	5 (3.05)*
Reduced ossification of pubic bone	1 (0.59)	2 (1.23)	3 (1.91)	8 (4.88)*
Number of litters affected				
Number litters examined	22	22	22	22
one or two vertebral hemicentra incompletely fused	8 (9.38)	13 (15.73)	11 (10.33)	16 (13.28)*

* Significantly different from the control ($p < 0.05$).
For foetuses number in parenthesis = percentage. For litters number in parenthesis = % mean

Conclusion: The NOEL for maternal toxicity was 18 mg/kg bw/day based on lower food consumption and body weight at 90 mg/kg bw/day. The NOEL for foetal toxicity was 90 mg/kg bw/day based on the reduced foetal weight and slight increases in the incidence of minor skeletal variations at 450 mg/kg bw/day.

b). Prenatal development toxicity studies in the rabbit.

a) Captan: teratogenicity study in the rabbit (Tinston, D.J. 1991; IIA, 5.6.2.1/01 *)*

The study was a US EPA Guideline 83-3 compliant study. Captan (purity 91.2%) was administered by oral gavage to pregnant New Zealand White rabbits at dose levels of 0, 10, 30 and 100 mg/kg bw/day in corn oil on days 7 to 19 of gestation inclusive (20 dams/dose). Parameters evaluated in dams were clinical signs (daily), body weight (days-1, 4, 7 to 19, 22, 26 and 30 of gestation), food consumption (at intervals during the study). On day 30 females were sacrificed and a full in utero macroscopic examination performed followed by a detailed examination of the foetal pathology.

Treated dams had an increased incidence of few or no faeces compared to the control. Increased incidences of diarrhoea in all treated groups and mucus in the faeces in 100 mg/kg bw/day dams were observed. One 100 mg/kg bw/day female was killed following signs of abortion. There was a dose-related reduction in maternal body weight gain in 30 and 100 mg/kg bw/day dams, which was most marked during days 7 to 10. Compensatory body weight gain was evident during the post-dosing period in the 100 mg/kg bw/day dams (Table B.6.10.2.3). A dose-related reduction in food consumption was also seen in the 30 and 100 mg/kg bw/day females, followed by a compensatory increase in food consumption by 100 mg/kg bw/day dams, particularly on days 26 to 30 (Table B.6.10.2.4). The low dose group was unaffected.

Table B.6.10.2.3: Developmental toxicity study in the rabbit: body weight of dams

Period (days)	Body weight gain (g) at dose (mg/kg bw/day)			
	0	**10**	**30**	**100**
1 - 7	145.2	137.5	172.9	159.6
7 - 19	238.2	205.5	57.2*	-159.3**
7 - 10	15.6	40.2	-68.0*	-142.5**
10 - 13	85.9	52.5	68.8	11.2**
13 - 16	145.9	122.8	59.3*	23.0**
16 - 19	-9.3	-9.8	-2.9	-51.0
19 - 30	249.4	288.8	300.3	502.3**
19 - 22	31.1	53.1	51.4	150.4**
22 - 26	125.6	141.9	146.7	176.9
26 - 30	91.7	93.8	102.2	175.0**
1 - 30	632.7	631.8	530.4	502.6

Significantly different from the control, * ($p < 0.05$), ** ($p < 0.01$).

Table B.6.10.2.4: Developmental toxicity study in the rabbit: food consumption by dams

Period (days)	Food consumption (g/day) at dose (mg/kg bw/day)			
	0	**10**	**30**	**100**
1 - 7	205.3	209.7	208.9	188.5
7 - 19	163.7	158.8	126.7*	56.8**
7 - 10	156.9	170.6	108.7**	45.7**
10 - 13	183.3	186.4	156.4	77.3**
13 - 16	162.1	176.4	125.0	90.9*
16 - 19	152.3	151.7	116.8	42.5**
19 - 30	197.8	200.5	178.6	204.7
19 - 22	196.9	213.8	167.4	157.2
22 - 26	212.6	222.6	254.5	224.3
26 - 30	183.7	184.5	164.9	251.6**

Significantly different from the control, * ($p < 0.05$), ** ($p < 0.01$).

There was no evidence in the dams of treatment-related effects on the incidence of macroscopic findings.

There was no treatment-related effect on pregnancy rate. The incidence of pre-implantation loss in 100 mg/kg bw/day dams was not significantly affected. Post-implantation loss in 100 mg/kg bw/day dams was increased compared to the control and reflected the increased incidences of intra-uterine deaths. Mean total implantation loss was not affected by Captan treatment and as a result there was no adverse effect on the mean number of live foetuses compared to the controls. Mean foetal weight in the 100 mg/kg bw/day dose group was lower than the control. A summary of litter data is given in Table B.6.10.2.5.

Table B.6.10.2.5 Developmental toxicity study in the rabbit: litter data

Litter data parameter	Dose (mg/kg bw/day)			
	0	**10**	**30**	**100**
Corpora lutea (mean)	10.54	10.23	9.80	10.42
Pre-implantation loss (transformed mean)	0.490	0.428	0.369	0.291
Post-implantation loss (transformed mean)	0.311	0.337	0.325	0.485*
Implantations (mean)	8.46	8.23	8.50	9.50
Intra-uterine deaths (mean % early)	3.1	4.7	0.0	10.7
Intra-uterine deaths (mean % late)	3.5	4.2	9.5	11.9
Live foetuses (mean)	7.85	7.38	7.50	7.17
Mean gravid uterine weight (g)	514.8	481.2	472.7	440.3
Mean litter weight (g)	339.2	319.9	310.3	271.4
Mean foetal weight (g)	45.64	44.90	43.30	37.99**

Significantly different from the control, * ($p < 0.05$), ** ($p < 0.01$).

The incidence of foetuses with major defects was increased in the 100 mg/kg bw/day dose group compared to the control. Eight foetuses from five litters had at least one abnormality compared to one in the control. Four of the eight foetuses affected in the 100 mg/kg bw/day dose group were from one litter. There was no compound-related effect on the incidence of defects involving the cardiac blood vessels but there was an increased incidence of foetuses with defects of the head in both the 30 and 100 mg/kg bw/day groups. In the latter group, two of the three affected foetuses were litter mates. Of the remaining types of defects all but one occurred in the 100 mg/kg bw/day group. The possibility of the defects being treatment-related was considered equivocal because of the small numbers involved, the type of specific minor defects and the fact that several foetuses were littermates. The data provided no convincing evidence for a compound relationship.

The overall incidence of minor skeletal defects was unaffected by treatment, although the incidence of unossified 6th and 7th lumbar transverse processes and asymmetric alignment of the pelvic girdle was increased in the 100 mg/kg bw/day dose group.

There were no external or visceral variants. Treatment-related effects were seen in the incidence of the following skeletal variants in the 100 mg/kg bw/day dose group; odontoid partially ossified (increase); normal length extra 13th ribs (increase); 27 pre-sacral vertebrae (increase): asymmetric development of 1st and 2nd sacral vertebrae (increase); 4th, 5th, 6th and 7th lumbar transverse processes partially ossified; 2nd lumbar transverse processes partially ossified; 3rd lumbar transverse processes fully ossified. The effects on ossification of the lumbar transverse processes reflect reduced ossification that was associated with reduced foetal weight. The majority of these variants were also seen in the 30 mg/kg bw/day dose group. The overall incidence of foetuses with extra 13th rib was increased in 30 and 100 mg/kg bw/day dose groups compared to the control (60.8, 52.1, 77.3 and 77.6% affected in the control, 10, 30 and 100 mg/kg bw/day dose groups).

An increase in manus scores, reflecting the decrease in ossification was observed in the 100 mg/kg bw/day dose group (mean score 2.56, $p < 0.01$) compared to the control (mean score 2.24). The mean per score was 2.0 for all dose groups.

A summary of the incidence of defects and variants is given in Table B.6.10.2.6. The type and incidence of major defects is summarised in Table B.6.10.2.7.

Table B.6.10.2.6 Developmental toxicity study in the rabbit: summary of foetal defects and variants

Incidence of foetal defects and variants	Dose (mg/kg bw/day)			
	0	**10**	**30**	**100**
Number of litters examined	13	13	10	12
External and visceral:				
Number of foetuses examined	102	96	75	86
Number of foetuses with major defects	1	0	2	6*
Number of foetuses with minor defects only	1	3	6*	8**
Skeletal defects:				
Number of foetuses examined	102	96	75	85
Number of foetuses with major defects	0	0	1	4*
Number of foetuses with minor defects only	37	41	25	36
Variants:				
Number of foetuses examined	102	96	75	85
Number of foetuses showing variants	102	96	75	85

Significantly different from the control, * ($p < 0.05$), ** ($p < 0.01$).

Table B.6.10.2.7 Developmental toxicity study in the rabbit: summary of type and incidence of defects.

Type and incidence of major defects	Dose (mg/kg bw/day)			
	0	**10**	**30**	**100**
Gross torso malformations	-	-	-	1 (61A)
Encephalocoele, open eyes, gross malformations of the skull	-	-	-	1 (70K)
Microphthalmia	-	-	1 (51A)	-
Mid-brain ventricles extremely dilated, cebocephaly	-	-	-	1 (72D)
Mandibles fused, lower jaw shortened	-	-	1 (49F)	-
Maxillae fused	-	-	-	2 (72D, 72G)
Aorta extremely enlarged	1 (100)	-	1 (49F)	1 (63B)
Pulmonary artery extremely enlarged	-	-	1 (49F)	-
Pulmonary artery extremely reduced	-	-	-	1 (63B)
Subclavian artery absent	-	-	1 (49F)	-
11th rib and thoracic arch absent	-	-	-	1 (72E)
Omphalocoele	-	-	-	1 (72B)
Forepaw extremely flexed	-	-	1 (51A)	2 (64B, 70K)
Pollex absent - bilateral	-	-	-	1 (70K)
Number of foetuses with major defects in the head region	0	0	2	3
Number of foetuses with major defects involving the cardiac blood vessels	1	0	1	1
Number of foetuses with other major defects	0	0	1	5
Number of foetuses with at least one major defect	1	0	2	8

Foetus identity in parenthesis (Dam + foetus letter).

Conclusions: The administration of Captan at dose levels of 30 and 100 mg/kg bw/day was associated with maternal toxicity and slightly delayed foetal development. Increases in defects at these dose levels provided no consistent evidence of a treatment-relationship due to the low incidence and diverse nature of the abnormalities seen. The NOAEL was 30 mg/kg bw/day for the foetus and 10 mg/kg bw/day for the dam.

b) Captan: Teratology study in the rabbit. (Rubin, Y.. 1987a; IIA, 5.6.2.1/02*)*

The study was a USEPA Guideline 83-3 compliant study. Captan (purity 91%) was administered by oral gavage to pregnant New Zealand White rabbits at dose levels of 0, 10, 40 and 160 mg/kg bw/day (14 to 18 dams/dose) in a vehicle of [redacted] on days 7 to 19 of gestation inclusive (day of mating = day 0). Parameters evaluated in dams were clinical signs (daily), body weight (days 0, 3, 7 to 19, 22, and 29 of gestation), food intake (twice weekly). On day 29 of gestation, females were sacrificed and a full in utero macroscopic examination performed followed by a detailed examination of the foetal pathology.

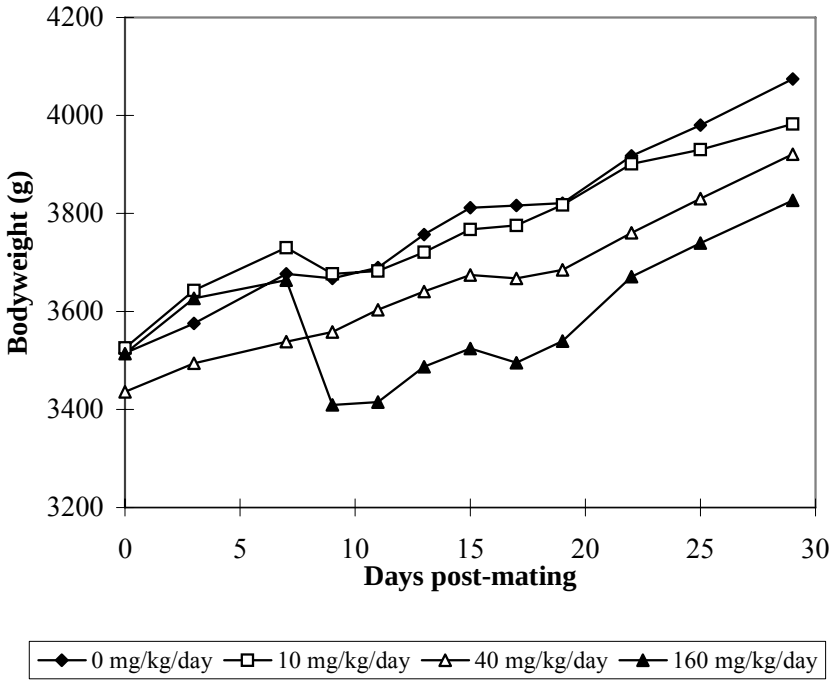
One 160 mg/kg bw/day dam was sacrificed after aborting on day 26. Foetuses in the left uterine horn were autolytic and those in the right horn were dead. The relation of these foetal deaths to treatment was unclear. A second 160 mg/kg bw/day dam was sacrificed after aborting on day 18. Reduced faecal output was observed in 160 mg/kg bw/day dose group animals. Food consumption was reduced in the 160 mg/kg bw/day dams over the entire dosing period. A compensatory increase in food consumption was observed on days 24 to 26 (Table B.6.10.2.8). In 40 mg/kg bw/day dams a moderate reduction in food consumption was observed on days 15 to 19. The significance of a decrease in food consumption in 10 mg/kg bw/day dams on days 27 to 29 was unlikely to be unrelated to treatment. Body weight in 160 mg/kg bw/day dams was decreased compared to the control over the entire dosing period and did not fully recover in the post-dosing period (Fig.2).

Table B.6.10.2.8 Developmental toxicity study in the rabbit: mean food consumption by dams (g/animal/day)

Gestation day	Dose group (mg/kg bw/day)			
	0	**10**	**40**	**160**
1 - 4	193	215	210	216
5 - 7	238	228	210	229
8 - 10	210	203	196	35***
1 - 14	204	198	184	58***
15 - 19	223	212	186**	104***
20 - 23	202	199	199	212
24 - 26	168	143	183	216***
27 - 29	179	133***	177	192

Significantly different from the control, ** ($p < 0.01$), *** ($p < 0.001$), students t-test.

Figure 2. Developmental toxicity study in the rabbit: body weight of dams (mean)



Post-implantation loss was increased in the 160 mg/kg bw/day dose group compared to the control with one case of total resorption (Table B.6.10.2.9). Administration of Captan had no consistent dose-related effect on the incidence of pre-implantation loss. Foetal weight and crown rump length were unaffected by treatment.

Table B.6.10.2.9: Developmental toxicity study in the rabbit: summary of litter parameters

Litter data parameter	Dose group (mg/kg bw/day)				
	0	10	40	160	
				includes total litter resorption	excludes total litter resorption
Resorptions					
early	0.4 ± 0.8	0.4 ± 0.5	0.3 ± 0.6	1.8 ± 2.8	1.0 ± 1.2
late	0.2 ± 0.5	0.2 ± 0.6	0.2 ± 0.4	0.3 ± 0.7	0.4 ± 0.7
total	0.6 ± 1.0	0.6 ± 0.9	0.4 ± 0.9	2.1 ± 2.8*	1.4 ± 1.4
Implantation loss					
pre (%)	10.0 ± 2.4	7.3 ± 2.3**	21.0 ± 2.1***	10.0 ± 2.9	11.0 ± 2.9
post(%)	5.8 ± 2.0	6.9 ± 1.8	5.7 ± 2.1	19.6 ± 11.2***	13.2 ± 2.8***

Significantly different from the control, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (students t-test).

There were no remarkable findings observed at necropsy and no apparent increases in the number of minor foetal variations. The principle findings at skeletal evaluation were an increase in the number of foetuses in the 160 mg/kg bw/day dose group with a 13th lumbar rib (57.1% and 79% in the control and 160 mg/kg bw/day dose groups, respectively) and a shift in the articulation of the ilium from the first to the second sacral vertebra in the 160 mg/kg bw/day dose group (Table B.6.10.2.10). Reduced or incomplete ossification of the hyoid bone was increased in the 10 and 160 mg/kg bw/day dose groups, but not in the 40 mg/kg bw/day dose group. The absence of this finding in the intermediate dose group indicated that this finding was not treatment-related.

Table B.6.10.2.10: Developmental toxicity study in the rabbit: summary of skeletal variations

Incidence of foetal skeletal variations	Dose group (mg/kg bw/day)			
	0	**10**	**40**	**160**
Number of foetuses affected				
Number foetuses examined	156	127	100	100
Reduced or incomplete ossification of hyoid bone	14 (19.0)	26 (20.5)**	12 (12.0)	24 (24.0)**
13th lumber rib present bilaterally	89 (57.1)	73 (57.5)	68 (68.0)	79 (79.0)***
Ilium articulating with 1st or 1st and 2nd sacral vertebra (bilaterally)	69 (44.2)	56 (44.1)	36 (36.0)	23 (23.0)***
Ilium articulating with 1st or 1st and 2nd sacral vertebra (unilaterally)	10 (6.4)	6 (4.7)	5 (5.0)	1 (1.0)*
Number of litters affected				
Number litters examined	16	13	13	11
Reduced or incomplete ossification of hyoid bone	7 (8.9)	7 (20.5)	4 (12.5)	10 (22.5)***
13th lumber rib present bilaterally	16 (57.6)	12 (59.0)	12 (66.2)	11 (79.7)**
Ilium articulating with 1st or 1st and 2nd sacral vertebra (bilaterally)	16 (44.9)	12 (43.9)	11 (36.9)	10 (23.9)*
Ilium articulating with 1st or 1st and 2nd sacral vertebra (unilaterally)	8 (6.8)	5 (5.4)	5 (5.8)	1 (1.3)*

Significantly different from the control, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Conclusions: The NOEL for maternal toxicity was 10 mg/kg bw/day based on reduced food consumption and body weight in dams administered Captan at 40 mg/kg bw/day. The NOEL for foetal toxicity was 40 mg/kg bw/day based on post-implantation loss at 160 mg/kg bw/day.

c). Review of a prenatal development toxicity study for tetrahydrophthalimide (THPI)

a) THPI: Prenatal toxicity study in the rabbit by oral gavage administration (Blee, M.A.B. 2006).

Technical grade THPI, purity >96%, was used. The study was GLP compliant and run to current international regulatory guidelines: OECD 414, US EPA OPPTS 870.3700 and Japanese Ministry of Agriculture, Forestry and Fisheries 12 Nohsan No. 8147.

Twenty-five female rabbits, of the New Zealand White strain, per dosage group were mated with males of the same strain and source and were dosed orally by gavage with THPI at 0, 5, 10 or 22.5 mg/kg/day from Gestation Day (GD) 6 to GD 28. On GD 29 dams were sacrificed and a full in utero macroscopic examination performed followed by a detailed examination of the foetal pathology. Microscopic examination of the maternal duodenum was conducted on the control and top dose groups.

There were no treatment-related deaths and no clinical signs that were attributed to treatment. Bodyweight (Table B.6.10.2.11) and food consumption (Table B.6.10.2.12) were considered not adversely affected by treatment.

Table B.6.10.2.11 : Bodyweight - group mean values (kg) for females during gestation (GD)

Group and THPI dose mg/kg bw/day		GD						
		0	6	7	14	21	28	29
Control 0	Mean	3.96	4.06	4.06	4.13	4.16	4.22	4.24
	SD	0.53	0.58	0.58	0.59	0.58	0.56	0.55
Gp 2 5	Mean	4.12	4.20	4.21	4.27	4.31	4.38	4.39
	SD	0.52	0.50	0.49	0.50	0.52	0.51	0.51
Gp 3 10	Mean	4.03	4.13	4.14	4.19	4.23	4.32	4.33
	SD	0.57	0.60	0.60	0.58	0.58	0.53	0.52
Gp 4 22.5	Mean	4.06	4.18	4.18	4.21	4.23	4.26	4.28
	SD	0.54	0.55	0.56	0.56	0.59	0.57	0.57

Table B.6.10.2.12 : Food consumption - group mean values (g/animal/day) for females during gestation (GD)

Group and THPI dose mg/kg bw/day		GD					
		1	6	7	14	21	28
Control 0	Mean	163	164	169	114	128	98
	SD	39	29	31	54	49	37
Gp 2 5	Mean	169	165	163	111	130	92
	SD	29	36	39	58	42	47
Gp 3 10	Mean	173	167	170	118	124	102
	SD	25	27	24	55	49	50
Gp 4 22.5	Mean	164	162	155	116	112	84
	SD	32	29	31	53	43	41

Macroscopic examination at necropsy of the dams did not reveal any treatment-related observations and microscopic examination of sections of the duodenum from animals in the Control and 22.5 mg/kg/day groups did not reveal any treatment-related findings indicative of GI-tract irritation.

Treatment did not adversely affect pregnancy outcome. Litter parameters as assessed by the numbers of corpora lutea, implantations, resorptions, live young and the extent of implantation loss were considered unaffected by treatment (Table B.6.10.2.13). Foetal and placental weights were unaffected by treatment with THPI (Table 15). The in utero progress and development of the foetuses up to GD 29 was similarly also unaffected by treatment

Table B.6.10.2.13 : Litter data - group mean values on GD 29

Group and THPI dose mg/kg bw/day		Corpora Lutea	Implantations	Resorptions		Live young		% implantation loss	
				Early	Late	Male	Female	Pre-	Post-
Control 0	Mean	11.3	9.3	0.6	0.4	4.8	3.4	19.2	10.6
	SD	2.2	3.3			2.0	2.0		
Gp 2 5	Mean	12.1	10.0	0.4	0.3	4.5	4.9	16.1	6.5
	SD	2.7	2.5			1.7	2.2		
Gp 3 10	Mean	12.1	10.3	0.4	0.9	4.4	4.7	14.8	11.9
	SD	1.4	2.3			1.9	1.2		
Gp 4 22.5	Mean	11.9	9.8	0.4	0.5	4.4	4.5	17.3	8.5
	SD	1.3	2.1			1.7	2.1		

Table B.6.10.2.14 : Placental and foetal weights - group mean values (g) on GD 29

Group and THPI dose mg/kg bw/day		Placental weight	Foetal weight		
			Males	Females	Overall
Control 0	Mean	5.5	39.0	37.3	38.7
	SD	0.9	7.0	6.5	6.9
Gp 2 5	Mean	5.6	39.6	39.0	39.5
	SD	0.7	5.7	5.7	5.4
Gp 3 10	Mean	5.1	36.3	36.3	36.4
	SD	0.7	5.1	4.6	4.5
Gp 4 22.5	Mean	5.5	38.2	37.8	38.0
	SD	0.9	6.6	7.1	6.6

Foetal pathology examinations did not reveal any major skeletal/visceral malformations or abnormalities (Table B.6.10.2.15) or changes in minor skeletal abnormalities/variants (Table B.6.10.2.16) that were outside concurrent or the laboratories historical control data ranges (see report for full details). Thus foetal development was unaffected by maternal treatment with THPI.

Table B.6.10.2.15: Foetal examinations - major abnormalities - group incidences

	Foetuses				Litters			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Number examined	149	224	191	215	18	24	21	24
Number affected	0	1	4	0	0	1	3	0
Absent paraflocculus: lumbar to caudal spina bifida: fused 2nd to 3rd lumbar vertebral centra resulting in kyphosis: malrotated hindlimb	-	1	-	-	-	1	-	-
Absent paraflocculus: lumbar to caudal spina bifida occulta: brachyury: gastroschisis: imperforate anus: malrotated and hyperflexion left hindlimb	-	-	1	-	-	-	1	-
Encephalocoele:disorganised/misshapen cranium	-	-	1	-	-	-	1	-
Lumbar scoliosis	-	-	1	-	-	-	1	-
Absent kidney/ureter	-	-	1	-	-	-	1	-

Table B.6.10.2.16: Foetal examinations – minor skeletal abnormalities/variants - group incidences

		Foetuses				Litters			
Group		**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Number examined		149	223	187	214	18	24	21	24
Number intact		73	113	93	105	18	24	21	24
Skeletal abnormalities									
Cranial	fissures / extra sutures	2	-	2	-	2	-	2	-
	bridge of ossification parietal to interparietal	-	1	-	1	-	1	-	1
	bent cornua of hyoid	-	-	-	1	-	-	-	1
Vertebral elements abnormality									
	cervical	-	1	1	-	-	1	1	-
	thoracic	-	1	4	1	-	1	3	1
	caudal	1	-	-	1	1	-	-	1
	additional centre	-	1	2	1	-	1	2	1
	scoliosis, minimal	-	1	1	-	-	1	1	-
Ribs	medially/distally thickened	1	1	2	-	1	1	2	-
	fused/partially fused	-	1	1	-	-	1	1	-
	non articulated	-	1	2	-	-	1	2	-
	malpositioned/thickened/ misshapen articulating surface	-	1	1	1	-	1	1	1
	interrupted	1	-	-	-	1	-	-	-
	additional/absent	-	2	3	-	-	2	2	-
Sternebrae	additional centre(s)	1	1	-	-	1	1	-	-
	misshapen/wide/fragmented	-	4	2	-	-	4	2	-
	bridge of ossification/fused	1	2	2	-	1	2	2	-
	bipartite ossified/offset alignment	-	3	2	1	-	3	2	1

Group 1 = control, 0 mg/kg bw/day; Group 2 = THPI 5 mg/kg bw/day
Group 3 = THPI 10 mg/kg bw/day; Group 4 = THPI 22.5 mg/kg bw/day

Table B.6.10.2.16: Foetal examinations – minor skeletal abnormalities/variants - group incidences (continued)

		Foetuses				Litters			
Group		**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Number examined		149	223	187	214	18	24	21	24
Number intact		73	113	93	105	18	24	21	24
Costal cartilage	offset alignment	-	2	2	-	-	2	2	-
	branched/thickened/fused	-	2	3	-	-	2	3	-
	additional/absent	-	1	2	-	-	1	2	-
	partial	-	-	1	-	-	-	1	-
	perforated xiphoid cartilage	1	-	1	-	1	-	1	-
	6th not connected to sternum	-	-	1	-	-	-	1	-
	7th not connected to sternum	6	18	4	9	2	7	2	7
	8th connected to sternum	-	-	-	1	-	-	-	1
Appendicular	elongated acromion/metacromion process	1	3	-	-	1	2	-	-
	short tail, minimal	1	-	-	-	1	-	-	-
Total affected by one or more of the above		15	27	11	15	7	14	8	13
Rib and vertebral configuration									
Cervical rib		6	5	-	-	4	5	-	-
Short/rudimentary 1st rib		-	1	2	-	-	1	2	-
Number with 12/13 or 13/13 ribs		93	131	121	143	18	23	21	24
18 thoracolumbar vertebrae		-	-	1	-	-	-	1	-
20 thoracolumbar vertebrae		51	38	50	61	12	15	13	21
Offset alignment pelvic girdle		-	3	1	3	-	3	1	3

Table B.6.10.2.16: Foetal examinations – minor skeletal abnormalities/variants - group incidences (continued)

		Foetuses				Litters			
Group		**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Number examined		149	223	187	214	18	24	21	24
Number intact		73	113	93	105	18	24	21	24
Incomplete ossification / unossified									
Enlarged anterior/posterior fontanelle		-	-	1	1	-	-	1	1
Cranial		-	-	-	1	-	-	-	1
Vertebral element	cervical	-	2	2	-	-	2	2	-
	thoracic/lumbar	-	-	1	-	-	-	1	-
	caudal	-	-	1	-	-	-	1	-
Sternebrae	5^{th}	17	37	23	29	8	16	11	11
	other	10	12	21	13	5	8	9	7
	total	24	46	39	40	10	19	14	15
Caudal vertebrae		-	-	1	-	-	-	1	-
Epiphyses		13	5	18	11	6	5	7	7
Pubes		2	-	2	4	1	-	2	3
Astragalus		5	1	3	7	1	1	3	5
Calcaneum		-	-	-	1	-	-	-	1
Metacarpals/phalanges		21	23	27	23	7	12	11	12
Precocious ossification									
Small anterior fontanelle		-	-	-	1	-	-	-	1
Ossified olecranon processes		-	-	-	1	-	-	-	1

Conclusion: Maternal administration of THPI by oral gavage did not induce demonstrable maternal toxicity and did not affect the progress or outcome of the pregnancies. The development of the foetus was unperturbed and foetal pathology was considered to be normal.

d) Studies on the anti-microbial potential of Captan or THPI

a) Captan: Determination of minimum inhibitory concentrations against selected micro-organisms representative of the rabbit gut micro-flora (Akhurst, L.C. 2005a).

Captan can have bacteriostatic or bactericidal activity (e.g. see Guan et al, 2005). It may, therefore, be postulated that Captan could affect the rabbit gut micro-flora and that an imbalance in the micro-flora may have consequences for the pregnant rabbit on both maternal and embryo-foetal nutrition. Such changes could, in theory, affect the developing foetus. The rabbit is a species particularly susceptible to gastrointestinal disturbances that may in part be mediated through changes in the gut micro-flora. To assess potential effects on micro-organisms representative of rabbit gut micro-flora the minimum inhibitory concentration (MIC) assay is an internationally accepted test for antimicrobial susceptibility testing and is commonly used to assess the effectiveness of intentional antimicrobial compounds. The test was adapted to assess selected microorganisms representative of the rabbit gut micro-flora.

The study was conducted using an agar dilution procedure for determination of MIC values. The method was based on procedures described by the British Society for Antimicrobial Chemotherapy (Journal of Antimicrobial Chemotherapy 2001, 48, Supplement S1, 5-16). Ten species of the genus *Bacteroides*, one genus of *Enterococcus faecalis* and four isolates of *Candida albicans* were tested. Final concentrations of Captan of 2000, 1000, 500, 200, 100, 50, 20, 10, 5 or 2 µg/ml were tested and solvent control and growth control plates were employed. Plates were incubated at 37°C for 48 hours. The lowest test substance concentration that completely inhibited growth of the test organism was recorded as the MIC.

Captan demonstrated marked antimicrobial activity towards all microorganisms tested, although was more active against the yeast, *Candida albicans*, than the bacterial organisms. MIC values were in the range 20 –50 µg/ml for *Bacteroides* sp., 50 – 500 µg/ml for *Enterococcus faecalis* and <2-5 µg/ml for *Candida albicans*.

Conclusion: Captan demonstrated significant antimicrobial activity against organisms selected as representatives of rabbit gut flora species tested in this study. Captan has clear antimicrobial activity.

b) THPI: Determination of minimum inhibitory concentrations against selected micro-organisms representative of the rabbit gut micro-flora (Akhurst, L.C. 2005b).

THPI is not thought to have the same anti-microbial activity as the parent molecule Captan, primarily because it is not capable of generating the highly reactive moiety thiophosgene, which in conjunction with Captan is considered to be responsible for the molecule's mode of action on micro-organisms.

The test was essentially as that described above for Captan.

The study was conducted using an agar dilution procedure for determination of MIC values. Ten species of the genus *Bacteroides*, one genus of *Enterococcus faecalis* and four isolates of *Candida albicans* were tested. Final concentrations of THPI of 1000, 500, 200, 100, 50, 20, 10, 5, 2 or 1 µg/ml were tested and solvent control and growth control plates were employed. Plates were incubated at 37°C for 48 hours. The lowest test substance concentration that completely inhibited growth of the test organism was recorded as the MIC.

THPI demonstrated no antimicrobial activity towards *Bacteroides* sp., *Enterococcus faecalis*, or *Candida albicans* when tested up to a concentration of 1000 µg/ml.

Conclusion: THPI demonstrated no antimicrobial activity against organisms selected as representatives of rabbit gut flora species tested in this study. It is therefore unlikely that this molecule has the potential to affect the micro-flora of the rabbit GI tract.

2) Discussion and conclusions drawn from position paper

The rat study of Rubin (1997b) showed that Captan was not teratogenic, but in the presence of notable maternal toxicity did have a slight effect on the growth of the foetus at 450 mg/kg bw/day. The foetal NOEL was therefore 90 mg/kg bw/day. In the rabbit study of Tinston (1991) maternal toxicity was seen at the highest dose of 100 mg/kg bw/day and associated with this was an increase in post-implantation loss, reduced foetal body weight and an increased incidence of foetal abnormalities. There were no teratogenic effects. At the intermediate dosage (30 mg/kg bw/day) some maternal toxicity was evident (changes in defaecation, reduced food intake and lower body weight gain) and a slight, but not significant, increase in post-implantation loss. As this latter finding was slight, and statistically not significant, it was compared to historical control data (Moxon, 2004) and was shown to be within the range considered normal for the strain of rabbit investigated. The lowest dosage tested in this study was 10 mg/kg bw/day and no adverse effects were seen at this dose level.

From this study it can be concluded that the NOAEL for embryo-foetal effects was 30 mg/kg bw/day. In another rabbit developmental study conducted on Captan (Rubin, 1987a) the NOAEL for foetal toxicity was 40 mg/kg bw/day. The developmental NOAEL in this study was again based on the incidence of post-implantation losses at the top dose group (160 mg/kg bw/day) where clear signs of maternal toxicity were evident (reduced food intake and lower body weight gain). The two rabbit studies would appear to generally agree that a NOAEL of 30 to 40 mg/kg bw/day for embryo-foetal effects would be a reasonable conclusion based on these studies, and that embryo-foetal effects were clearly associated with maternal toxicity.

A developmental toxicity study conducted with the Captan metabolite THPI did not show any evidence of maternal or foetal toxicity in the rabbit (Blee, 2006). This was perhaps not too surprising as THPI cannot produce the reactive moiety thiophosgene, that in conjunction with Captan is considered to be responsible for the acute toxicological effects (e.g. irritancy) seen with this molecule. Thus the maternal effects that for Captan were characterised by low food consumption with an associated lower body weight gain were not present for THPI. This suggests that the known irritancy effects of Captan (particularly on the GI-tract) were probably responsible for the maternal effects seen with Captan. Such effects could have been exacerbated by the gavage dosing technique that would have resulted in local high concentrations in the stomach. Moreover the lack of foetal toxicity with THPI points to maternal effects as critical to the slight delays in foetal development seen with Captan. Such effects could be related to maternal well being, and nutrition, and not in this case to intrinsic toxicity. Indeed in a recent publication Cappon et al (2005) concluded that feed restriction in the rabbit may lead to developmental effects such as abortion, reduced foetal weight and changes in ossification – effects associated with reduced maternal weight performance. The data for Captan would also suggest that this may be the case for this molecule.

It is also seems that the rabbit appears to be more sensitive to GI-tract perturbation than the rat – as demonstrated by the effects on food consumption and concomitant body weight gain in this species. The effect is probably related to GI-tract irritancy following degradation of Captan to form the reactive and short-lived moiety thiophosgene. Such effects would appear to be due to local GI-tract irritancy rather than systemic toxicity considering the very rapid reaction of Captan with thiol groups and rapid hydrolysis in more alkaline conditions to produce thiophosgene. In such circumstances it is questionable whether the rabbit is the most appropriate model when considering the known irritancy of Captan. Furthermore, the rabbit is dependent on its gut micro-flora to maintain a healthy nutritional status which means that compounds known to possess significant antimicrobial activity may have an affect on the well being of the animal (e.g. oral antibiotic use in rabbits may often have adverse consequences mostly because of undesirable effects on beneficial micro-organisms, e.g. see Hawk and Leary, 2004 and Morris, 1995). The bacteriostatic/bactericidal activity of Captan may affect the production of caecotrophs that are critical to nutrition in the rabbit. These caecotrophs are generally produced 4 – 6 hours after eating by fermentation of ingested food in the caecum and are composed primarily of bacteria that contain fatty acids, amino acids, vitamins and minerals that were derived from the food but would otherwise not be available for absorption. The rabbit ingests these soft green pellets directly from the anus and digests the bacteria with their internal load of nutrients. The rabbit's dependency on ingestion of caecotrophs for overall nutrition may be adversely affected by the bacteriostatic/bactericidal action of Captan. The MIC study with Captan (Akhurst, 2005a) proved that this molecule has significant antimicrobial activity that may affect the production of caecotrophs whereas its stable metabolite, THPI (Akhurst, 2005b), did not. These data suggest that the effects on maternal nutrition and foetal development in the rabbit may also have a nutritional deficit component. Overall the findings indicate that the rabbit is not the most appropriate model for assessing embryo-foetal development when compounds that are irritants or bacteriostatic/bactericidal are administered by bolus dosing.

The 2004 JMPR, without the benefit of the THPI prenatal developmental and MIC studies, concluded that 30 mg/kg bw/day was a NOAEL for embryo-foetal effects in the rabbit. Furthermore, they stated that:

"The maternal toxicity and associated increases in skeletal variations and foetal body-weight reductions observed in studies of developmental toxicity in rabbits are likely to be caused by

high local concentrations of Captan and are not considered to be relevant to dietary exposure. However, the observed intra-uterine deaths and foetal malformations could not, with confidence, be attributed to maternal toxicity."

The 2004 JMPR proposal is considered to be a conservative approach. Their overall assessment of developmental toxicity data is however supported by the publication of Solecki at al (2005) on ARfD setting. In that publication, it is clearly stated:

"…that ARfDs based on reductions in foetal body weight gain arising from multiple dose studies are generally thought to be conservative."

The review of Solecki at al (2005) also makes it clear that it is *"…important to distinguish between a developmental effect from a secondary response"*, i.e. one that is as a consequence of maternal toxicity. The paper also advocates that maternal toxicity in pre-natal developmental studies may not be appropriate for ARfD setting by stating that:

"Maternal toxicity following repeated dosing in developmental toxicity studies may not be appropriate for setting an ARfD unless clinical observations or other toxicity in the dams are observed after a single dose of the test substance."

Considering the new data presented in current position statement, in particular the developmental toxicity study in the rabbit with THPI that the JMPR thought critical, and the criteria for setting an ARfD (EC, 2001; JMPR, 2004 and Solecki et al, 2005) it is proposed that an ARfD for Captan is not warranted.

The reasons for this are:

a) There were no adverse effects that might be considered to be as a consequence of acute exposure e.g. LD50 > 2000 mg/kg bw.
b) Teratogenicity was not evident.
c) Embryo-foetal effects were associated with distinct maternal toxicity.
d) No statistically significant embryo-foetal effects were seen at the intermediate dosage in the rabbit study of Tinston (30 mg/kg bw/day).
e) Slight (statistically non significant) embryo-foetal effects at 30 mg/kg bw/day (post-implantation loss) were within the historical control data range.
f) The slight embryo-foetal effects observed were most probably secondary to maternal toxicity and caused by high local concentrations of Captan produced by administration by gavage and are not considered to be relevant to dietary exposure.
g) Data from a prenatal developmental study with THPI showed that this major metabolite caused no maternal or foetal toxicity, suggesting that the maternal effects seen with Captan (based on local irritant effects) were mostly responsible for the slight foetal effects seen with the parent molecule.
h) The rabbit may be considered to be a less appropriate experimental animal, as it appears to be very sensitive to local GI-tract irritancy and possible perturbation of its gut micro-flora. Such effects may not reflect systemic exposure.

It is the conclusion of the position paper that the weight of evidence for Captan suggests that setting an acute reference dose for Captan is unnecessary.

B.6.10.2 References relied on

Annex point /reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
##	Akhurst, L.C.	2005a	Captan: Determination of minimum inhibitory concentrations against selected microorganisms representative of the rabbit gut micro-flora. Huntingdon Life Sciences, UK, unpublished report No. MAK 888/052848 (company file: R-18666).	Y	Makhteshim
##	Akhurst, L.C.	2005b	THPI: Determination of minimum inhibitory concentrations against selected microorganisms representative of the rabbit gut micro-flora. Huntingdon Life Sciences, UK, unpublished report No. 890/053252 (company file: R-18735).	Y	Makhteshim
##	Blee, M.A.B.	2006	THPI: Prenatal toxicity study in the rabbit by oral gavage. Report MAK 864/055232 administration (Company file: R-18202). GLP, Unpublished.	Y	Makhteshim
##	Cappon, G.D., Fleeman, T.L., Chapin, R.E. and Hurtt, M.E..	2005	Effects of feed restriction during organogenesis on embryo-foetal development in rabbit. Birth Defects Research Part B: Developmental and Reproductive Toxicology Volume 74, Issue 5, Pages 424 – 430 Not GLP; Published.	N	-
##	European Commission	2001	EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL Draft Guidance Document GUIDANCE FOR THE SETTING OF AN ACUTE REFERENCE DOSE (ARfD); 7199/VI/99 rev. 5, 05/07/2001. Published.	N	-
##	Hawk, C.T. and Leary, S.L..	2004	Formulary for laboratory animals. In association with the American College of Laboratory Animal Medicine. Iowa State University Press (Blackwell Publishing). See http://dcminfo.wustl.edu/pdf/PDF/Text.pdf	N	-
##	Guan, T.T., Blank, G. and Holley, R.A.	2005	Survival of pathogenic bacteria in pesticide solutions and on treated tomato plants. J. Food. Prot. 2005 Feb; 68(2):296-304. Published.	N	-

Annex point /reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
##	Anon	1991-2004	JMPR, FAO/WHO (1991-2004). Reports Available on the FAO website: http://www.fao.org/WAICENT/FAOINFO/AGRICULT/AGP/AGPP/Pesticid/Default.HTM	N	-
##	JMPR, FAO/WHO.	2004	Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues Rome, Italy, 20–29 September 2004. Published.	N	-
##	Morris, T. H.	1995	Antibiotic Therapeutics in Laboratory Animals. Laboratory Animals 29: 16-36, also see http://www.medirabbit.com/Unsafe_medication/dangerous_antibiotics.htm GLP, Unpublished.	N	-
##	Moxon, M.E.	2004	Historical control data for the New Zealand White Rabbit. [redacted] 026293 (company file R-17425).	Y	Makhteshim
IIA, 5.6.2.1/02	Rubin, Y.	1987a	Captan: Teratogenicity study in the rabbit. [redacted] MAK/099/CAP(company file: R-4429). GLP, Unpublished	Y	Makhteshim
IIA, 5.6.2.2/01	Rubin, Y.	1987b	Captan: teratology study in the rat. [redacted] unpublished report number MAK/097/CAP (company file: R-4364). GLP, Unpublished	Y	Makhteshim
##	Solecki, R., Davies, L., Dellarco, V., Dewhurst. I., van Raaij, M and Tritscher, A.	2005	Review: Guidance on setting of acute reference dose (ARfD) for pesticides. Food and Chemical Toxicology, 43; 1569-1593. Published	N	-
IIA, 5.6.2.1/01	Tinston, D.J.	1991	Captan: Teratogenicity study in the rabbit. [redacted] P3039 (company file R-6148). GLP, Unpublished	Y	Makhteshim
##	US EPA	1999	Reregistration Eligibility Decision (RED) CAPTAN: Available on the US EPA website: http://www.epa.gov/oppsrrd1/REDs/0120red.pdf	N	-

information presented in Addendum, not referenced in original submission

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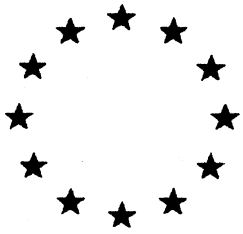

ECCO-Meetings

Captan

Volume 3

Annex B
Addendum: definition of the residue

Rapporteur Member State: Italy

B.7.3 Definition of the residue (Annex IIA 6.7; Annex IIIA 8.6)

Captan: The residue definition for the fungicide captan should be captan only as the metabolites THPI, 3-OH-THPI and 5-OH-THPI are neither of toxicological significance nor pose a significant dose to humans,.

The collective data (toxicological data and residue data leading to estimated dose to humans) support the conclusion that the residue definition for captan should be **captan only**.

The DG SANCO Guideline notes (European Commission, 1997): Residue Definition – Of the three general considerations that are fundamental to the decision as to whether or not specific metabolites/degradation products should be included in the definition and expression of a residue, two are relevant to this discussion: (1) Their basic toxicology and (2) Their presence in significant amounts.

1) THPI basic toxicology

Four lines of evidence show that the metabolites of captan are not of toxicological significance:
a) Direct measurements of toxicity.
b) QSAR Analysis
c) Measurement of minimal inhibitory concentration (MIC)
d) Comparison of captan and its major metabolite in bioassays that are particularly sensitive to the toxicological properties of captan.

a) Direct measurements of toxicity

THPI is not acutely toxic. Its LD50 in rats is above 10 g/kg bw (Elsea, 1955).

THPI is not mutagenic. When tested in the multiple strains in the Ames Assay, it is negative (Carver, 1986).

THPI is not a developmental toxin. When tested at 75 mg/kg bw/day in Dutch Belted rabbits (Kennedy *et al.,* 1968) or 22.5 mg/kg bw/day in New Zealand white rabbits (Blee, 2006), developmental abnormalities were not seen.

b) QSAR Analysis

THPI does not have structural alerts that indicate this metabolite poses a toxicological risk (Chaudry, 2005).

The hydroxylation of organic structures is considered a detoxification mechanism since hydroxylation makes a compound more polar which increases the potential for molecular conjugation and consequently facilitates excretion; thus, the hydroxylated metabolites of THPI are considered less toxic than THPI (*www.isu.edu/~watwmari/detox.doc*).

c) Measurement of minimal inhibitory concentration (MIC)

The MIC assay is designed to assess antimicrobial activity and efficacy *in vitro*. The study was deigned to assess the effects of THPI on micro-flora representative of that in the rabbit GI-tract. Ten species of *Bacteroides* and four isolates of *Candida albicans* were incubated in the presence of THPI at biologically significant concentrations. THPI had no antimicrobial activity (Akhurst, 2005).

d) Comparison of captan and its major metabolite in fish bioassays that are particularly sensitive to the toxicological properties of captan.

The most sensitive bioassays for measuring toxicity of captan are those involving aquatic organisms. This follows from the mode of action of captan, which is irritation-based, due to its

reactivity of the captan side chain with the thiol group. This reactive side chain is not present on the THPI metabolite. This high reactivity of the side chain of captan produces irritation to the tissues as well as to gill membranes in fish. THPI, has low reactivity and is not an irritant.

THPI was found to be non-toxic to fish species tested. The rainbow trout LC_{50} assay is able to distinguish the toxicity of captan and THPI in a dramatic way. The data for captan and THPI are noted below (Jenkins, 2002,Kent, 1994):

Rainbow trout 96 hour Static LC_{50}:
Captan 0.215 mg/L
THPI >120 mg/L

Ratio of THPI toxicity to captan toxicity is >500-fold. This decrease in toxicity attests to the relative innocuous character of THPI compared to the parent, captan.

In conclusion, THPI poses no significant toxicological risk for adverse effects.

2) Their presence in significant amounts

The following maximum residues have been found in milk and meat from dairy cows fed 10 ppm captan (the estimated maximum dose, based on captan use and cattle feed components) (Wiebe, 1991):

		Metabolite	
	THPI	3-OH-THPI	5-OH-THPI
Milk	<0.01	0.02	<0.01 mg/kg
Meat	0.02	0.02	(0.003) mg/kg

LOQ: 0.01 mg/kg

The less than Level of Quantification in the milk is consistent with an extensive market basket survey of milk sampled at the point of purchase from around the United States. There were no residues of THPI in all 224 milk samples analysed (Slesinski and Wilson, 1992).

Consumption of meat and milk calculated according to the worst case scenarios resulted with maximum possible daily intake of THPI in the most sensitive consumer groups of 0.00039 mg/kg bw/day (toddlers), 0.00053 mg/kg bw/day (infants).

The maximum possible daily intake of 3-OH-THPI are 0.00122 mg/kg bw/day (toddlers), 0.00203 mg/kg bw/day (infants).

The maximum possible daily intake of 5-OH-THPI are 0.00031 mg/kg bw/day (toddlers), 0.00051 mg/kg bw/day (infants).

The maximum possible daily intake of THPI, -3-OH-THPI and 5-OH-THPI (taking into consideration the most sensitive population group) are very low and significantly lower than the ADI for captan for the most sensitive consumer groups for animal products.
(Detailed calculations appear under point 2.c) below.)

Considering the low toxicity of captan metabolites and the low dose to humans that these metabolites represent, when calculated using conservative assumptions, there is no basis for rationally including these metabolites in the captan residue expression.

In conclusion, the residue expression for captan should be expressed as parent compound, captan, only.

The references submitted in support of the above position are summarised below.

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1) THPI basic toxicology

a) Tetrahydrophthalimide: Acute oral administration - rats (Elsea, J.R., 1955; IIA 7.3/01).

The captan metabolite THPI, referred to in the report as phthalimide (N-trichloromethylthiophthalimide), purity 97%, in [redacted] was administered orally by gavage to groups of five fasted male rats as either a 10% or 40% w/v suspension at dose levels of 1.00, 2.15, 4.64 or 10.00 g/kg bw. Animals were observed for signs of toxicity on the day of administration and for seven days thereafter. Animals were subject to gross necropsy.

The study pre-dated regulatory guidelines and GLP, but was performed at a reputable laboratory, and the result is considered valid.

There were no deaths. On the day of dosing, all animals appeared depressed and showed laboured respiration and diarrhoea. Animals at the 2.15 mg/kg bw and above also showed slight ataxia. From 24 hours post-dose, animals at 1.00 and 2.15 mg/kg bw appeared normal. Animals at 4.54 and 10.00 mg/kg bw appeared depressed and showed soft, light coloured faeces for one to three days following dosing. All groups gained weight during the study. Necropsy revealed mottled and granular livers in the majority of animals in all groups receiving the test material.

Conclusion: The acute oral LD_{50} of THPI in the male rat is greater than 10 g/kg bw. In accordance with 93/21/EEC classification is not required.

b) Microbial/Mammalian Microsome Mutagenicity Plate Incorporation Assay with Tetrahydrophthalimide (Carver, J.H., 1986; IIA 7.3/02)

NOTE: The summary below already appears in the DAR under B.6.8.1a Toxicity studies of metabolites as referred to in the introduction point (vii).

The mutagenicity of the captan metabolite THPI (purity 99.9%) in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 and in the tryptophan-deficient strain of *Escherichia coli* WP2 uvrA was investigated at concentrations of 0.1 to 10 mg/plate in the presence and absence of metabolic activation (S-9 mix). The test substance was dissolved in DMSO. S-9 mix was obtained from the liver of arochlor induced rats. The positive control substance with metabolic activation was 2-aminoanthracene (strains TA98, TA100, TA1537 and WP2 uvrA). Positive controls without metabolic activation were 2-nitrofluorene (strain TA98), sodium azide (strains TA100 and TA1535), ICR-191 (strain TA1537, WP2 uvrA), 2-aminoacridine (TA1537), danthron (TA102), mitomycin (TA102), 1-ethyl 2-nitroso-3-nitrosoguanidine (WP2 uvrA). All concentrations were run in triplicate and the results were confirmed by an independent experiment.
The study was conducted according to an in-house method basically in agreement with the OECD Guideline 471, and in compliance to Good Laboratory Practice.

results: there was no cytotoxicity at any of the concentrations tested. No reproducible increases in mutant frequency were observed with the *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 or the *E. coli* strain WP2 uvrA, with or without metabolic activation. The tester strains responded to the positive controls as expected.

Conclusion: Under the conditions of the test THPI was not mutagenic in the *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 or the *E. coli* strain WP2 uvrA in the presence or absence of metabolic activation.

c*) An investigation of the teratogenic potential of captan, folpet, and difolatan (Kennedy, G., Fancher, O. E., and Calandra, J. C., 1968; IIA 7.3/03).*

Study of effects of captan, folpet, the captan metabolite tetrahydrophthalimide (THPI), and the folpet metabolite phthalimide (PI) on the pregnant rabbit. Technical grade captan and folpet, and pure samples of THPI and PI were used. The related fungicide difoltan and the structurally similar drug thalidomide were also tested. The latter may be considered a positive control.

The study predated guidelines and was not to GLP. However, the study demonstrated that foetal malformations could be induced by a known positive control, and is considered valid.

Test materials were administered in gelatine capsules to groups of mated female Dutch Belted rabbits from day 6 to day 16 of pregnancy. Animals were weighed at three day intervals and killed on day 29, when uterine contents were examined, and foetuses examined. Live foetuses were placed in an incubator for 24 hours after which they were killed and dissected. The carcasses were cleared and the skeleton stained with alizarin and examined. THPI was administered at 75 mg/kg bw/day to a group of 9 females. The study also investigated possible strain effects, testing New Zealand White (NZW) rabbits and Dutch Belted rabbits with captan. Two control groups, one of each strain, received empty capsules only. Thalidomide was administered at 75.0 mg/kg bw/day to both strains of rabbit.

Maternal weight gains were not adversely affected by THPI at 75.0 mg/kg/day, and there were no deaths.

Incidence of foetal resorptions was marginally higher with THPI.

One control foetus (of 105, from 17 litters) showed shortening and flexure of the forelimb. There were no malformations in the 57 foetuses from 9 dams treated with THPI. Post-natal survival, crown-rump length, foetal weight and incidence of visceral and skeletal anomalies were not adversely affected by maternal treatment with THPI. Thalidomide induced typical 'clubbing' (phocomelia) in 38 of 100 foetuses from 17 litters.

The results are summarised below (Table B.7.3.1).

Table B.7.3.1: Summary of effects of captan, THPI and controls in rabbits

Compound	Oral dose (mg/kg)	No. of pregnant females	Rabbit strain	No. of implants	No of resorptions	No of normal foetuses	No. (%) malformed foetuses	Mean litter size
Control	-	7	DB	52	0	51	1 (1.9)	7.4
	-	10	NZW	66	2	64	0 (0)	6.4
Thalidomide	75.0	7	BD	55	15	26	14 (35.0)	5.7
		10	NZW	74	10	40	24 (37.5)	6.4
Captan	75.0	6	DB	43	1	42	0 (0)	7.0
	18.75	6	NZW	46	11	35	0 (0)	5.8
	37.5	7	NZW	56	2	54	0 (0)	7.7
	75.0	5	NZW	39	33	6	0 (0)	1.2
THPI	75.0	9	DB	66	9	57	0 (0)	6.3

Conclusion: Tetrahydrophthalimide (THPI) showed no adverse effects on the developing rabbit foetus.

d) THPI: Prenatal toxicity study in the rabbit by oral gavage administration (Blee, M.A.B., 2006 IIA 7.3/04)

A study of the effects of THPI on the pregnant rabbit was conducted. Technical grade THPI, purity >96%, was used. The study was GLP compliant and run to current international regulatory guidelines: OECD 414, US EPA OPPTS 870.3700 and Japanese Ministry of Agriculture, Forestry and Fisheries 12 Nohsan No. 8147.

Twenty-five female rabbits, of the New Zealand White strain, per dosage group were mated with males of the same strain and source and were dosed orally by gavage with THPI at 0, 5, 10 or 22.5 mg/kg/day from Gestation Day (GD) 6 to GD 28. Dams were killed on GD 29 of pregnancy, and uterine parameters recorded. Foetuses were examined macroscopically at necropsy and subsequently by detailed internal visceral examination of the head or at skeletal examination. Microscopic examination of the maternal duodenum was conducted on the control and top dose groups.

There were no treatment-related deaths and no clinical signs that were attributed to treatment. Bodyweight (Table B.7.3.2) and food consumption (Table B.7.3.3) were considered not to be adversely affected by treatment.

Macroscopic examination at necropsy of the dams did not reveal any treatment-related observations and microscopic examination of sections of the duodenum from animals in the Control and 22.5 mg/kg/day groups did not reveal any treatment-related findings.

Treatment did not adversely affect pregnancy outcome. Litter parameters as assessed by the numbers of corpora lutea, implantations, resorptions, live young and the extent of implantation loss were considered unaffected by treatment (Table B.7.3.4). Foetal and placental weights were unaffected by treatment with THPI (Table B.7.3.5). The *in utero* progress and development of the fetuses up to GD 29 was similarly also unaffected by treatment

Treatment did not adversely affect pregnancy outcome, embryo-foetal survival post-implantation, and fetal and placental weights were considered to be unaffected by treatment with THPI . The *in utero* progress and development of the fetuses up to GD 29 was unaffected by treatment.

Foetal pathology examinations did not reveal any skeletal or visceral major malformations/abnormalities or changes in minor skeletal abnormalities or variants that were outside concurrent or the laboratories historical control data ranges. Thus foetal development was unaffected by maternal treatment with THPI.

It may be concluded that maternal administration of THPI did not induce demonstrable maternal toxicity and did not affect the outcome of the pregnancies. Foetal development was considered to be normal.

Table B.7.3.2: Bodyweight - group mean values (kg) for females during gestation (GD)

Group	:	1	2	3	4
Compound	:	Control	-------Tetrahydrophthalimide ----		
Dosage (mg/kg/day)	:	0	5	10	22.5

Group		GD						
		0	6	7	14	21	28	29
1	Mean	3.96	4.06	4.06	4.13	4.16	4.22	4.24
	SD	0.53	0.58	0.58	0.59	0.58	0.56	0.55
	n	18	18	18	18	18	18	18
2	Mean	4.12	4.20	4.21	4.27	4.31	4.38	4.39
	SD	0.52	0.50	0.49	0.50	0.52	0.51	0.51
	n	24	24	24	24	24	24	24
3	Mean	4.03	4.13	4.14	4.19	4.23	4.32	4.33
	SD	0.57	0.60	0.60	0.58	0.58	0.53	0.52
	n	21	21	21	21	21	21	21
4	Mean	4.06	4.18	4.18	4.21	4.23	4.26	4.28
	SD	0.54	0.55	0.56	0.56	0.59	0.57	0.57
	n	24	24	24	24	24	24	24

Table B.7.3.3: Food consumption - group mean values (g/animal/day) for females during gestation (GD)

Group	:	1	2	3	4
Compound	:	Control	-------Tetrahydrophthalimide ----		
Dosage (mg/kg/day)	:	0	5	10	22.5

Group		GD					
		1	6	7	14	21	28
1	Mean	163	164	169	114	128	98
	SD	39	29	31	54	49	37
	n	17	18	18	18	18	18
2	Mean	169	165	163	111	130	92
	SD	29	36	39	58	42	47
	n	24	24	24	24	24	24
3	Mean	173	167	170	118	124	102
	SD	25	27	24	55	49	50
	n	21	21	21	21	21	21
4	Mean	164	162	155	116	112	84
	SD	32	29	31	53	43	41
	n	24	24	24	24	24	24

Table B.7.3.4: Litter data - group mean values on GD 29

Group	:	1	2	3	4
Compound	:	Control	--------	Tetrahydrophthalimide	--------
Dosage (mg/kg/day)	:	0	5	10	22.5

Group		Corpora Lutea	Implantations	Resorptions		Live young		% implantation loss	
				Early	Late	Male	Female	Pre-	Post-
1	Mean	11.3	9.3	0.6	0.4	4.8	3.4	19.2	10.6
	SD	2.2	3.3			2.0	2.0		
	n	18	18	18	18	18	18	18	18
2	Mean	12.1	10.0	0.4	0.3	4.5	4.9	16.1	6.5
	SD	2.7	2.5			1.7	2.2		
	n	24	24	24	24	24	24	24	24
3	Mean	12.1	10.3	0.4	0.9	4.4	4.7	14.8	11.9
	SD	1.4	2.3			1.9	1.2		
	n	21	21	21	21	21	21	21	21
4	Mean	11.9	9.8	0.4	0.5	4.4	4.5	17.3	8.5
	SD	1.3	2.1			1.7	2.1		
	n	24	24	24	24	24	24	24	24

Table B.7.3.5: Placental and foetal weights - group mean values (g) on GD 29

Group	:	1	2	3	4
Compound	:	Control	--------	Tetrahydrophthalimide	--------
Dosage (mg/kg/day)	:	0	5	10	22.5

Group		Placental weight	Foetal weight		
			Males	Females	Overall
1	Mean	5.5	39.0	37.3	38.7
	SD	0.9	7.0	6.5	6.9
	n	18	18	17	18
2	Mean	5.6	39.6	39.0	39.5
	SD	0.7	5.7	5.7	5.4
	n	24	24	24	24
3	Mean	5.1	36.3	36.3	36.4
	SD	0.7	5.1	4.6	4.5
	n	21	21	21	21
4	Mean	5.5	38.2	37.8	38.0
	SD	0.9	6.6	7.1	6.6
	n	24	24	24	24

e) Assessment of the activity, toxicity and mutagenicity potential of THPI, using structure activity relationships (Chaudhry, Q., 2005; IIA 7.3/05). [This report was previously submitted with the toxicology addendum in March 2005.]

THPI was evaluated for their potential for activity, toxicity and mutagenicity using a Structure Activity Relationship (SAR) approach. The technique, referred to as Deduction of Risk from Existing Knowledge (DEREK), uses specialist software 'DEREK for Windows' (DfW) developed by Llhasa Ltd. The software works by matching structural entities in a query structure with structural alerts that are associated with different toxicity endpoints (toxicophores). A structural alert is the set of structural features in a molecule that makes a toxicologist suspect that the substance may show a particular toxic effect. DfW can predict alerts for carcinogenicity, irritation (e.g. of the skin, eye and gastrointestinal tract), genotoxicity, respiratory sensitisation, skin sensitisation, thyroid toxicity and a range of miscellaneous effects for bacteria and a range of mammalian species including man. The programme used 482 structural alerts associated with the different endpoints.

DfW also predicts the likelihood of each effect using descriptive terms ranging from 'certain' to 'impossible' ('certain', 'probable', 'plausible', 'equivocal', 'doubted', 'improbable', 'impossible'), or 'open' or 'contradicted' in the case of findings where there is a prediction both that the proposition is true and that it is false.

There were no structural alerts in THPI.

In conclusion, computer predictions using DfW indicate that THPI is not expected to exhibit mutagenic activity, genotoxicity, irritation, sensitisation or thyroid toxicity.

f) THPI: Determination of minimal inhibitory concentrations against selected micro-organisms representative of the rabbit gut micro-flora (Akhurst, L.C., 2005 IIA 7.3/06).

It has been postulated that captan may affect the rabbit GI tract micro-flora and that an imbalance in the micro-flora may have consequences for the pregnant rabbit on both maternal and embryo-foetal nutrition. Such changes could, in theory, affect the developing foetus. The rabbit is a species particularly susceptible to gastrointestinal disturbances which may in part be mediated through changes in the GI tract micro-flora. An *in vitro* approach to demonstrate changes in representative rabbit GI tract micro-flora was considered to be a simple and straightforward way to evaluate the potential effects of THPI on such micro-organisms.

THPI is not thought to have the same anti-microbial activity as the parent molecule captan partly because it is not capable of generating the highly reactive moiety thiophosgene.

The minimum inhibitory concentration (MIC) assay is an internationally accepted test for antimicrobial susceptibility testing and is commonly used to assess the effectiveness of intentional antimicrobial compounds. The test was adapted to assess selected micro-organisms representative of the rabbit gut micro-flora.

The study was conducted using an agar dilution procedure for determination of MIC values. Ten species of the genus Bacteroides, one genus of *Enterococcus faecalis* and four isolates of *Candida albicans* were tested. Final concentrations of THPI of 1000, 500, 200, 100, 50, 20, 10, 5 , 2 or 1 µg/ml were tested and solvent control and growth control plates were employed. The lowest test substance concentration that completely inhibited growth of the test organism was recorded as the MIC.

THPI demonstrated no antimicrobial activity towards *Bacteroides sp*., *Enterococcus faecalis* or *Candida albicans* when tested up to a concentration of 1000 µg/ml.

It may be concluded that THPI demonstrated no antimicrobial activity against organisms selected as representatives of rabbit GI tract flora species tested in this study. It is unlikely that this molecule has the potential to affect the micro-flora of the rabbit GI tract.

2) Their presence in significant amounts

a) National Milk Survey (Slesinski, R., S. and Wilson, A. E., 1992; IIA 7.3/07).

Samples of whole milk were collected from 224 retail outlets of different sizes, including supermarkets and convenience stores (but not wholesale outlets nor roadside stalls), from 48 different states in the USA at various times over a 12-month period (January to December 1991). The stores selected for sampling were taken at random from a database of 95,000 outlets representing 83.8% of all grocery store sales in 1989. Two samples of 1.9 L (sample 'A' and a back-up sample 'B') were purchased from each store by shoppers. The samples were packed in dry ice and transferred to the analytical laboratory and stored frozen until analysis. Control samples were obtained by the laboratory from local stores.

Each sample was analysed for captan, THPI, trans-3-hydroxy THPI and trans-5-hydroxy THPI. Captan residues were extracted with benzene, filtered, subjected to partition and column clean-up and then quantified using a gas chromatograph equipped with a halogen-specific Coulson Electrolytic Conductivity detector; the GC column was packed with 10% SP 2100 on 80/100 mesh Supelcoport. THPI, trans-3-hydroxy THPI and trans-5-hydroxy THPI residues were extracted with acetone, filtered, subjected to partition clean-up. The residues were derivatised by trimethylsilylation and quantified by gas chromatography on a DB-17 capillary column and a mass selective detector (MSD) operating in the selective ion mode. The LOQ for all analytes was 0.005 mg/L.

Acceptable recoveries were obtained from samples fortified at 0.005 and 0.01 mg/L..

Conclusion: Residues of captan, THPI, trans-3-hydroxy THPI and trans-5-hydroxy THPI were below the LOQ in all 224 milk samples.

b) Captan: Magnitude of Residue of captan metabolites in bovine meat and milk (Wiebe, L. A., 1991; IIA 7.3/08).

Captan technical active substance (purity 89.3%; batch number PJB-1601 CTCS) was administered orally in gelatine capsules daily in the feed for 29 days to groups of four Holstein dairy cattle at dietary concentration of 0, 10, 30 and 100 mg/kg diet. Milk was collected twice daily before treatment, on selective days during treatment, and one, three and six days after treatment. Three cattle from each group were sacrificed three hours after treatment was complete and the remaining one after an additional seven days. Concentrations of THPI, 3-OH THPI (*cis* and *trans*) and 5-OH THPI (*cis* and *trans*) were determined in tissues and milk using gas liquid chromatography with mass-selective detection.

For milk, there were 48 determinations for each of the analytes and mean recoveries for each metabolite at all fortification levels were 93 - 98%. For tissues there were 11 or 12 determinations for each of the analytes and mean recoveries for all fortification levels were 95 - 106% (fat), 91 - 105% (kidney), 67 - 83% (liver) and 95 - 101% (muscle).

In the residue study milk samples were extracted within 159 days of collection and tissue samples within 317 days of collection. In the stability test, there was no reduction in levels of captan metabolites following storage at -20°C in the different commodities for up to six months (milk) or four months (tissues). The results of later samplings are reported by Meyers and Wiebe (1995 - see Point B.7.6.4.b) and the residues were found to be stable in milk and tissues following storage at -20°C for at least three years.

No residues of the metabolites *cis*-3-OH THPI or *cis*-5-OH THPI were detected in milk or tissues following administration of captan.

Residues in milk plateaued on day 1 of administration for all dosing levels. Within one day after the end of dosing, residues were not detected in the milk following 10 and 30 mg captan/kg and within three days after dosing there were no residues in the milk following 100 mg captan/kg. Residue levels in tissues were generally similar to those in the milk though residues in the fat were lower. THPI was the major metabolite in fat, liver and muscle and trans-3-OH THPI occurred at higher levels than trans-5-OH THPI.

Total residues were calculated by adding the individual values for the metabolites, corrected for the molecular mass. Thus, THPI (molecular mass 151.2) and 3-OH THPI/5-OH THPI (molecular mass 167.2) are multiplied by 2.0 and 1.8, respectively, to convert metabolite residues to captan (molecular mass 300.6). Residues below the limit of determination (< 0.01 mg/kg) are assumed to be zero for the purposes of the addition. Total residues were 0.04 mg captan equivalents in milk and < 0.01 - 0.08 mg captan equivalents/kg in tissues following administration of 10 mg captan/kg for 29 days. Following administration of 30 mg/kg, residues in milk and tissues were 0.17 and 0.06 - 0.38 mg captan equivalents/kg; following administration of 100 mg/kg, residues in milk and tissues were 0.89 and 0.21 - 1.11 mg captan equivalents/kg.

After the end of dosing, residues in the tissues dissipated within seven days.

Average residues of captan metabolites in milk during and after the dosing period are given in Table B.7.3.6

Average residues of captan metabolites in milk during the dosing period and residues in tissues at the end of the 29-day administration period are given in Table B.7.3.7.

Table B.7.6: Residues in milk following administration of captan to dairy cow for 29 days

Day	Dose rate (mg/kg diet)	Mean residue in milk (mg/kg)				
		THPI	*trans*-3-OH THPI	*trans*-5-OH THPI	*cis*-3-OH THPI	*cis*-5-OH THPI
1	10	< 0.01	0.023	< 0.01	< 0.01	< 0.01
	30	0.028	0.083	0.013	< 0.01	< 0.01
	100	0.153	0.310	0.060	< 0.01	< 0.01
4	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.020	0.063	< 0.01	< 0.01	< 0.01
	100	0.160	0.245	0.035	< 0.01	< 0.01
7	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.025	0.063	< 0.01	< 0.01	< 0.01
	100	0.298	0.265	0.035	< 0.01	< 0.01
10	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.016	0.060	< 0.01	< 0.01	< 0.01
	100	0.190	0.183	0.025	< 0.01	< 0.01
14	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.030	0.060	< 0.01	< 0.01	< 0.01
	100	0.173	0.200	0.030	< 0.01	< 0.01
21	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.030	0.060	< 0.01	< 0.01	< 0.01
	100	0.198	0.210	0.033	< 0.01	< 0.01
28	10	< 0.01	0.018	< 0.01	< 0.01	< 0.01
	30	0.030	0.063	< 0.01	< 0.01	< 0.01
	100	0.208	0.225	0.035	< 0.01	< 0.01
30*	10	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	30	0.01	< 0.01	< 0.01	< 0.01	< 0.01
	100	0.02	0.10	< 0.01	< 0.01	< 0.01
32*	10	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	30	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	100	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

Residues in milk and tissues from untreated controls were below the limit of determination except for one milk sample which contained 0.02 mg THPI/kg on Day 10.
Values of < 0.01 mg/kg are assumed to be 0.005 mg/kg for calculation of means (unless all replicate values are < 0.01 mg/kg in which case the mean is given as < 0.01 mg/kg).
* After dosing; one animal only per dose (four animals per dose at other time points).

Table B.7.3.7: Residues in tissues and milk following administration of captan to dairy cow for 29 days

Commodity	Dose rate (mg/kg diet)	Mean residue (mg/kg)				
		THPI	*trans*-3-OH THPI	*trans*-5-OH THPI	*cis*-3-OH THPI	*cis*-5-OH THPI
milk	10	< 0.01	0.02	< 0.01	< 0.01	< 0.01
	30	0.03	0.06	< 0.01	< 0.01	< 0.01
	100	0.20	0.23	0.04	< 0.01	< 0.01
fat	10	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	30	0.03	< 0.01	< 0.01	< 0.01	< 0.01
	100	0.08	0.03	< 0.01	< 0.01	< 0.01
kidney	10	0.02	0.02	< 0.01	< 0.01	< 0.01
	30	0.09	0.09	0.02	< 0.01	< 0.01
	100	0.25	0.27	0.07	< 0.01	< 0.01
liver	10	0.02	< 0.01	< 0.01	< 0.01	< 0.01
	30	0.12	0.04	< 0.01	< 0.01	< 0.01
	100	0.31	0.11	< 0.01	< 0.01	< 0.01
muscle	10	0.02	0.02	< 0.01	< 0.01	< 0.01
	30	0.07	0.06	0.01	< 0.01	< 0.01
	100	0.24	0.18	0.04	< 0.01	< 0.01

Residues in milk and tissues from untreated controls were below the limit of determination except for one milk sample which contained 0.02 mg THPI/kg.

Conclusion, following administration of captan to dairy cattle at a dietary concentration of 10, 30 and 100 mg/kg for 29 days, total residues in milk over the dosing period were 0.04, 0.17 and 0.89 mg captan equivalents/kg. In tissues, residues following the three doses were < 0.01 - 0.08, 0.06 - 0.38 and 0.21 - 1.11 mg captan equivalents/kg, respectively, with the highest levels found in the kidney and the lowest levels in the fat. THPI was the major metabolite in most tissues and no residues of *cis*-3-OH THPI or *cis*-5-OH THPI were found in milk or tissues above the limit of determination. Residue levels of all metabolites reduced during the withdrawal period and following all dose levels were below the limit of determination in milk and tissues after three days and seven days, respectively.

c) Dietary Risk assessment of Captan Metabolites: THPI, 3-hydroxy and 5-hydroxy THPI

The dietary risk assessment for THPI and the 3-OH and 5-OH THPI metabolites was calculated based on the residues found in milk and meat from dairy cows fed 10 ppm captan The rate of 10 mg/kg diet is greater than the worst-case intake of captan (based on residues in pomace calculated from the MRL in apple) for beef and dairy cattle as shown below:

Captan is recommended in pome fruit, tomatoes and peaches/nectarines. Fruit pomace (apple) can be used for cattle feed at a maximum of a 10% of the diet in dairy cattle and a 30% of the diet in beef cattle. Captan is not recommended on any crops which are fed to hens or pigs.

The potential dietary exposure of dairy and beef cattle to captan is calculated below based on a worst-case (using the MRL) and a more realistic case (using the STMR) according to Commission Working Document 7031/VI/95 rev 4 of 22 July 1996.

Worst-case calculation of captan intake in cattle (based on MRL values)

Based on a MRL of 5 mg/kg for apple and a mean transfer factor of 1.1 in apple pomace (residue in pomace = 5.5 mg/kg), the maximum residue concentration in feed of beef cattle is 107.8 mg captan/animal/day (Table B.7.3.8). This gives an estimated daily feeding rate of 7.2 mg captan/kg diet (107.8/15), assuming 15 kg as the daily intake of dry matter for cattle of

350 kg body weight, or 0.31 mg/kg bw /day (107.8/350). The maximum dietary concentration is 5.5 mg captan/kg fresh diet (107.8/19.6).

For dairy cattle, the maximum residue concentration in feed is 47.85 mg captan/animal/day (Table B.7.3.8). This gives an estimated daily feeding rate of 2.4 mg captan/kg diet (47.85/20), assuming 20 kg as the daily intake of dry matter for cattle of 550 kg body weight, or 0.09 mg/kg bw /day (47.85/550). The maximum dietary concentration is 5.5 mg captan/kg fresh diet (47.85/8.7).

Table B.7.3.8: Worst-case calculation of captan dietary exposure level in cattle (based on MRL values)

Animal/ Crop commodity consumed	% Diet contribution (dry weight)	Intake of dry matter (kg/animal /day)[1]	% Dry matter content	Intake of fresh material (kg/animal/ day)[2]	Captan residue in commodity (mg/kg)	Intake (mg captan / animal/ day)[3]
Beef cattle/ Apple pomace	30	4.5	23	19.6	5.5	107.8
Dairy cattle/ Apple pomace	10	2.0	23	8.7	5.5	47.85

[1] % diet contribution x total intake (15 kg for beef cattle; 20 kg for dairy cattle).
[2] Dry matter intake corrected for dry matter content (23%).
[3] Intake of fresh material x captan residue.

Realistic calculation of captan intake in cattle (based on STMR values)

Based on a STMR of 1.3 mg/kg for apple and a mean transfer factor of 1.1 in apple pomace (residue in pomace = 1.4 mg/kg), the maximum residue concentration in feed of beef cattle is 27.44 mg captan/animal/day (Table B.7.3.9). This gives an estimated daily feeding rate of 1.8 mg captan/kg diet (27.44/15), assuming 15 kg as the daily intake of dry matter for cattle of 350 kg body weight or 0.08 mg/kg bw /day (27.44/350). The maximum dietary concentration is 1.4 mg captan/kg fresh diet (27.44/19.6).

For dairy cattle, the maximum residue concentration in feed is 12.18 mg captan/animal/day (Table B.7.3.9). This gives an estimated daily feeding rate of 0.6 mg captan/kg diet (12.18/20), assuming 20 kg as the daily intake of dry matter for cattle of 550 kg body weight or 0.02 mg/kg bw /day (12.18/550). The maximum dietary concentration is 1.4 mg captan/kg fresh diet (12.18/8.7).

Table B.7.3.9: Realistic calculation of captan dietary exposure level in cattle (based on STMR values)

Animal/ Crop commodity consumed	% Diet contribution (dry weight)	Intake of dry matter (kg/animal /day)[1]	% Dry matter content	Intake of fresh material (kg/animal/ day)[2]	Captan residue in commodity (mg/kg)	Intake (mg captan / animal/ day)[3]
Beef cattle/ Apple pomace	30	4.5	23	19.6	1.4	27.44
Dairy cattle/ Apple pomace	10	2.0	23	8.7	1.4	12.18

[1] % diet contribution x total intake (15 kg for beef cattle; 20 kg for dairy cattle).
[2] Dry matter intake corrected for dry matter content (23%).
[3] Intake of fresh material x captan residue.

Based on the dietary burden calculations, the worst-case and realistic case intakes for captan are summarised in Table B.7.3.10. The rate of 10 mg/kg diet as used in the feeding study is greater than the worst-case intake (and greater than the realistic intake) of captan for beef and dairy cattle.

Table B.7.3.10: Intake of captan in cattle

Animal	Calculated dietary intake (mg captan/kg diet)	
	Worst-case (based on MRL)	Realistic case (based on STMR)
Beef cattle	7.2	1.8
Dairy cattle	2.4	0.6

The following residues have been found in milk and meat from dairy cows fed 10 ppm captan (the estimated maximum dose, based on captan use and cattle feed components) (Wiebe, 1991):

Table B.7.3.11: Residues of THPI, 3-OH-THPI and 5-OH-THPI in meat and milk following administration of captan to dairy cow for 29 days

Commodity	Dose rate (mg/kg diet)	Mean residue (mg/kg)		
		THPI	3-OH THPI	5-OH THPI
milk	10	< 0.01 (0.005)*	0.02	< 0.01 (0.005)*
uscle	10	0.02	0.02	< 0.01 (0.005)*

Residues in milk and tissues from untreated controls were below the limit of determination except for one milk sample which contained 0.02 mg THPI/kg.

* Since the LOQ was 0.01 mg/kg, one half of the LOQ (i.e., 0.005 mg/kg) as worst case scenario was taken into consideration when residues were below the LOQ.

Estimation of the potential and actual exposure through diet and other means

Chronic exposure

Theoretical Maximum Daily Intake (TMDI)

The TMDI is calculated by multiplying the MRL/residues by the estimated average daily consumption for a given food commodity.

$TMDI = \sum MRL \times F$

where:
MRL = Maximum residue limit/residue for a given animal product
F = Consumption of that animal product.

This calculation is performed using:

1) An International diet (European Region) based on data from the World Health Organisation (WHO)[1].
2) The UK Dietary model (PSD, 1999[2])

[1] WHO (1989). Guidelines for predicting dietary intake of pesticide residues. Prepared by the joint UNEP/FAO/WHO Food Contamination Monitoring Programme in collaboration with the Codex Committee on Pesticide Residues. World Health Organisation, Geneva.

WHO European diet

The TMDI calculation is presented in Table B.7.3.12

Table B.7.3.12: Consumption of milk and meat based on WHO diet

Commodity	Consumption (kg/person/day)
Total milk	0.3408
Cattle meat	0.0633

Table B.7.3.13: TMDI calculation for THPI, 3-OH-THPI and 5-OH-THPI based on WHO diet

Commodity	THPI (mg/kg)	TMDI for THPI (mg/person/ day)	3-OH-THPI (mg/kg)	TMDI for 3-OH-THPI (mg/person/ day	5-OH-THPI (mg/kg)	TMDI for 5-OH-THPI (mg/person/day
Total milk	0.005	0.0017	0.02	0.0068	0.005	0.0017
Cattle meat	0.02	0.0013	0.02	0.0013	0.005	0.0003
Total TMDI		**0.0030**		**0.0081**		**0.0020**

The total TMDI for **THPI in milk and meat** will be max 0.0030 mg/person/day or **0.0000** mg/kg bw/day for a 60 kg adult.
The total TMDI for **3-OH-THPI** is 0.0081 mg/person/day or **0.0001** mg/kg bw/day for a 60 kg adult.
The total TMDI for **5-OH-THPI** is 0.0020 mg/person/day or **0.0000** mg/kg bw/day for a 60 kg adult.

UK diet

UK consumption data of animal products for adults, children, toddlers and infants (mean consumers and high, i.e. 97.5th percentile, consumers) are presented in Table B.7.3.14.

Table B.7.3.14: UK consumption data for adults, children, toddlers and infants

Comm-odity	Consumption data (kg/day)							
	Adults (70.1 kg bw)		Children (43.6 kg bw)		Toddlers (14.5 kg bw)		Infants (8.7 kg bw)	
	Mean	High [1]	Mean	High	Mean	High	Mean	High
Milk	0.2573	0.6659	0.0304	0.6745	0.3064	0.8017	0.3377 5	0.8719
Meat	0.0841	0.2050	0.0641	0.1339	0.0276	0.0869	0.1339	0.0121

Since the milk and meat consumption (high levels) by toddlers and infants represents the worst case for risk assessments. The TMDI for THPI and hydroxylated THPI metabolites was calculated for these sub- populations.

[2] PSD (1999). Guidance on the estimation of dietary intakes of pesticides residues. The Registration Handbook. Pesticides Safety Directorate, Ministry of Agriculture, Fisheries and Food.

Table B.7.3.15: TMDI calculation for THPI for toddlers and infants based on UK high consumption intakes

Commodity	THPI (mg/kg)	TMDI (mg/kg bw/day)	
		Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
Milk	0.005	0.0003	0.0005
Meat	0.02	0.0001	0.0000
Total exposure		**0.0004**	**0.0005**

The TMDIs of THPI are 0.0004 mg/kg bw/day (toddlers), 0.0005 mg/kg bw/day (infants).

Table B.7.3.16: TMDI calculation for 3- OH-THPI for toddlers and infants based on UK high consumption intakes

Commodity	3-OH-THPI (mg/kg)	TMDI (mg/kg bw/day) [1]	
		Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
milk	0.02	0.0011	0.0020
meat	0.02	0.0001	0.0000
Total exposure		**0.0012**	**0.0020**

The worst case for TMDIs for milk and meat of 3-OH-THPI are 0.0012 mg/kg bw/day (toddlers), 0.0020 mg/kg bw/day (infants).

Table B.7.3.17: TMDI calculation for 5-OH-THPI for toddlers and infants based on UK high consumption intakes

Commodity	5-OH-THPI (mg/kg)	TMDI (mg/kg bw/day) [1]	
		Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
milk	0.005	0.0003	0.0005
meat	0.005	0.0000	0.0000
Total exposure		**0.0003**	**0.0005**

The worst case TMDIs from milk and meat of 5-OH-THPI are 0.0003 mg/kg bw/day (toddlers), 0.0005 mg/kg bw/day (infants).

Comparison of TMDI with ADI

The worst case TMDI values of THPI, 3-OH-THPI and 5-OH-THPI for the most sensitive consumer groups and diets are summarised in table B.7.3.18.

Table B.7.3.18: TMDI values for different consumer groups and diets

Diet	Body weight (kg)	TMDI (mg/kg bw/day)		
		THPI (%ADI)	3-OH-THPI (%ADI)	5-OH-THPI (%ADI)
WHO adult	60	0.0000 (0)	0.0001 (0.1)	0.0000 (0)
UK toddler	14.5	0.0004 (0.4)	0.0012 (1.2)	0.0003 (0.3)
UK infant	8.7	0.0005 (0.5)	0.0020 (2.0)	0.0005 (0.5)

Based on the proposed ADI for captan of 0.1 mg/kg bw/day, the TMDI for THPI represents 0% to 0.5% of the ADI for the most sensitive consumer groups and different dietary intakes.

Based on the proposed ADI for captan of 0.1 mg/kg bw/day, the TMDI for 3-OH- THPI represents 0.1% to 2% of the ADI for the most sensitive consumer groups and different dietary intakes.

Based on the proposed ADI for captan of 0.1 mg/kg bw/day, the TMDI for 5-OH- THPI represents 0% to 0.5% of the ADI for the most sensitive consumer groups and different dietary intakes.

Conclusion

The maximum possible daily intake of THPI, -3-OH-THPI and 5-OH-THPI (taking into consideration the most sensitive population group) are very low and significantly lower than the ADI for captan for the most sensitive consumer groups for animal products.

There is therefore a large margin of safety for all consumer groups.

d) Toxicity of THPI to aquatic organisms

NOTE: The summaries below already appear in the DAR under B.9.2 Effects on aquatic organisms (Annex IIA 8.2; Annex IIIA 10.2), B.9.2.1 Acute toxicity to aquatic organisms

(i) THPI: acute toxicity to rainbow trout (Oncorhynchus mykiss) (Kent, S.J. et al. 1994a; IIA, 8.2.1/10; IIA 7.3/09)

The 96-hour acute toxicity of THPI (metabolite of captan; purity 96% w/w) to the rainbow trout (*Oncorhynchus mykiss*) was determined in a limit test with a static system with aeration. Groups of ten fish in 27.5 L glass tanks containing 20 L test solution (15°C, 16:8 hour light/dark regime) were exposed to a nominal concentration of THPI (dissolved in [redacted] at 120 mg/L in comparison with a dilution water only (dechlorinated filtered tap water, total hardness approx. 27 mg $CaCO_3$/L) control and a solvent only (100 µL [redacted] L) control for four days. The fish were not fed for 24 hours prior to, or during, exposure. The test solutions were not changed during the study. Samples of the test solutions were taken for analysis of the THPAM content (by HPLC) at the start of exposure and after 48 and 96 hours. Measurements of pH, dissolved oxygen and temperature were taken daily. Mortality and behaviour were recorded at 24-hour intervals after the start of exposure.

The study met the essential criteria of OECD 203. One fish used in the water only control was slightly smaller than recommended (50 ± 10 mm) but this is not considered to have affected the validity of the study. It was conducted according to Good Laboratory Practice.

The mean measured concentration of THPI in the dosed medium was 100% of the nominal value and so the results are presented as nominal values. The physical and chemical parameters of the test solutions remained at expected values during the study (pH 7.3 to 7.8 for both treatments).

There were no symptoms of toxicity or mortalities during the study.

Conclusion: The 96-hour LC_{50} of THPI to the rainbow trout under static conditions was greater than 120 mg/L. The NOEC was equal to or greater than120 mg/L based on the absence of toxicological symptoms observed at the dose tested. The 24, 48 and 72-hour LC_{50} values were also greater than 120 mg/L.

(ii) Captan: acute toxicity to rainbow trout (Jenkins, C.A. 2002a; IIA, 8.2.1/03; IIA 7.3/10)

The 96-hour acute toxicity of captan technical (purity 95.2% w/w) to rainbow trout (*Oncorhynchus mykiss*, mean wet weight 1.9 g, mean fork length 5.3 cm) was determined in a static test system without replacement of the test medium. Groups of seven fish in glass aquaria containing 35 L of test medium (12 to 17°C, 16:8 hour light/dark regime) were exposed to nominal concentrations of captan (dissolved in [redacted] at 30.1, 66.1, 145, 320 and 704 µg/L in comparison with a dilution water control treatment (dechlorinated, softened tap water, total hardness approximately 180 mg $CaCO_3$/L) and a solvent control treatment (100 µL [redacted] L) for four days. The fish were not fed for 21 hours prior to, or during, exposure. Samples of the stock solutions (captan in [redacted] were taken for analysis of captan by HPLC at the start of the test. Measurements of pH, dissolved oxygen and temperature were taken daily in all test vessels and hardness was measured at the start of the test. Temperature was monitored continuously in the control medium. Mortality and behaviour were recorded at 15 minutes, 2, 4, 24, 48, 72 and 96 hours after the start of exposure.

The study met the essential criteria of OECD 203 and EC Methods Part C 1. It was conducted according to Good Laboratory Practice.

Measured concentrations of captan in the stock solutions ranged from 91 to 102% of the nominal values. The results of the toxicity test are based on nominal concentrations of captan. The physical and chemical parameters of the test media remained at expected values during the study (pH 7.8 to 8.5, dissolved oxygen 88 to 106 % ASV, temperature 12.4 to 13.5°C and total hardness 178 to 180 mg $CaCO_3$/L).

At 320 and 704 µg/L, all fish exhibited hyperventilation within 15 minutes of exposure and were dead at 24 and four hours, respectively. At 66.1 and 145 µg/L, all fish were affected within 24 hours of exposure, exhibiting hyperventilation, darkened pigmentation and/or lethargy. Between 72 and 96 hours, some fish at 145 µg/L and six out of seven fish at 66.1 µg/L appeared to have recovered and were normal. At 30.1 µg/L, all fish appeared normal throughout the test. The darkened pigmentation in fish in the control treatments was ascribed to aggressive behaviour by one fish in each vessel. When the aggressive fish was screened from the other fish they appeared normal.

Conclusion: The 96-hour LC_{50} of captan technical to rainbow trout under static test conditions was 0.215 mg/L (with 95% confidence limits of 145 to 320 µg/L). Adjusting for the purity of captan in captan technical (95.2 %), the 96-hour LC_{50} was 0.205 mg/L (with 95% confidence limits of 0.138 to 0.305 mg/L). The NOEC was 0.0301 mg/L based on reversible toxic symptoms at 0.0661 mg captan technical/L.

A comparison of the toxicity of captan and THPI to rainbow trout is given in Table B.7.3.19. **Captan is more toxic to fish than THPI with a ratio of >500-fold.**

Table B.7.3.19: Summary of acute toxicity of captan and THPI to rainbow trout

Compound	LC_{50} (mg/L)	Reference
captan	0.215	Jenkins, C.A. 2002a; IIA, 8.2.1/03; IIA 7.3/08
THPI	> 120	Kent, S.J. et al. 1994a; IIA, 8.2.1/10; IIA 7.3/07

B.7.17 References relied on

B.7.17.1 Active substance

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
IIA, 7.3/01	Elsea, J.R.	1955	Tetrahydrophthalimide: Acute oral administration - rats. [redacted] Not GLP; Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/02	Carver, J.H.	1986	Microbial/mammalian microsome mutagenicity plate incorporation assay with tetrahydrophthalimide. Chevron Chemical Company, unpublished report No. CEHC 2618, 27 (Company file: R-4409/TMN-0863). GLP; Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/03	Kennedy, G., Fancher, O. E., Calandra, J. C.	1968	An investigation of the teratogenic potential of captan, folpet, and difolatan. *Toxicology and Applied Pharmacology* **13**, 420-430. (Company file R-0169) Not GLP; Published.	N	-
IIA, 7.3/04	Blee, M.A.B.	2006	THPI: Prenatal toxicity study in the rabbit by oral gavage administration. Company file: Report MAK 864/053232. (Company file: R-18202) GLP, Unpublished.	Y	Makhteshim
IIA, 7.3/05	Chaudhry, Q.	2005	Assessment of the activity, toxicity and mutagenicity potential of THPI and THPAM, using structure activity relationships. Central Science Laboratory, report dated 4 February 2005 (Company file: R-18028). Not GLP, Unpublished	Y	Makhteshim
IIA, 7.3/06	Akhurst, L.C.	2005	THPI: Determination of minimum inhibitory concentrations against selected micro-organisms representative of the rabbit gut micro-flora. Report MAK 890/053252 (Company file: R-18735). GLP, Unpublished	Y	Makhteshim
IIA, 7.3/07	Slesinski, R., S., Wilson, A. E	1992	National Milk Survey. Technical Assessment Systems, Inc., Washington, DC, Report 92-01. (Company file R-6147). GLP; Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/08	Wiebe, L.A.	1991	Captan: Magnitude of the residue of captan metabolites in bovine meat and milk. [redacted] unpublished report No. RR 91-033B (Company file: R-6730/TMN-0355). GLP; Unpublished.	Y	Makhteshim/ Arysta Paris

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
IIA, 7.3/09	Kent, S.J., Sankey, S.A., Caunter J.E., Magor, S.E.	1994a	THPI: acute toxicity to rainbow trout (*Oncorhynchus mykiss*). [redacted] Report BL5237/B. (Company file: R-8288/TMN-0025). GLP, Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/10	Jenkins, C.A,	2002a	Captan: acute toxicity to rainbow trout. [redacted] Report MAK660/013072. (Company file: R-12335/TMN-0020A). GLP, Unpublished.	Y	Makhteshim/ Arysta Paris

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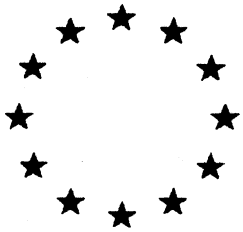


ECCO-Meetings

Captan

Volume 3

Annex B
Addendum: definition of the residue

Rapporteur Member State: Italy

B.7.3 Definition of the residue (Annex IIA 6.7; Annex IIIA 8.6)

Captan: The residue definition for the fungicide captan should be captan only as the metabolites THPI, 3-OH-THPI and 5-OH-THPI are neither of toxicological significance nor pose a significant dose to humans,.

The collective data (toxicological data and residue data leading to estimated dose to humans) support the conclusion that the residue definition for captan should be **captan only**.

The DG SANCO Guideline notes (European Commission, 1997): Residue Definition – Of the three general considerations that are fundamental to the decision as to whether or not specific metabolites/degradation products should be included in the definition and expression of a residue, two are relevant to this discussion:
(1) Their basic toxicology and
(2) Their presence in significant amounts.

Introduction
Captan was discussed at the December 10-13, 2007 EFSA meeting (PRAPeR 2007). At issue is the Definition of the Residue; specifically, whether the definition should include captan only or captan with one or more degradates.

The decision on whether one or more degradates should be part of the residue definition rests on the toxicity of these compounds and whether their respective toxicities exceed the threshold level of concern that triggers inclusion.

Analysis of data related to this issue has been ongoing. It was earlier proposed that the residue definition should be captan + THPI:
The metabolism of captan in plants has been adequately elucidated. Captan forms the major part of residue and only one metabolite, THPI has been identified as contributing in a significant way to the toxicological burden. The levels of THPI are drastically increased in case of processing of treated commodities involving a heating step. However the information on the behaviour of captan under processing conditions should be further investigated by degradation studies under representative hydrolytic conditions.

"Although argumentation has been presented tending to demonstrate that THPI is of lower toxicity than the parent compound, the available data are not sufficient to firmly conclude on its toxicological non relevance. Therefore the residue definition in plant commodities should be the sum of captan and THPI" (EFSA 2006).

The Rapporteur Member State proposes that the residue definition should be captan, only:
Captan: The residue definition for the fungicide captan should be captan only as the metabolites THPI, 3-OH-THPI and 5-OH-THPI are neither of toxicological significance nor pose a significant dose to humans.

The collective data (toxicological data and residue data leading to estimated dose to humans) support the conclusion that the residue definition for captan should be captan only (EC 2008).

The most recent discussion resulted in a request for additional data or argumentation regarding the toxicological significance of captan's degradates as they impact the residue definition.

The Chairman reported that there were three crop metabolites under discussion, THPI, 3OH - THPI and 5 OH -THPI. For the first one there was an acute oral study, two *in vitro* bacterial genotoxicity tests and a developmental study available while for the latter two no studies were existing.

EFSA reported that in groundwater THPI and THPAM (another captan metabolite) were found and consequently according to SANCO/221/2000 – rev10, further information on would be required on those two metabolites (see EFSA conclusion, March 2006).

It was agreed that the RMS provides further information on the following endpoints on the metabolites THPI, 3OH -THPI and 5 OH-THPI: Acute toxicity, genotoxicity, carcinogenicity, relevance of dog study and developmental effects in comparison to the parent compound (PRAPeR 2007).

This discussion document discusses captan's degradates THPI, 3-OH THPI, 5-OH-THPI and THPAM and concludes that captan's residue should be defined as parent only.

Definition of the Residue

There are competing needs when one sets out to define the definition of the residue (OECD 2006). On one hand there is the desire to consider the toxicity of the parent as well as the toxicity of all metabolites, degradates or other transformation products such that a sound risk assessment can be made and all relevant metabolites/degradates included. On the other hand there is the practical matter of defining the MRL such that it can, in fact, be monitored.

Guidance provided by OECD on the definition of the residue, as it relates to toxicity, includes the following (OECD 2006):
In order to assess metabolite/degradate toxicity and determine its potential effects, available information on the metabolite/degradate or similar compounds in databases or publications is evaluated. In most cases, however, toxicity data specific to the metabolite/degradate in question are not available or are limited to acute oral median lethal dose tests. In these instances weight of evidence evaluations are used to assess the toxic potential of the metabolite/degradate relative to that of the parent compound. The goal is to predict whether the metabolite/degradate is likely to be significantly less toxic than the parent, have comparable toxicity, be potentially significantly more toxic than the parent, or possess a different mechanism of toxicity. In many instances, it will not be clear as to whether a metabolite/degradate has the same mechanism of toxicity and/or how the level of toxicity would compare to that of the parent. The default position in such cases would be that the metabolite/degradate elicits the same effect as the parent and at comparable doses (i.e., equal toxicity) (OECD 2006).

Captan Degradates

There are limited toxicological data on captan degradates, particularly 3-OH-THPI and 5-OH-THPI. Fortunately, analysis of the chemical properties of these degradates, compared to the parent compound, captan, provide insights into their respective toxicity spectrum.

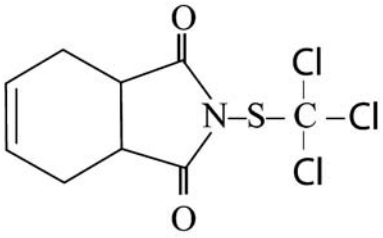
<u>The basis of captan's toxicity</u>

Both acute and chronic toxicity endpoints are directly associated with the chemical structure of captan and its interaction with biological materials. Specifically, it is the trichloromethylthio, TCMT, moiety that is responsible for both its pesticidal action and mammalian toxicity. The TCMT moiety reacts with thiol groups resulting in the denaturing of proteins and the degradation of captan. The reactive product of this degradation, thiophosgene, continues the degradation of thiols as well as other functional groups. The relatively stable product of this degradation is tetrahydrophthalimide, THPI, the carrier end of the molecule for TCMT.

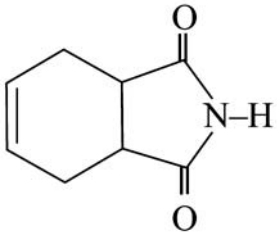
The stable degradates THPI and its further metabolites 3-OH-THPI and 5-OH-THPI do not contain TCMT; do not react with thiol groups; do not generate thiophosgene; and, cannot, therefore, induce toxicity reactions that mimic the parent. This is not so evident from acute toxicity, since both parent and degradates are relatively non-toxic; but it is quite evident from mutagenicity studies, repeat dose studies, and developmental toxicity studies. Absent the compound-specific data that EFSA seeks, we ask the Experts to reconsider the physical/chemical properties of captan and its degradates and the reasoned expectation of toxicity (supported by available studies, particularly with THPI) that captan's degradates/metabolites are not of toxicologic concern and should not be part of the Definition of Residue.

<u>Comparative structures</u>

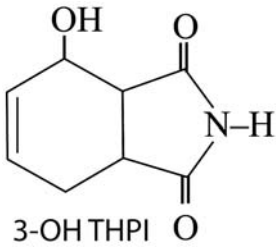
The structures of captan and its degradates/metabolites are noted below.



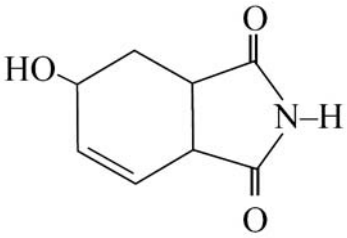
Captan



THPI

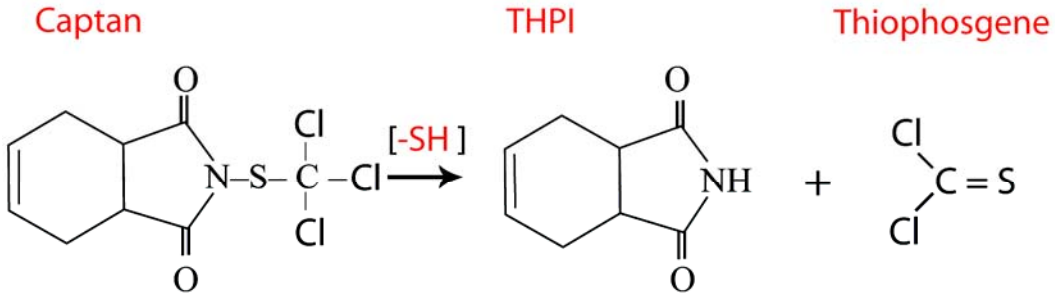


3-OH THPI



5-OH THPI

Note that the main degradate (THPI) and secondary metabolites (3-OH and 5-OH THPI) do not contain the trichloromethylthio moiety and cannot replicate the chemical reaction that characterizes captan's toxicity:



Captan Metabolism

It is the process by which THPI is generated that is responsible for the irritative nature of captan.

Toxicity of Captan's metabolites.

Acute toxicity
Both captan and THPI have acute oral toxicity values greater than 5 g/kg bw. Acute toxicity of the hydroxyl THPI metabolites are not available but it is expected that these, also, will have low toxicity.

Both captan and THPI have low oral toxicity and it can be judged that THPI's hydroxy metabolites also have low oral toxicity.

Genotoxicity
There is a stark difference between captan and THPI with regard to genotoxicity when assayed by *in vitro* test systems. Captan is mutagenic *in vitro* while THPI is not mutagenic. The mutagenicity has been associated with the generation of thiophosgene (Lukens 1966, Rideg 1982).

THPI, 3-OH THPI and 5-OH THPI do not react with thiols, do not generate thiophosgene and are not mutagenic (THPI)(Carver 1985) or expected to be mutagenic (3-OH THPI and 5-OH THPI).

It can be concluded that THPI and its hydroxy metabolites are not genotoxic.

Carcinogenicity
Captan induces gastrointestinal tumors in mice, primarily in the duodenum. Mechanistic data have been developed that elucidate the mode of action (MOA) responsible for these tumors. The salient features of the MOA are:

- Captan is not mutagenic *in vivo.*
- Captan is a local irritant to the villi of the duodenal lining.
- Villi are damaged and sloughed off into the duodenal lumen.
- The basal cells of the duodenal crypts respond with marked proliferation.
- Transformed cells, normally dormant, are resident in the crypt compartment.
- Increased proliferative pressure promotes these transformed cells to tumors.

Corollaries to this MOA include:

- Captan's local irritation is due to the trichloromethylthio moiety (TCMT)
- The TCMT moiety is essential for the development of tumors.
- A threshold exists for TCMT-induced irritation and subsequent tumors.
- THPI, lacking TCMT, cannot replicate captan's MOA for tumor induction.

- THPI, therefore, cannot be carcinogenic in a similar way to captan.

This MOA has been reviewed by outside Experts and by the US EPA. The supporting data were sufficiently robust as to have EPA revise their cancer classification of captan. In announcing this reclassification, EPA wrote:

"In 2004, the CTF (Captan Task Force) submitted the results of the Peer Review Panel meeting to the EPA for review. EPA reviewed this information and determined that the weight of evidence indicates that captan's carcinogenicity is limited to a single tumor type (adenomas and adenocarcinomas in the small intestine, primarily the proximal portion of the duodenum) in both sexes of a single species (mouse). EPA agreed that the results of the rat bioassays provide no evidence that captan is associated with kidney tumors in male rats or uterine tumors in female rats, and, therefore, these tumors do not add to the weight-of-evidence considerations of the carcinogenicity of captan.

"The Agency accepts the proposed mode of action as set forth by the CTF that suggests that "captan induces adenomas and adenocarcinomas in the duodenum of the mouse by a nongenotoxic mode of action involving cytotoxicity and regenerative cell hyperplasia that exhibits a clear dose threshold. These responses are reversible following cessation of captan exposure. There is a strong causal association (dose-response, temporality) indicating that tumor formation is secondary to cytotoxicity and hyperplasia and that the latter s a key event in the sequential cascade of events leading to cancer" (US EPA 2004).

Oncogenicity studies with THPI or its hydroxy metabolites have not been conducted (although these compounds were tested by way of captan's degradation / metabolism in the bioassays). The fact that there were no systemic tumors, judged treatment-related, attests to the fact that captan's degradates are not carcinogenic. In essence:

- Essentially 100% of captan fed to rodents is degraded to THPI.
- Oral administration of captan, therefore, results in systemic dosing of THPI.
- THPI is metabolized in mammals to 3-OH and 5-OH THPI; thus,
- Rodent bioassays with captan test for the systemic carcinogenicity of THPI and its metabolites.
- Rodent bioassays do not produce evidence of systemic tumors.

It can be concluded that THPI and its hydroxy metabolites are not carcinogenic.

<u>Relevance of dog study in comparison to the parent compound</u>
The one-year dog study with captan showed that the fungicide was tolerated well (Blair 1988). The NOAEL was determined to be 300 mg/kg bw/day, the highest dose tested (doses: 0, 12.5, 60, or 300 mg/kg bw/day by capsule administration).

In the four-week range-finding study at 0, 30, 60, 300, 600, or 1000 mg/kg bw/day, animals administered 300 mg/kg bw/day and above had higher rates of emesis (Blair 1987). There was a treatment-related decrease in body weight at 300, 600 and 1000 mg/kg bw/day but no effects on hematology, clinical chemistry, urinalysis or macroscopic changes. One of the two males at 1000 mg/kg bw/day showed fatty changes in the liver and the collecting tubules of the kidneys.

There are no comparable dog studies with THPI or its hydroxy metabolites (although, as before, the dogs were exposed to both THPI and its metabolites via the degradation and metabolism of captan). In fact, *only* THPI and its hydroxy metabolites were present systemically in the dog. This follows from the rapid degradation of captan as soon as it is exposed to blood (Gordon et al. 2000).

It can be concluded that THPI and its hydroxy metabolites are not toxic to the dog.

Relevance of developmental effects in comparison to the parent compound
Captan is not a frank teratogen, but has been associated with secondary developmental delays in fetuses associated with primary maternal toxicity. The maternal toxicity is due to the irritative nature of captan on the gastrointestinal tract. This is particularly important in rabbits where captan not only may induce irritation, but it also can adversely affect the intestinal bacterial flora that is critical for optimum nutrition, e.g., the MIC assays (Akhurst 2005).

THPI is not teratogenic, nor does it induce maternal toxicity at equivalent captan doses (Blee 2006). The question of dose selection for the THPI developmental study and its relevance to maternal toxicity is addressed below.

Dose selection for the THPI study.
Doses for the special developmental study with THPI (Blee 2006) were selected considering the degradation toxicokinetics of captan and the toxicological question posed. In summary,

- The purpose of the study was to investigate whether THPI, *generated from the administered captan*, contributed to the effects seen in rabbits.
- Captan decomposes to THPI in a stochiometric manner (one molecule captan results in one molecule THPI); thus, on a mg/kg bw basis the ratio of doses is approximately 2:1 (captan molecular weight: 300.5; THPI molecular weight: 151.1).
- A bolus dose of captan results in a slow increase of systemic THPI as captan is degraded in the intestine and as it is absorbed into blood and degraded.
- In comparison, a bolus dose of THPI results in a marked increase in systemic THPI, since it is water soluble and readily absorbed; thus, bolus dosing of THPI at levels even below half that of the bolus captan dose would be expected to produce peak blood levels far in excess of those produced by captan alone.
- Since the developmental toxicity of THPI was investigated at captan-relevant doses, the issue of maternal toxicity was moot.

Since systemic dosing of THPI results in the generation of 3-OH and 5-OH THPI, all three degradation products were tested in the rabbit developmental study with THPI.

It can be concluded that THPI and its hydroxy metabolites are not developmental toxins.

Discussion
The rationale for not including captan's metabolites in the residue definition has been set forth (EC 2008). These include the low toxicity of these compounds, the lack of structural alerts upon QSAR analysis, and the comparative MIC data:
Captan: The residue definition for the fungicide captan should be captan only as the metabolites THPI, 3-OH-THPI and 5-OH-THPI are neither of toxicological significance nor pose a significant dose to humans.
The collective data (toxicological data and residue data leading to estimated dose to humans) support the conclusion that the residue definition for captan should be **captan only**.

Analysis of the basic chemistry of captan and its degradates supports the RMS recommendations. Neither THPI nor its hydroxy metabolites have the reactive TCMT moiety that is responsible for captan's fungicidal and mammalian toxicity.

Conclusion
In all toxicological studies where comparisons can and have been made, captan is responsible for noted effects, not its degradates / metabolites: THPI, 3-OH THPI, or 5-OH THPI. Studies include mutagenicity, developmental toxicity, carcinogenicity, Minimum Inhibitory Concentration (in vitro), and repeat dose studies in dogs.

The Residue Definition for captan that best reflects its toxicity and the toxicity of its degradates is "captan only."

1) THPI basic toxicology

Four lines of evidence show that the metabolites of captan are not of toxicological significance:
a) Direct measurements of toxicity.
b) QSAR Analysis
c) Measurement of minimal inhibitory concentration (MIC)
d) Comparison of captan and its major metabolite in bioassays that are particularly sensitive to the toxicological properties of captan.

a) Direct measurements of toxicity

THPI is not acutely toxic. Its LD50 in rats is above 10 g/kg bw (Elsea, 1955). Its lack of reactive functional groups is consistent with this low oral toxicity.

While both captan and THPI are relatively nontoxic to mammals, the differential toxicity that is due to irritation is noted when assayed in systems sensitive to this endpoint.

THPI is not mutagenic. When tested in the multiple strains in the Ames Assay, it is negative (Carver, 1986).

THPI has effectively been tested in both short-term and lifetime studies since administration of captan results in the systemic presence of THPI, THPI metabolites.

There are no target organs of toxicity nor endpoints of concern identified with the administration of THPI and THPI metabolites (as captan) other than generalized effects such as decrease in weight gain. THPI (captan) is not a systemic carcinogen.[3] In dietary toxicity studies with captan, the primary target organ is the gastrointestinal tract. The initial endpoint is irritation of the intestinal mucosa due to the interaction of captan and its reactive degradate, thiophosgene, with thiols associated with the epithelial cells of the duodenum. THPI is the compound that is absorbed systemically when captan is administered. THPI and its metabolites, 3-OH-THPI, 5-OH-THPI, and THPAM acids account for the bulk of the administered captan dose and are excreted in the urine. Captan is not detected in the urine. Effects observed in the gastrointestinal tract are the result of captan and thiophosgene while systemic effects are the result of either secondary toxicity due to the primary GI irritation or to direct actions of THPI and its metabolites. Generalized weight depression is judged a secondary effect of captan, not a primary effect of THPI.

THPI is not a developmental toxin. When tested at 75 mg/kg bw/day in Dutch Belted rabbits (Kennedy *et al.,* 1968) or 22.5 mg/kg bw/day in New Zealand white rabbits (Blee, 2006), developmental abnormalities were not seen.

b) QSAR Analysis

THPI does not have structural alerts that indicate this metabolite poses a toxicological risk (Chaudry, 2005).

[3] **The carcinogenicity of captan in the mouse is due to the parent compound, not THPI or THPI metabolites.**

The hydroxylation of organic structures is considered a detoxification mechanism since hydroxylation makes a compound more polar which increases the potential for molecular conjugation and consequently facilitates excretion; thus, the hydroxylated metabolites of THPI are considered less toxic than THPI (*www.isu.edu/~watwmari/detox.doc*).

c) Measurement of minimal inhibitory concentration (MIC)

The MIC assay is designed to assess antimicrobial activity and efficacy *in vitro*. The study was deigned to assess the effects of THPI on micro-flora representative of that in the rabbit GI-tract. Ten species of *Bacteroides* and four isolates of *Candida albicans* were incubated in the presence of THPI at biologically significant concentrations. THPI had no antimicrobial activity (Akhurst, 2005).

d) Comparison of captan and its major metabolite in fish bioassays that are particularly sensitive to the toxicological properties of captan.

The most sensitive bioassays for measuring toxicity of captan are those involving aquatic organisms. This follows from the mode of action of captan, which is irritation-based, due to its reactivity of the captan side chain with the thiol group. This reactive side chain is not present on the THPI metabolite. This high reactivity of the side chain of captan produces irritation to the tissues as well as to gill membranes in fish. THPI, has low reactivity and is not an irritant.

THPI was found to be non-toxic to fish species tested. The rainbow trout LC_{50} assay is able to distinguish the toxicity of captan and THPI in a dramatic way. The data for captan and THPI are noted below (Jenkins, 2002,Kent, 1994):

Rainbow trout 96 hour Static LC_{50}:

Captan	0.215 mg/L
THPI	>120 mg/L

Ratio of THPI toxicity to captan toxicity is >500-fold. This decrease in toxicity attests to the relative innocuous character of THPI compared to the parent, captan.

In conclusion, THPI poses no significant toxicological risk for adverse effects.

2) Their presence in significant amounts

Plants

The metabolism of captan in plants proceeds according to the pathway shown below and each of the metabolites formed is also observed as a metabolite of captan in mammalian studies. No plant unique metabolites are formed.

Captan → THPI → THPAM → conjugation and incorporation into natural products

The metabolite THPI was present at levels less than 10% of the total radioactive residue in radiolabelled studies conducted in tomatoes, lettuce and apples. These residues of THPI are not considered significant in relation to the amount of captan present. The metabolites 3-OH-THPI and 5-OH-THPI were not detected in measurable amounts in plant studies and therefore do not form a significant pathway of metabolism in plants. These metabolites are observed more prominently in mammalian species due to their higher metabolic capacity compared to plants.

A summary of the residues is shown in the following tables.

Summary of Radioactive Residues in Tomato Fruit Following Treatment of Plants with Captan (report No. MEF-0009/8808900; Company file: R-4992/TMN-0394 and report No. MEF-0010/8805420: Company file: R-4993/TMN-0393)

Identity	^{14}C-Trichloromethyl label	^{14}C-Cycohexene ring label

	% TRR	ppm	% TRR	ppm
Captan	76.6	5.29	81.5	5.48
Captan epoxide	0.2	0.01	0.4	0.03
THPI	--	--	4.5	0.30
Other free metabolites	9.5[a]	0.66	5.2[c]	0.35
Polar and/or conjugates	10.4[b]	0.72	7.5[d]	0.50
Non extractable residues	3.3	0.23	0.9	0.06
Total radioactive residue	--	6.90	--	6.72

a Multi-component, at least 8 metabolites.
b Multi-component, 9% show to contain at least 5 metabolites.
c Multi-component, at least 9 metabolites.
d Multi-component, at least 4 metabolites.

Summary of Radioactive Residues in Lettuce Leaves Following Treatment of Plants with Captan (report No. MEF-0009/8808900; Company file: R-4992/TMN-0394 and report No. MEF-0010/8805420: Company file: R-4993/TMN-0393)

Identity	^{14}C-Trichloromethyl label		^{14}C-Cycohexene ring label	
	% TRR	ppm	% TRR	ppm
Captan	76.2	52.2	77.2	49.7
Captan epoxide	0.3	0.21	0.6	0.39
THPI	--	--	9.5	6.12
THPI epoxide	--	--	0.9	0.58
Other free metabolites	5.2[a]	3.56	4.3[c]	2.77
Polar and/or conjugates	4.6[b]	3.15	4.5[d]	2.90
Non extractable residues	13.7	9.39	3.0	1.93
Total radioactive residue	--	68.5	--	64.4

a Multi-component, at least 7 metabolites.
b Multi-component, at least 4 metabolites.
c Multi-component, at least 7 metabolites.
d Multi-component, at least 3 metabolites.

Summary of Radioactive Residues in Apple Fruit Following Treatment of Trees with Captan (report No. MRC-B-44; Company file: TMN-0396)

Identity	**^{14}C-Carbonyl label**						
	Fruit wash		**Peel**		**Pulp**		**Total**
	% TRR	**ppm**	**% TRR**	**ppm**	**% TRR**	**ppm**	**%TRR**
Captan	70.78	--	1.65	1.348	0.16	0.029	72.6
Captan epoxide	<0.90	--	0.02	0.019	0.14	0.025	<1.1
THPI	5.11	--	0.75	0.308	0.78	0.069	6.6
THPI epoxide	<0.90	--	0.10	0.047	0.01	0.001	<1.0
THPAM	0.35	--	0.53	0.241	0.05	0.005	0.9
Uncharacterised[a]	11.56	--	1.44	--	1.56	--	14.6
Residue	--	--	2.60	--	0.7	--	3.3
Total	89.6	--	7.1	--	3.4	--	100.1

Results from Tree No. 3 harvested 20 days after treatment, most relevant to GAP.
a Containing several products more polar than captan but not identified as any known metabolites.
% TRR values shown were re-calculated from results in the original report which were expressed as a percentage of the relative amount of radioactivity in each extract.

Animals

The following maximum residues have been found in milk and meat from dairy cows fed 10 ppm captan (the estimated maximum dose, based on captan use and cattle feed components) (Wiebe, 1991):

	Metabolite		
	THPI	3-OH-THPI	5-OH-THPI
Milk	<0.01	0.02	<0.01 mg/kg
Meat	0.02	0.02	(0.003) mg/kg

LOQ: 0.01 mg/kg

The less than Level of Quantification in the milk is consistent with an extensive market basket survey of milk sampled at the point of purchase from around the United States. There were no residues of THPI in all 224 milk samples analysed (Slesinski and Wilson, 1992).

Consumption of meat and milk calculated according to the worst case scenarios resulted with maximum possible daily intake of THPI in the most sensitive consumer groups of 0.00039 mg/kg bw/day (toddlers), 0.00053 mg/kg bw/day (infants).

The maximum possible daily intake of 3-OH-THPI are 0.00122 mg/kg bw/day (toddlers), 0.00203 mg/kg bw/day (infants).

The maximum possible daily intake of 5-OH-THPI are 0.00031 mg/kg bw/day (toddlers), 0.00051 mg/kg bw/day (infants).

The maximum possible daily intake of THPI, -3-OH-THPI and 5-OH-THPI (taking into consideration the most sensitive population group) are very low and significantly lower than the ADI for captan for the most sensitive consumer groups for animal products.
(Detailed calculations appear under point 2.c) below.)

Considering the low toxicity of captan metabolites and the low dose to humans that these metabolites represent, when calculated using conservative assumptions, there is no basis for rationally including these metabolites in the captan residue expression.

In conclusion, the residue expression for captan should be expressed as parent compound, captan, only.

The references submitted in support of the above position are summarised below.

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1) THPI basic toxicology

a) Tetrahydrophthalimide: Acute oral administration - rats (Elsea, J.R., 1955; IIA 7.3/01).

The captan metabolite THPI, referred to in the report as phthalimide (N-trichloromethylthiophthalimide), purity 97%, in [redacted] was administered orally by gavage to groups of five fasted male rats as either a 10% or 40% w/v suspension at dose levels of 1.00, 2.15, 4.64 or 10.00 g/kg bw. Animals were observed for signs of toxicity on the day of administration and for seven days thereafter. Animals were subject to gross necropsy.

The study pre-dated regulatory guidelines and GLP, but was performed at a reputable laboratory, and the result is considered valid.

There were no deaths. On the day of dosing, all animals appeared depressed and showed laboured respiration and diarrhoea. Animals at the 2.15 mg/kg bw and above also showed slight ataxia. From 24 hours post-dose, animals at 1.00 and 2.15 mg/kg bw appeared normal. Animals at 4.54 and 10.00 mg/kg bw appeared depressed and showed soft, light coloured faeces for one to three days following dosing. All groups gained weight during the study. Necropsy revealed mottled and granular livers in the majority of animals in all groups receiving the test material.

Conclusion: The acute oral LD_{50} of THPI in the male rat is greater than 10 g/kg bw. In accordance with 93/21/EEC classification is not required.

b) Microbial/Mammalian Microsome Mutagenicity Plate Incorporation Assay with Tetrahydrophthalimide (Carver, J.H., 1986; IIA 7.3/02)

NOTE: The summary below already appears in the DAR under B.6.8.1a Toxicity studies of metabolites as referred to in the introduction point (vii).

The mutagenicity of the captan metabolite THPI (purity 99.9%) in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 and in the tryptophan-deficient strain of *Escherichia coli* WP2 uvrA was investigated at concentrations of 0.1 to 10 mg/plate in the presence and absence of metabolic activation (S-9 mix). The test substance was dissolved in DMSO. S-9 mix was obtained from the liver of arochlor induced rats. The positive control substance with metabolic activation was 2-aminoanthracene (strains TA98, TA100, TA1537 and WP2 uvrA). Positive controls without metabolic activation were 2-nitrofluorene (strain TA98), sodium azide (strains TA100 and TA1535), ICR-191 (strain TA1537, WP2 uvrA), 2-aminoacridine (TA1537), danthron (TA102), mitomycin (TA102), 1-ethyl 2-nitroso-3-nitrosoguanidine (WP2 uvrA). All concentrations were run in triplicate and the results were confirmed by an independent experiment.
The study was conducted according to an in-house method basically in agreement with the OECD Guideline 471, and in compliance to Good Laboratory Practice.

results: there was no cytotoxicity at any of the concentrations tested. No reproducible increases in mutant frequency were observed with the *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 or the *E. coli* strain WP2 uvrA, with or without metabolic activation. The tester strains responded to the positive controls as expected.

Conclusion: Under the conditions of the test THPI was not mutagenic in the *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 or the *E. coli* strain WP2 uvrA in the presence or absence of metabolic activation.

c*) An investigation of the teratogenic potential of captan, folpet, and difolatan (Kennedy, G., Fancher, O. E., and Calandra, J. C., 1968; IIA 7.3/03).*

Study of effects of captan, folpet, the captan metabolite tetrahydrophthalimide (THPI), and the folpet metabolite phthalimide (PI) on the pregnant rabbit. Technical grade captan and folpet, and pure samples of THPI and PI were used. The related fungicide difoltan and the structurally similar drug thalidomide were also tested. The latter may be considered a positive control.

The study predated guidelines and was not to GLP. However, the study demonstrated that foetal malformations could be induced by a known positive control, and is considered valid.

Test materials were administered in gelatine capsules to groups of mated female Dutch Belted rabbits from day 6 to day 16 of pregnancy. Animals were weighed at three day intervals and killed on day 29, when uterine contents were examined, and foetuses examined. Live foetuses were placed in an incubator for 24 hours after which they were killed and dissected. The carcasses were cleared and the skeleton stained with alizarin and examined. THPI was administered at 75 mg/kg bw/day to a group of 9 females. The study also investigated possible strain effects, testing New Zealand White (NZW) rabbits and Dutch Belted rabbits with captan. Two control groups, one of each strain, received empty capsules only. Thalidomide was administered at 75.0 mg/kg bw/day to both strains of rabbit.

Maternal weight gains were not adversely affected by THPI at 75.0 mg/kg/day, and there were no deaths.

Incidence of foetal resorptions was marginally higher with THPI.

One control foetus (of 105, from 17 litters) showed shortening and flexure of the forelimb. There were no malformations in the 57 foetuses from 9 dams treated with THPI. Post-natal survival, crown-rump length, foetal weight and incidence of visceral and skeletal anomalies

were not adversely affected by maternal treatment with THPI. Thalidomide induced typical 'clubbing' (phocomelia) in 38 of 100 foetuses from 17 litters.

The results are summarised below (Table B.7.3.1).

Table B.7.3.1: Summary of effects of captan, THPI and controls in rabbits

Compound	Oral dose (mg/kg)	No. of pregnant females	Rabbit strain	No. of implants	No of resorptions	No of normal foetuses	No. (%) malformed foetuses	Mean litter size
Control	-	7	DB	52	0	51	1 (1.9)	7.4
	-	10	NZW	66	2	64	0 (0)	6.4
Thalidomide	75.0	7	BD	55	15	26	14 (35.0)	5.7
		10	NZW	74	10	40	24 (37.5)	6.4
Captan	75.0	6	DB	43	1	42	0 (0)	7.0
	18.75	6	NZW	46	11	35	0 (0)	5.8
	37.5	7	NZW	56	2	54	0 (0)	7.7
	75.0	5	NZW	39	33	6	0 (0)	1.2
THPI	75.0	9	DB	66	9	57	0 (0)	6.3

Conclusion: Tetrahydrophthalimide (THPI) showed no adverse effects on the developing rabbit foetus.

d) THPI: Prenatal toxicity study in the rabbit by oral gavage administration (Blee, M.A.B., 2006 IIA 7.3/04)

A study of the effects of THPI on the pregnant rabbit was conducted. Technical grade THPI, purity >96%, was used. The study was GLP compliant and run to current international regulatory guidelines: OECD 414, US EPA OPPTS 870.3700 and Japanese Ministry of Agriculture, Forestry and Fisheries 12 Nohsan No. 8147.

Twenty-five female rabbits, of the New Zealand White strain, per dosage group were mated with males of the same strain and source and were dosed orally by gavage with THPI at 0, 5, 10 or 22.5 mg/kg/day from Gestation Day (GD) 6 to GD 28. Dams were killed on GD 29 of pregnancy, and uterine parameters recorded. Foetuses were examined macroscopically at necropsy and subsequently by detailed internal visceral examination of the head or at skeletal examination. Microscopic examination of the maternal duodenum was conducted on the control and top dose groups.

There were no treatment-related deaths and no clinical signs that were attributed to treatment. Bodyweight (Table B.7.3.2) and food consumption (Table B.7.3.3) were considered not to be adversely affected by treatment.

Macroscopic examination at necropsy of the dams did not reveal any treatment-related observations and microscopic examination of sections of the duodenum from animals in the Control and 22.5 mg/kg/day groups did not reveal any treatment-related findings.

Treatment did not adversely affect pregnancy outcome. Litter parameters as assessed by the numbers of corpora lutea, implantations, resorptions, live young and the extent of implantation loss were considered unaffected by treatment (Table B.7.3.4). Foetal and placental weights were unaffected by treatment with THPI (Table B.7.3.5). The *in utero* progress and development of the fetuses up to GD 29 was similarly also unaffected by treatment

Treatment did not adversely affect pregnancy outcome, embryo-foetal survival post-implantation, and fetal and placental weights were considered to be unaffected by treatment with THPI . The *in utero* progress and development of the fetuses up to GD 29 was unaffected by treatment.

Foetal pathology examinations did not reveal any skeletal or visceral major malformations/abnormalities or changes in minor skeletal abnormalities or variants that were outside concurrent or the laboratories historical control data ranges. Thus foetal development was unaffected by maternal treatment with THPI.

It may be concluded that maternal administration of THPI did not induce demonstrable maternal toxicity and did not affect the outcome of the pregnancies. Foetal development was considered to be normal.

Table B.7.3.2: Bodyweight - group mean values (kg) for females during gestation (GD)

Group	:	1	2	3	4
Compound	:	Control	-------Tetrahydrophthalimide ----		
Dosage (mg/kg/day)	:	0	5	10	22.5

Group			GD						
			0	6	7	14	21	28	29
1	Mean		3.96	4.06	4.06	4.13	4.16	4.22	4.24
	SD		0.53	0.58	0.58	0.59	0.58	0.56	0.55
	n		18	18	18	18	18	18	18
2	Mean		4.12	4.20	4.21	4.27	4.31	4.38	4.39
	SD		0.52	0.50	0.49	0.50	0.52	0.51	0.51
	n		24	24	24	24	24	24	24
3	Mean		4.03	4.13	4.14	4.19	4.23	4.32	4.33
	SD		0.57	0.60	0.60	0.58	0.58	0.53	0.52
	n		21	21	21	21	21	21	21
4	Mean		4.06	4.18	4.18	4.21	4.23	4.26	4.28
	SD		0.54	0.55	0.56	0.56	0.59	0.57	0.57
	n		24	24	24	24	24	24	24

Table B.7.3.3: Food consumption - group mean values (g/animal/day) for females during gestation (GD)

Group	:	1	2	3	4
Compound	:	Control	-------Tetrahydrophthalimide ----		
Dosage (mg/kg/day)	:	0	5	10	22.5

Group		GD					
		1	6	7	14	21	28
1	Mean	163	164	169	114	128	98
	SD	39	29	31	54	49	37
	n	17	18	18	18	18	18
2	Mean	169	165	163	111	130	92
	SD	29	36	39	58	42	47
	n	24	24	24	24	24	24
3	Mean	173	167	170	118	124	102
	SD	25	27	24	55	49	50
	n	21	21	21	21	21	21
4	Mean	164	162	155	116	112	84
	SD	32	29	31	53	43	41
	n	24	24	24	24	24	24

Table B.7.3.4: Litter data - group mean values on GD 29

Group	:	1	2	3	4
Compound	:	Control	-------- Tetrahydrophthalimide --------		
Dosage (mg/kg/day)	:	0	5	10	22.5

Group		Corpora	Implantations	Resorptions		Live young		% implantation loss	
		Lutea		Early	Late	Male	Female	Pre-	Post-
1	Mean	11.3	9.3	0.6	0.4	4.8	3.4	19.2	10.6
	SD	2.2	3.3			2.0	2.0		
	n	18	18	18	18	18	18	18	18
2	Mean	12.1	10.0	0.4	0.3	4.5	4.9	16.1	6.5
	SD	2.7	2.5			1.7	2.2		
	n	24	24	24	24	24	24	24	24
3	Mean	12.1	10.3	0.4	0.9	4.4	4.7	14.8	11.9
	SD	1.4	2.3			1.9	1.2		
	n	21	21	21	21	21	21	21	21
4	Mean	11.9	9.8	0.4	0.5	4.4	4.5	17.3	8.5
	SD	1.3	2.1			1.7	2.1		
	n	24	24	24	24	24	24	24	24

Table B.7.3.5: Placental and foetal weights - group mean values (g) on GD 29

Group	:	1	2	3	4
Compound	:	Control	-------- Tetrahydrophthalimide --------		
Dosage (mg/kg/day)	:	0	5	10	22.5

Group		Placental	Foetal weight		
		weight	Males	Females	Overall
1	Mean	5.5	39.0	37.3	38.7
	SD	0.9	7.0	6.5	6.9
	n	18	18	17	18
2	Mean	5.6	39.6	39.0	39.5
	SD	0.7	5.7	5.7	5.4
	n	24	24	24	24
3	Mean	5.1	36.3	36.3	36.4
	SD	0.7	5.1	4.6	4.5
	n	21	21	21	21
4	Mean	5.5	38.2	37.8	38.0
	SD	0.9	6.6	7.1	6.6
	n	24	24	24	24

e) Assessment of the activity, toxicity and mutagenicity potential of THPI, using structure activity relationships (Chaudhry, Q., 2005; IIA 7.3/05). [This report was previously submitted with the toxicology addendum in March 2005.]

THPI was evaluated for their potential for activity, toxicity and mutagenicity using a Structure Activity Relationship (SAR) approach. The technique, referred to as Deduction of Risk from Existing Knowledge (DEREK), uses specialist software 'DEREK for Windows' (DfW) developed by Lhasa Ltd. The software works by matching structural entities in a query structure with structural alerts that are associated with different toxicity endpoints (toxicophores). A structural alert is the set of structural features in a molecule that makes a toxicologist suspect that the substance may show a particular toxic effect. DfW can predict alerts for carcinogenicity, irritation (e.g. of the skin, eye and gastrointestinal tract), genotoxicity, respiratory sensitisation, skin sensitisation, thyroid toxicity and a range of miscellaneous effects for bacteria and a range of mammalian species including man. The programme used 482 structural alerts associated with the different endpoints.

DfW also predicts the likelihood of each effect using descriptive terms ranging from 'certain' to 'impossible' ('certain', 'probable', 'plausible', 'equivocal', 'doubted', 'improbable', 'impossible'), or 'open' or 'contradicted' in the case of findings where there is a prediction both that the proposition is true and that it is false.

There were no structural alerts in THPI.

In conclusion, computer predictions using DfW indicate that THPI is not expected to exhibit mutagenic activity, genotoxicity, irritation, sensitisation or thyroid toxicity.

g) THPI: Determination of minimal inhibitory concentrations against selected micro-organisms representative of the rabbit gut micro-flora (Akhurst, L.C., 2005 IIA 7.3/06).

It has been postulated that captan may affect the rabbit GI tract micro-flora and that an imbalance in the micro-flora may have consequences for the pregnant rabbit on both maternal and embryo-foetal nutrition. Such changes could, in theory, affect the developing foetus. The rabbit is a species particularly susceptible to gastrointestinal disturbances which may in part be mediated through changes in the GI tract micro-flora. An *in vitro* approach to demonstrate changes in representative rabbit GI tract micro-flora was considered to be a simple and straightforward way to evaluate the potential effects of THPI on such micro-organisms.

THPI is not thought to have the same anti-microbial activity as the parent molecule captan partly because it is not capable of generating the highly reactive moiety thiophosgene.

The minimum inhibitory concentration (MIC) assay is an internationally accepted test for antimicrobial susceptibility testing and is commonly used to assess the effectiveness of intentional antimicrobial compounds. The test was adapted to assess selected micro-organisms representative of the rabbit gut micro-flora.

The study was conducted using an agar dilution procedure for determination of MIC values. Ten species of the genus Bacteroides, one genus of *Enterococcus faecalis* and four isolates of *Candida albicans* were tested. Final concentrations of THPI of 1000, 500, 200, 100, 50, 20, 10, 5 , 2 or 1 µg/ml were tested and solvent control and growth control plates were employed. The lowest test substance concentration that completely inhibited growth of the test organism was recorded as the MIC.

THPI demonstrated no antimicrobial activity towards *Bacteroides sp.*, *Enterococcus faecalis* or *Candida albicans* when tested up to a concentration of 1000 µg/ml.

It may be concluded that THPI demonstrated no antimicrobial activity against organisms selected as representatives of rabbit GI tract flora species tested in this study. It is unlikely that this molecule has the potential to affect the micro-flora of the rabbit GI tract.

2) Their presence in significant amounts

a) *Plant metabolism study of [trichloromethyl-^{14}C] captan. (Chen, Y.S. 1988a; Annex IIA, 6.1/01 IIA 7.3/07)*

[Trichloromethyl-^{14}C] captan (radiochemical purity 99.6%; specific activity 38.0 mCi/mmole) formulated in [redacted] was applied four times at seven day intervals as a foliar spray to five lettuce plants (variety Paris Island Cos) and five tomato plants (variety Patio, E hybrid) at a rate of approximately 4.48 kg a.s./ha. The first sprays were applied on the 8 May 1987 when the lettuce had 12 - 16 leaves and when the first tomato fruit had formed. The treated crop was maintained in a glasshouse at 18 - 29°C and plants were harvested three hours after the final spray had been applied. The plants were separated into parts, combusted and radioactive residues were determined by liquid scintillation counting (LSC). Metabolites were characterised by thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC) and mass spectrometry (MS).

^{14}C radioactivity was mainly found in the leaves and fruit of tomato and the leaves of lettuce. The distribution of total radioactive residues (TRR) is given in Table 6.1-1and Table 6.1-2.

Table 6.1-1 Distribution of TRR and residue levels in tomatoes and lettuce following application of [trichloromethyl-^{14}C] captan

Crop part	% TRR	Residue (mg captan equivalents/kg)
Tomato		
leaves	62.1	128.5
stems	9.2	21.8

roots	0.2	0.20
fruit	28.5	6.90[1]
Lettuce		
leaves	98.7	68.5
roots	1.3	1.34

[1] Calculated from the relative weights of whole fruit, pulp and juice.

Table 6.1-2 Distribution of TRR and residue levels in tomato fruit and processed tomato fruit following application of [trichloromethyl-^{14}C] captan

Crop part	% TRR	Residue (mg captan equivalents/kg)
Surface wash	79.6	-
Juice	14.7	1.22
Pulp	5.7	2.94

The majority of the residue in tomatoes and lettuce was captan. Captan epoxide was also identified as a minor metabolite. The distribution of metabolites in the tomato fruit was similar to that in the tomato leaves and stems and similar to that in lettuce. The distribution of the characterised metabolites is given in **Table 6.1-3**. The non-extractable residues were distributed in carbohydrates, proteins and lignin due to incorporation of the labile ^{14}C into natural products.

Table 6.1-3 Characterisation of ^{14}C radioactivity in tomatoes and lettuce following application of [trichloromethyl-^{14}C] captan

Identity of residue	% Relative radioactivity (mg/kg captan equivalents)		
	Tomato plant[1]	Tomato fruit[2]	Lettuce leaves
captan	80.8 (92.7)	76.6 (5.29)	76.2 (52.2)
captan epoxide	0.3 (0.34)	0.2 (0.014)	0.3 (0.21)
other free metabolites	6.9 (7.91)	9.5 (0.66)	5.2 (3.56)
polar and conjugates	4.8 (5.50)	10.4 (0.72)	4.6 (3.15)
non-extractable	7.2 (8.26)	3.3 (0.23)	13.7 (9.39)

[1] Leaves + stems.
[2] Determined by the addition of radioactivity in the acetone surface rinse, tomato juice and pulp calculated using weight/volume ratios for whole fruit, pulp, juice and acetone rinse.

In conclusion, following four foliar applications at a rate of 4.48 kg a.s./ha, captan was not readily metabolised in tomato or lettuce, with most of the residue remaining on the plant or fruit surface. The trichloromethyl moiety was mainly released as ^{14}C carbon dioxide suggesting that in the plant, captan was metabolised to form THPI which was further metabolised. The major plant residue was captan.

b) *Plant metabolism study of [cyclohexene-1,2-^{14}C] captan. (Chen, Y.S. 1988b; IIA, 6.1/02 IIA 7.3/08)*

[Cyclohexene-1,2-^{14}C] captan (radiochemical purity 98.7%; specific activity 16.6 mCi/mmole) formulated in [redacted] was applied four times at seven day intervals as a foliar spray post-emergence to five lettuce plants (variety Paris Island Cos) and five tomato plants (variety Patio, E hybrid) at a rate of approximately 4.48 kg a.s./ha. The first sprays were applied on the 8 May 1987 when the lettuce had 12 - 16 leaves and when the first tomato fruit had formed. The treated crop was maintained in a glasshouse at 18 - 29°C and plants were harvested three hours after the final spray had been applied. The plants were separated into parts, combusted and radioactive residues were determined by LSC. Metabolites were characterised by TLC, HPLC and MS.

^{14}C radioactivity was mainly found in the leaves and fruit of tomato and the leaves of lettuce. The distribution of TRR is given in Table 6.1-4 and 6.1-5. The majority of the residue in leaves and stems was extractable with solvents.

Table 6.1-4 Distribution of TRR and residue levels in tomatoes and lettuce following application of [cyclohexene-1,2-^{14}C] captan

Crop part	% TRR	Residue (mg captan equivalents/kg)
Tomato		
leaves	70.4	202.1
stems	9.7	30.1
roots	0.2	0.21
fruit	19.7	6.72[1]
Lettuce		
leaves	99.7	64.4
roots	0.3	0.30

[1] Calculated from the relative weights of whole fruit, pulp and juice.

Table 6.1-5 Distribution of TRR and residue levels in processed tomato fruit following application of [cyclohexene-1,2-^{14}C] captan

Crop part	% TRR	Residue (mg captan equivalents/kg)
Surface wash	88.9	-
Juice	8.9	0.71
Pulp	2.2	1.18

The majority of the residue in tomatoes and lettuce was captan. Captan epoxide was also identified as a minor metabolite. The distribution of metabolites in the tomato fruit was the same as that in the tomato leaves and stems. The distribution of the characterised metabolites is given in Table 6.1-6. The non-extractable residues were distributed in carbohydrates, proteins and lignin.

Table 6.1-6 Characterisation of ^{14}C radioactivity in tomatoes and lettuce following application of [cyclohexene-1,2-^{14}C] captan

Identity of residue	% Relative radioactivity (mg/kg captan equivalents)		
	Tomato plant[1]	Tomato fruit[2]	Lettuce leaves
captan	70.4 (127.6)	81.5 (5.48)	77.2 (49.7)
captan epoxide	0.4 (0.73)	0.4 (0.03)	0.6 (0.39)
THPI	4.6 (8.34)	4.5 (0.30)	9.5 (6.12)
THPI epoxide	-	-	0.9 (0.58)
other free metabolites	6.9 (12.5)	5.2 (0.35)	4.3 (2.77)
polar and conjugates	8.9 (16.1)	7.5 (0.50)	4.5 (2.90)
non-extractable	8.8 (16.0)	0.9 (0.06)	3.0 (1.93)

[1] Leaves + stems.
[2] Determined by the addition of radioactivity in the acetone surface rinse, tomato juice and pulp calculated using weight/volume ratios for whole fruit, pulp, juice and acetone rinse.

In conclusion, following four foliar applications at a rate of 4.48 kg a.s./ha, captan was not readily metabolised in tomato or lettuce. Most of the residue (70% min) remaining on the plant or fruit surface was unmetabolised captan. In the plant, captan was metabolised to form THPI which was further metabolised.

c) *The fate of captan [carbonyl-^{14}C] on field-grown apple trees. (DeBaun, J.R. et al. 1975; IIA, 6.1/03 IIA 7.3/09)*

[Carbonyl-^{14}C] captan (radiochemical purity > 96%; specific activity 6.2 mCi/mmole) formulated as a wettable powder was applied as a foliar spray to one branch of a field-grown four year old apple tree (variety Golden Delicious) in a spray chamber with 10 ml of a spray solution at a concentration of 0.12 kg a.s./hL. Four separate trees were treated with one, two or three sprays applied in the same way on the following dates: Tree 1 - 11 May + 11 June + 11 July, Tree 2 - 11 June + 11 July, Tree 3 - 11 July, Tree 4 - 31 July. The treated branch was

removed after application on 31 July and fruit and foliage were analysed for radioactive residues by LSC. Metabolites were characterised by TLC.

The majority of the ^{14}C radioactivity was found on the surface of the fruit and the foliage. TRR in the surface wash decreased with the longer interval between first application and harvest whereas in other fruit fractions TRR increased slowly. After 20 days, which is the most appropriate interval according to the GAP, radioactive residues in the surface wash represented 89.6% of the TRR. Extractable residues in the peel accounted for 4.5% of the TRR, and non extractable residues accounted for 2.6% of the TRR. In the pulp, these fractions were 2.7 and 0.7% of the TRR, respectively.

The distribution of TRR is given in Table 6.1-7.

Table 6.1-7 Distribution of TRR in apple following application of [carbonyl-^{14}C] captan

Crop part	% TRR			
	Tree 4 (0 DAT[1])	Tree 3 (20 DAT)	Tree 2 (50 DAT)	Tree 1 (80 DAT)
fruit				
surface wash	95.8	89.6	81.4	64.2
peel extract	3.3	4.5	4.8	9.3
peel residue	0.9	2.6	4.4	4.4
pulp extract	0.8	2.7	7.7	17.2
pulp residue	0.2	0.7	1.7	4.9
foliage				
extract	98.5	84.9	71.5	84.2
residue	1.5	15.1	28.5	15.8

[1] Days between first treatment and harvest.

The majority (67 - 84%) of the radioactivity present in the fruit wash and in the foliage was identified as captan. THPI and THPAM represented 3.3 - 7.6% and 0.4 - 2.4% of the relative radioactivity, respectively. These compounds tended to decrease with the longer interval between first application and harvest. Other metabolites accounted for less than 1% of the relative radioactivity.

In the peel and pulp radioactive residues were low and captan was present at up to 46.0% and 15.0% of relative radioactivity, respectively. THPI and THPAM were the main metabolites at 33.1% and 12.0% of relative radioactivity, respectively, in the peel and 47.5% and 2.4% of relative radioactivity, respectively, in the pulp. Other metabolites occurred at very low levels. The uncharacterised material in the peel and pulp extracts following the harvest interval of 20 days, which is the most appropriate according to the GAP for apple, was only 1.44% and 1.56%, respectively, of the total radioactivity in the fruit.

The characterisation of residues is given in Table 6.1-3.

Table 6.1-3 Characterisation of ^{14}C radioactivity in apple following application of [carbonyl -^{14}C] captan

Identity of residue	% Relative radioactivity (mg captan equivalents/kg)			
	Tree 4 (0 DAT[1])	Tree 3 (20 DAT)	Tree 2 (50 DAT)	Tree 1 (80 DAT)
fruit wash				
captan	78.0	79.0	67.9	71.1
captan epoxide	< 1.0	< 1.0	< 1.0	< 1.0
THPI	7.6	5.7	6.1	5.2
THPI epoxide	< 1.0	< 1.0	< 1.2	< 1.4
THPAM	1.2	0.4	1.1	1.3
uncharacterised	~ 11.2	~ 12.9	~ 22.7	~ 20
foliage				
captan	84.4	74.4	67.4	71.4
captan epoxide	< 1.0	< 1.0	< 1.0	1.1
THPI	5.4	4.4	3.6	3.3
THPI epoxide	< 1.0	< 1.0	< 1.0	< 1.0
THPAM	2.1	2.4	2.0	0.7
uncharacterised	~ 6.1	~ 16.8	~ 25.0	~ 22.5
peel extract				
captan	46.0 (1.640)	36.7 (1.348)	24.7 (0.743)	20.6 (0.723)
captan epoxide	0.1 (0.004)	0.5 (0.019)	0.2 (0.006)	1.0 (0.037)
THPI	33.1 (0.594)	16.7 (0.308)	15.6 (0.236)	14.6 (0.257)
THPI epoxide	0.5 (0.010)	2.3 (0.047)	1.3 (0.022)	1.1 (0.021)
THPAM	8.1 (0.163)	11.7 (0.241)	12.0 (0.203)	12.0 (0.236)
uncharacterised	12.2	32.1	46.2	50.7
% uncharacterised in whole apple[2]	0.40	1.44	2.22	4.21
pulp extract				
captan	15.0 (0.022)	6.1 (0.029)	3.0 (0.028)	2.8 (0.030)
captan epoxide	3.7 (0.006)	5.0 (0.025)	2.8 (0.028)	1.0 (0.011)
THPI	47.5 (0.035)	28.8 (0.069)	18.0 (0.085)	13.4 (0.073)
THPI epoxide	2.0 (0.002)	0.5 (0.001)	5.6 (0.029)	3.3 (0.020)
THPAM	0.5 (0.004)	2.0 (0.005)	2.4 (0.013)	1.1 (0.007)
uncharacterised	31.3	57.6	68.2	78.4
% uncharacterised in whole apple[2]	0.25	1.56	5.25	13.48

[1] Days between first treatment and harvest.
[2] % of the total TRR in peel/pulp (from Table 6.1-7) x % uncharacterised in peel/pulp.

In conclusion, following one to three spray applications of captan to apple under field conditions, each at a concentration of 0.12 kg a.s./hL, the major residue was captan, predominantly recovered in the fruit wash (65-95% of the TRR). Captan remained on the surface of the apple fruit and on the leaves. There was a gradual translocation of the ^{14}C radioactivity from the surface of the fruit into the tissue but residues in the peel and pulp were remained very low. In the fruit captan was degraded to polar products, mainly THPAM and THPI.

d) National Milk Survey (Slesinski, R., S. and Wilson, A. E., 1992; IIA 7.3/10).

Samples of whole milk were collected from 224 retail outlets of different sizes, including supermarkets and convenience stores (but not wholesale outlets nor roadside stalls), from 48 different states in the USA at various times over a 12-month period (January to December 1991). The stores selected for sampling were taken at random from a database of 95,000 outlets representing 83.8% of all grocery store sales in 1989. Two samples of 1.9 L (sample 'A' and a back-up sample 'B') were purchased from each store by shoppers. The samples were packed in dry ice and transferred to the analytical laboratory and stored frozen until analysis. Control samples were obtained by the laboratory from local stores.

Each sample was analysed for captan, THPI, trans-3-hydroxy THPI and trans-5-hydroxy THPI. Captan residues were extracted with benzene, filtered, subjected to partition and column clean-up and then quantified using a gas chromatograph equipped with a halogen-specific Coulson Electrolytic Conductivity detector; the GC column was packed with 10% SP 2100 on 80/100 mesh Supelcoport. THPI, trans-3-hydroxy THPI and trans-5-hydroxy THPI residues were extracted with acetone, filtered, subjected to partition clean-up. The residues were derivatised by trimethylsilylation and quantified by gas chromatography on a DB-17 capillary column and a mass selective detector (MSD) operating in the selective ion mode. The LOQ for all analytes was 0.005 mg/L.

Acceptable recoveries were obtained from samples fortified at 0.005 and 0.01 mg/L..

Conclusion: Residues of captan, THPI, trans-3-hydroxy THPI and trans-5-hydroxy THPI were below the LOQ in all 224 milk samples.

e) Captan: Magnitude of Residue of captan metabolites in bovine meat and milk (Wiebe, L. A., 1991; IIA 7.3/11).

Captan technical active substance (purity 89.3%; batch number PJB-1601 CTCS) was administered orally in gelatine capsules daily in the feed for 29 days to groups of four Holstein dairy cattle at dietary concentration of 0, 10, 30 and 100 mg/kg diet. Milk was collected twice daily before treatment, on selective days during treatment, and one, three and six days after treatment. Three cattle from each group were sacrificed three hours after treatment was complete and the remaining one after an additional seven days. Concentrations of THPI, 3-OH THPI (*cis* and *trans*) and 5-OH THPI (*cis* and *trans*) were determined in tissues and milk using gas liquid chromatography with mass-selective detection.

For milk, there were 48 determinations for each of the analytes and mean recoveries for each metabolite at all fortification levels were 93 - 98%. For tissues there were 11 or 12 determinations for each of the analytes and mean recoveries for all fortification levels were 95 - 106% (fat), 91 - 105% (kidney), 67 - 83% (liver) and 95 - 101% (muscle).

In the residue study milk samples were extracted within 159 days of collection and tissue samples within 317 days of collection. In the stability test, there was no reduction in levels of captan metabolites following storage at -20°C in the different commodities for up to six months (milk) or four months (tissues). The results of later samplings are reported by Meyers and Wiebe (1995 - see Point B.7.6.4.b) and the residues were found to be stable in milk and tissues following storage at -20°C for at least three years.

No residues of the metabolites *cis*-3-OH THPI or *cis*-5-OH THPI were detected in milk or tissues following administration of captan.

Residues in milk plateaued on day 1 of administration for all dosing levels. Within one day after the end of dosing, residues were not detected in the milk following 10 and 30 mg captan/kg and within three days after dosing there were no residues in the milk following 100 mg captan/kg. Residue levels in tissues were generally similar to those in the milk though

residues in the fat were lower. THPI was the major metabolite in fat, liver and muscle and trans-3-OH THPI occurred at higher levels than trans-5-OH THPI.

Total residues were calculated by adding the individual values for the metabolites, corrected for the molecular mass. Thus, THPI (molecular mass 151.2) and 3-OH THPI/5-OH THPI (molecular mass 167.2) are multiplied by 2.0 and 1.8, respectively, to convert metabolite residues to captan (molecular mass 300.6). Residues below the limit of determination (< 0.01 mg/kg) are assumed to be zero for the purposes of the addition. Total residues were 0.04 mg captan equivalents in milk and < 0.01 - 0.08 mg captan equivalents/kg in tissues following administration of 10 mg captan/kg for 29 days. Following administration of 30 mg/kg, residues in milk and tissues were 0.17 and 0.06 - 0.38 mg captan equivalents/kg; following administration of 100 mg/kg, residues in milk and tissues were 0.89 and 0.21 - 1.11 mg captan equivalents/kg.

After the end of dosing, residues in the tissues dissipated within seven days.

Average residues of captan metabolites in milk during and after the dosing period are given in Table B.7.3.6

Average residues of captan metabolites in milk during the dosing period and residues in tissues at the end of the 29-day administration period are given in Table B.7.3.7.

Table B.7.6: Residues in milk following administration of captan to dairy cow for 29 days

Day	Dose rate (mg/kg diet)	Mean residue in milk (mg/kg)				
		THPI	*trans*-3-OH THPI	*trans*-5-OH THPI	*cis*-3-OH THPI	*cis*-5-OH THPI
1	10	< 0.01	0.023	< 0.01	< 0.01	< 0.01
	30	0.028	0.083	0.013	< 0.01	< 0.01
	100	0.153	0.310	0.060	< 0.01	< 0.01
4	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.020	0.063	< 0.01	< 0.01	< 0.01
	100	0.160	0.245	0.035	< 0.01	< 0.01
7	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.025	0.063	< 0.01	< 0.01	< 0.01
	100	0.298	0.265	0.035	< 0.01	< 0.01
10	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.016	0.060	< 0.01	< 0.01	< 0.01
	100	0.190	0.183	0.025	< 0.01	< 0.01
14	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.030	0.060	< 0.01	< 0.01	< 0.01
	100	0.173	0.200	0.030	< 0.01	< 0.01
21	10	< 0.01	0.020	< 0.01	< 0.01	< 0.01
	30	0.030	0.060	< 0.01	< 0.01	< 0.01
	100	0.198	0.210	0.033	< 0.01	< 0.01
28	10	< 0.01	0.018	< 0.01	< 0.01	< 0.01
	30	0.030	0.063	< 0.01	< 0.01	< 0.01
	100	0.208	0.225	0.035	< 0.01	< 0.01
30*	10	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	30	0.01	< 0.01	< 0.01	< 0.01	< 0.01
	100	0.02	0.10	< 0.01	< 0.01	< 0.01
32*	10	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	30	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	100	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

Residues in milk and tissues from untreated controls were below the limit of determination except for one milk sample which contained 0.02 mg THPI/kg on Day 10.
Values of < 0.01 mg/kg are assumed to be 0.005 mg/kg for calculation of means (unless all replicate values are < 0.01 mg/kg in which case the mean is given as < 0.01 mg/kg).
* After dosing; one animal only per dose (four animals per dose at other time points).

Table B.7.3.7: Residues in tissues and milk following administration of captan to dairy cow for 29 days

Commodity	Dose rate (mg/kg diet)	Mean residue (mg/kg)				
		THPI	*trans*-3-OH THPI	*trans*-5-OH THPI	*cis*-3-OH THPI	*cis*-5-OH THPI
milk	10	< 0.01	0.02	< 0.01	< 0.01	< 0.01
	30	0.03	0.06	< 0.01	< 0.01	< 0.01
	100	0.20	0.23	0.04	< 0.01	< 0.01
fat	10	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	30	0.03	< 0.01	< 0.01	< 0.01	< 0.01
	100	0.08	0.03	< 0.01	< 0.01	< 0.01
kidney	10	0.02	0.02	< 0.01	< 0.01	< 0.01
	30	0.09	0.09	0.02	< 0.01	< 0.01
	100	0.25	0.27	0.07	< 0.01	< 0.01
liver	10	0.02	< 0.01	< 0.01	< 0.01	< 0.01
	30	0.12	0.04	< 0.01	< 0.01	< 0.01
	100	0.31	0.11	< 0.01	< 0.01	< 0.01
muscle	10	0.02	0.02	< 0.01	< 0.01	< 0.01
	30	0.07	0.06	0.01	< 0.01	< 0.01
	100	0.24	0.18	0.04	< 0.01	< 0.01

Residues in milk and tissues from untreated controls were below the limit of determination except for one milk sample which contained 0.02 mg THPI/kg.

Conclusion, following administration of captan to dairy cattle at a dietary concentration of 10, 30 and 100 mg/kg for 29 days, total residues in milk over the dosing period were 0.04, 0.17 and 0.89 mg captan equivalents/kg. In tissues, residues following the three doses were < 0.01 - 0.08, 0.06 - 0.38 and 0.21 - 1.11 mg captan equivalents/kg, respectively, with the highest levels found in the kidney and the lowest levels in the fat. THPI was the major metabolite in most tissues and no residues of *cis*-3-OH THPI or *cis*-5-OH THPI were found in milk or tissues above the limit of determination. Residue levels of all metabolites reduced during the withdrawal period and following all dose levels were below the limit of determination in milk and tissues after three days and seven days, respectively.

f) Dietary Risk assessment of Captan Metabolites: THPI, 3-hydroxy and 5-hydroxy THPI

The dietary risk assessment for THPI and the 3-OH and 5-OH THPI metabolites was calculated based on the residues found in milk and meat from dairy cows fed 10 ppm captan The rate of 10 mg/kg diet is greater than the worst-case intake of captan (based on residues in pomace calculated from the MRL in apple) for beef and dairy cattle as shown below:

Captan is recommended in pome fruit, tomatoes and peaches/nectarines. Fruit pomace (apple) can be used for cattle feed at a maximum of a 10% of the diet in dairy cattle and a 30% of the diet in beef cattle. Captan is not recommended on any crops which are fed to hens or pigs.

The potential dietary exposure of dairy and beef cattle to captan is calculated below based on a worst-case (using the MRL) and a more realistic case (using the STMR) according to Commission Working Document 7031/VI/95 rev 4 of 22 July 1996.

Worst-case calculation of captan intake in cattle (based on MRL values)

Based on a MRL of 5 mg/kg for apple and a mean transfer factor of 1.1 in apple pomace (residue in pomace = 5.5 mg/kg), the maximum residue concentration in feed of beef cattle is 107.8 mg captan/animal/day (Table B.7.3.8). This gives an estimated daily feeding rate of 7.2 mg captan/kg diet (107.8/15), assuming 15 kg as the daily intake of dry matter for cattle of

350 kg body weight, or 0.31 mg/kg bw /day (107.8/350). The maximum dietary concentration is 5.5 mg captan/kg fresh diet (107.8/19.6).

For dairy cattle, the maximum residue concentration in feed is 47.85 mg captan/animal/day (Table B.7.3.8). This gives an estimated daily feeding rate of 2.4 mg captan/kg diet (47.85/20), assuming 20 kg as the daily intake of dry matter for cattle of 550 kg body weight, or 0.09 mg/kg bw /day (47.85/550). The maximum dietary concentration is 5.5 mg captan/kg fresh diet (47.85/8.7).

Table B.7.3.8: Worst-case calculation of captan dietary exposure level in cattle (based on MRL values)

Animal/ Crop commodity consumed	% Diet contribution (dry weight)	Intake of dry matter (kg/animal /day)[1]	% Dry matter content	Intake of fresh material (kg/animal/ day)[2]	Captan residue in commodity (mg/kg)	Intake (mg captan / animal/ day)[3]
Beef cattle/ Apple pomace	30	4.5	23	19.6	5.5	107.8
Dairy cattle/ Apple pomace	10	2.0	23	8.7	5.5	47.85

[1] % diet contribution x total intake (15 kg for beef cattle; 20 kg for dairy cattle).
[2] Dry matter intake corrected for dry matter content (23%).
[3] Intake of fresh material x captan residue.

Realistic calculation of captan intake in cattle (based on STMR values)

Based on a STMR of 1.3 mg/kg for apple and a mean transfer factor of 1.1 in apple pomace (residue in pomace = 1.4 mg/kg), the maximum residue concentration in feed of beef cattle is 27.44 mg captan/animal/day (Table B.7.3.9). This gives an estimated daily feeding rate of 1.8 mg captan/kg diet (27.44/15), assuming 15 kg as the daily intake of dry matter for cattle of 350 kg body weight or 0.08 mg/kg bw /day (27.44/350). The maximum dietary concentration is 1.4 mg captan/kg fresh diet (27.44/19.6).

For dairy cattle, the maximum residue concentration in feed is 12.18 mg captan/animal/day (Table B.7.3.9). This gives an estimated daily feeding rate of 0.6 mg captan/kg diet (12.18/20), assuming 20 kg as the daily intake of dry matter for cattle of 550 kg body weight or 0.02 mg/kg bw /day (12.18/550). The maximum dietary concentration is 1.4 mg captan/kg fresh diet (12.18/8.7).

Table B.7.3.9: Realistic calculation of captan dietary exposure level in cattle (based on STMR values)

Animal/ Crop commodity consumed	% Diet contribution (dry weight)	Intake of dry matter (kg/animal /day)[1]	% Dry matter content	Intake of fresh material (kg/animal/ day)[2]	Captan residue in commodity (mg/kg)	Intake (mg captan / animal/ day)[3]
Beef cattle/ Apple pomace	30	4.5	23	19.6	1.4	27.44
Dairy cattle/ Apple pomace	10	2.0	23	8.7	1.4	12.18

[1] % diet contribution x total intake (15 kg for beef cattle; 20 kg for dairy cattle).
[2] Dry matter intake corrected for dry matter content (23%).
[3] Intake of fresh material x captan residue.

Based on the dietary burden calculations, the worst-case and realistic case intakes for captan are summarised in Table B.7.3.10. The rate of 10 mg/kg diet as used in the feeding study is greater than the worst-case intake (and greater than the realistic intake) of captan for beef and dairy cattle.

Table B.7.3.10: Intake of captan in cattle

Animal	Calculated dietary intake (mg captan/kg diet)	
	Worst-case (based on MRL)	Realistic case (based on STMR)
Beef cattle	7.2	1.8
Dairy cattle	2.4	0.6

The following residues have been found in milk and meat from dairy cows fed 10 ppm captan (the estimated maximum dose, based on captan use and cattle feed components) (Wiebe, 1991):

Table B.7.3.11: Residues of THPI, 3-OH-THPI and 5-OH-THPI in meat and milk following administration of captan to dairy cow for 29 days

Commodity	Dose rate (mg/kg diet)	Mean residue (mg/kg)		
		THPI	3-OH THPI	5-OH THPI
milk	10	< 0.01 (0.005)*	0.02	< 0.01 (0.005)*
uscle	10	0.02	0.02	< 0.01 (0.005)*

Residues in milk and tissues from untreated controls were below the limit of determination except for one milk sample which contained 0.02 mg THPI/kg.

* Since the LOQ was 0.01 mg/kg, one half of the LOQ (i.e., 0.005 mg/kg) as worst case scenario was taken into consideration when residues were below the LOQ.

Estimation of the potential and actual exposure through diet and other means

Chronic exposure

Theoretical Maximum Daily Intake (TMDI)

The TMDI is calculated by multiplying the MRL/residues by the estimated average daily consumption for a given food commodity.

$TMDI = \sum MRL \times F$

where:
MRL = Maximum residue limit/residue for a given animal product
F = Consumption of that animal product.

This calculation is performed using:

3) An International diet (European Region) based on data from the World Health Organisation (WHO)[4].
4) The UK Dietary model (PSD, 1999[5])

[4] WHO (1989). Guidelines for predicting dietary intake of pesticide residues. Prepared by the joint UNEP/FAO/WHO Food Contamination Monitoring Programme in collaboration with the Codex Committee on Pesticide Residues. World Health Organisation, Geneva.

[5] PSD (1999). Guidance on the estimation of dietary intakes of pesticides residues. The Registration Handbook. Pesticides Safety Directorate, Ministry of Agriculture, Fisheries and Food.

WHO European diet

The TMDI calculation is presented in Table B.7.3.12

Table B.7.3.12: Consumption of milk and meat based on WHO diet

Commodity	Consumption (kg/person/day)
Total milk	0.3408
Cattle meat	0.0633

Table B.7.3.13: TMDI calculation for THPI, 3-OH-THPI and 5-OH-THPI based on WHO diet

Commodity	THPI (mg/kg)	TMDI for THPI (mg/person/ day)	3-OH-THPI (mg/kg)	TMDI for 3-OH-THPI (mg/person/ day	5-OH-THPI (mg/kg)	TMDI for 5-OH-THPI (mg/person/day
Total milk	0.005	0.0017	0.02	0.0068	0.005	0.0017
Cattle meat	0.02	0.0013	0.02	0.0013	0.005	0.0003
Total TMDI		**0.0030**		**0.0081**		**0.0020**

The total TMDI for **THPI in milk and meat** will be max 0.0030 mg/person/day or **0.0000**5 mg/kg bw/day for a 60 kg adult.
The total TMDI for **3-OH-THPI** is 0.0081 mg/person/day or **0.0001** mg/kg bw/day for a 60 kg adult.
The total TMDI for **5-OH-THPI** is 0.0020 mg/person/day or **0.00003** mg/kg bw/day for a 60 kg adult.

UK diet

UK consumption data of animal products for adults, children, toddlers and infants (mean consumers and high, i.e. 97.5th percentile, consumers) are presented in Table B.7.3.14.

Table B.7.3.14: UK consumption data for adults, children, toddlers and infants

Comm-odity	Consumption data (kg/day)							
	Adults (70.1 kg bw)		Children (43.6 kg bw)		Toddlers (14.5 kg bw)		Infants (8.7 kg bw)	
	Mean	High [1]	Mean	High	Mean	High	Mean	High
Milk	0.2573	0.6659	0.0304	0.6745	0.3064	0.8017	0.3377 5	0.8719
Meat	0.0841	0.2050	0.0641	0.1339	0.0276	0.0869	0.1339	0.0121

Since the milk and meat consumption (high levels) by toddlers and infants represents the worst case for risk assessments. The TMDI for THPI and hydroxylated THPI metabolites was calculated for these sub- populations.

Table B.7.3.15: TMDI calculation for THPI for toddlers and infants based on UK high consumption intakes

Commodity	THPI (mg/kg)	TMDI (mg/kg bw/day)	
		Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
Milk	0.005	0.00027	0.0005
Meat	0.02	0.000119	0.000007
Total exposure		**0.0004**	**0.0005**

The TMDIs of THPI are 0.0004 mg/kg bw/day (toddlers), 0.0005 mg/kg bw/day (infants).

Table B.7.3.16: TMDI calculation for 3- OH-THPI for toddlers and infants based on UK high consumption intakes

Commodity	3-OH-THPI (mg/kg)	TMDI (mg/kg bw/day) [1]	
		Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
milk	0.02	0.0011	0.0020
meat	0.02	0.0001	0.000027
Total exposure		**0.0012**	**0.0020**

The worst case for TMDIs for milk and meat of 3-OH-THPI are 0.0012 mg/kg bw/day (toddlers), 0.0020 mg/kg bw/day (infants).

Table B.7.3.17: TMDI calculation for 5-OH-THPI for toddlers and infants based on UK high consumption intakes

Commodity	5-OH-THPI (mg/kg)	TMDI (mg/kg bw/day) [1]	
		Toddlers (14.5 kg bw)	Infants (8.7 kg bw)
milk	0.005	0.00027	0.0005
meat	0.005	0.00003	0.000007
Total exposure		**0.0003**	**0.0005**

The worst case TMDIs from milk and meat of 5-OH-THPI are 0.0003 mg/kg bw/day (toddlers), 0.0005 mg/kg bw/day (infants).

Comparison of TMDI with ADI

The worst case TMDI values of THPI, 3-OH-THPI and 5-OH-THPI for the most sensitive consumer groups and diets are summarised in table B.7.3.18.

Table B.7.3.18: TMDI values for different consumer groups and diets

Diet	Body weight (kg)	TMDI (mg/kg bw/day)		
		THPI (%ADI)	3-OH-THPI (%ADI)	5-OH-THPI (%ADI)
WHO adult	60	0.000005 (0.005)	0.000135 (0.1)	0.000033 (0.03)
UK toddler	14.5	0.0004 (0.4)	0.0012 (1.2)	0.0003 (0.3)
UK infant	8.7	0.0005 (0.5)	0.0020 (2.0)	0.0005 (0.5)

Based on the proposed ADI for captan of 0.1 mg/kg bw/day, the TMDI for THPI represents 0.005% to 0.5% of the ADI for the most sensitive consumer groups and different dietary intakes.

Based on the proposed ADI for captan of 0.1 mg/kg bw/day, the TMDI for 3-OH- THPI represents 0.1% to 2% of the ADI for the most sensitive consumer groups and different dietary intakes.

Based on the proposed ADI for captan of 0.1 mg/kg bw/day, the TMDI for 5-OH- THPI represents 0.03% to 0.5% of the ADI for the most sensitive consumer groups and different dietary intakes.

Conclusion

The maximum possible daily intake of THPI, -3-OH-THPI and 5-OH-THPI (taking into consideration the most sensitive population group) are very low and significantly lower than the ADI for captan for the most sensitive consumer groups for animal products.

There is therefore a large margin of safety for all consumer groups.

g) Toxicity of THPI to aquatic organisms

NOTE: The summaries below already appear in the DAR under B.9.2 Effects on aquatic organisms (Annex IIA 8.2; Annex IIIA 10.2), B.9.2.1 Acute toxicity to aquatic organisms

(i) THPI: acute toxicity to rainbow trout (Oncorhynchus mykiss) (Kent, S.J. et al. 1994a; IIA, 8.2.1/10; IIA 7.3/13)

The 96-hour acute toxicity of THPI (metabolite of captan; purity 96% w/w) to the rainbow trout (*Oncorhynchus mykiss*) was determined in a limit test with a static system with aeration. Groups of ten fish in 27.5 L glass tanks containing 20 L test solution (15°C, 16:8 hour light/dark regime) were exposed to a nominal concentration of THPI (dissolved in [redacted] at 120 mg/L in comparison with a dilution water only (dechlorinated filtered tap water, total hardness approx. 27 mg $CaCO_3$/L) control and a solvent only (100 µL [redacted]/L) control for four days. The fish were not fed for 24 hours prior to, or during, exposure. The test solutions were not changed during the study. Samples of the test solutions were taken for analysis of the THPAM content (by HPLC) at the start of exposure and after 48 and 96 hours. Measurements of pH, dissolved oxygen and temperature were taken daily. Mortality and behaviour were recorded at 24-hour intervals after the start of exposure.

The study met the essential criteria of OECD 203. One fish used in the water only control was slightly smaller than recommended (50 ± 10 mm) but this is not considered to have affected the validity of the study. It was conducted according to Good Laboratory Practice.

The mean measured concentration of THPI in the dosed medium was 100% of the nominal value and so the results are presented as nominal values. The physical and chemical parameters of the test solutions remained at expected values during the study (pH 7.3 to 7.8 for both treatments).

There were no symptoms of toxicity or mortalities during the study.

Conclusion: The 96-hour LC_{50} of THPI to the rainbow trout under static conditions was greater than 120 mg/L. The NOEC was equal to or greater than120 mg/L based on the absence of toxicological symptoms observed at the dose tested. The 24, 48 and 72-hour LC_{50} values were also greater than 120 mg/L.

(ii) Captan: acute toxicity to rainbow trout (Jenkins, C.A. 2002a; IIA, 8.2.1/03; IIA 7.3/14)

The 96-hour acute toxicity of captan technical (purity 95.2% w/w) to rainbow trout (*Oncorhynchus mykiss*, mean wet weight 1.9 g, mean fork length 5.3 cm) was determined in a static test system without replacement of the test medium. Groups of seven fish in glass aquaria containing 35 L of test medium (12 to 17°C, 16:8 hour light/dark regime) were exposed to nominal concentrations of captan (dissolved in [redacted] at 30.1, 66.1, 145, 320 and 704 µg/L in comparison with a dilution water control treatment (dechlorinated, softened tap water, total hardness approximately 180 mg $CaCO_3$/L) and a solvent control treatment (100 µL [redacted] L) for four days. The fish were not fed for 21 hours prior to, or during, exposure. Samples of the stock solutions (captan in [redacted] were taken for analysis of captan by HPLC at the start of the test. Measurements of pH, dissolved oxygen and temperature were taken daily in all test vessels and hardness was measured at the start of the test. Temperature was monitored continuously in the control medium. Mortality and behaviour were recorded at 15 minutes, 2, 4, 24, 48, 72 and 96 hours after the start of exposure.

The study met the essential criteria of OECD 203 and EC Methods Part C 1. It was conducted according to Good Laboratory Practice.

Measured concentrations of captan in the stock solutions ranged from 91 to 102% of the nominal values. The results of the toxicity test are based on nominal concentrations of captan. The physical and chemical parameters of the test media remained at expected values during the study (pH 7.8 to 8.5, dissolved oxygen 88 to 106 % ASV, temperature 12.4 to 13.5°C and total hardness 178 to 180 mg $CaCO_3$/L).

At 320 and 704 µg/L, all fish exhibited hyperventilation within 15 minutes of exposure and were dead at 24 and four hours, respectively. At 66.1 and 145 µg/L, all fish were affected within 24 hours of exposure, exhibiting hyperventilation, darkened pigmentation and/or lethargy. Between 72 and 96 hours, some fish at 145 µg/L and six out of seven fish at 66.1 µg/L appeared to have recovered and were normal. At 30.1 µg/L, all fish appeared normal throughout the test. The darkened pigmentation in fish in the control treatments was ascribed to aggressive behaviour by one fish in each vessel. When the aggressive fish was screened from the other fish they appeared normal.

Conclusion: The 96-hour LC_{50} of captan technical to rainbow trout under static test conditions was 0.215 mg/L (with 95% confidence limits of 145 to 320 µg/L). Adjusting for the purity of captan in captan technical (95.2 %), the 96-hour LC_{50} was 0.205 mg/L (with 95% confidence limits of 0.138 to 0.305 mg/L). The NOEC was 0.0301 mg/L based on reversible toxic symptoms at 0.0661 mg captan technical/L.

A comparison of the toxicity of captan and THPI to rainbow trout is given in Table B.7.3.19. **Captan is more toxic to fish than THPI with a ratio of >500-fold.**

Table B.7.3.19: Summary of acute toxicity of captan and THPI to rainbow trout

Compound	LC_{50} (mg/L)	Reference
captan	0.215	Jenkins, C.A. 2002a; IIA, 8.2.1/03; IIA 7.3/08
THPI	> 120	Kent, S.J. et al. 1994a; IIA, 8.2.1/10; IIA 7.3/07

B.7.17 References relied on

B.7.17.1 Active substance

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
7.3a	Lukens R.J.	1966	The fungitoxicity of compounds containing a trichloromethylthio-group. Journal of Agricultural Food Chemistry 14: 365-367.	N	Public domain
7.3b	Rideg K.	1982	Genetic toxicology of phthalimide-type fungicides. Mutation Research 97: 217.	N	Public domain
7.3c	US EPA	2004	Captan: Cancer Reclassification; Amendment of Reregistration Eligibility Decision; Notice of Availability. 69 Fed. Reg. 68357-68360 November 24, 2004.	N	Public domain
7.3d	Blair M.	1988	One Year Oral Toxicity Study in Dogs with Captan Technical. [redacted] Report no. [redacted] 153-198; R-5284. [redacted] 4083604, October 25, 1988.	N	Makhteshim Agan
7.3e	Blair M.	1987	Captan: Four week toxicity study (dogs). [redacted] Report no. [redacted] 153-197; R-4689. [redacted] 40893605, May 1, 1987.	N	Makhteshim Agan

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
7.3f	Gordon E.B. et al	2000	Measurement of the reaction between the fungicides captan or folpet and blood thiols. MANA. September 11, 2000.	Y	Makhteshim Agan
IIA, 7.3/01	Elsea, J.R.	1955	Tetrahydrophthalimide: Acute oral administration - rats. [redacted] Not GLP; Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/02	Carver, J.H.	1986	Microbial/mammalian microsome mutagenicity plate incorporation assay with tetrahydrophthalimide. Chevron Chemical Company, unpublished report No. CEHC 2618, 27 (Company file: R-4409/TMN-0863). GLP; Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/03	Kennedy, G., Fancher, O. E., Calandra, J. C.	1968	An investigation of the teratogenic potential of captan, folpet, and difolatan. *Toxicology and Applied Pharmacology* **13**, 420-430. (Company file R-0169) Not GLP; Published.	N	-
IIA, 7.3/04	Blee, M.A.B.	2006	THPI: Prenatal toxicity study in the rabbit by oral gavage administration. Company file: Report MAK 864/053232. (Company file: R-18202) GLP, Unpublished.	Y	Makhteshim
IIA, 7.3/05	Chaudhry, Q.	2005	Assessment of the activity, toxicity and mutagenicity potential of THPI and THPAM, using structure activity relationships. Central Science Laboratory, report dated 4 February 2005 (Company file: R-18028). Not GLP, Unpublished	Y	Makhteshim
IIA, 7.3/07	Akhurst, L.C.	2005	THPI: Determination of minimum inhibitory concentrations against selected micro-organisms representative of the rabbit gut micro-flora. Report MAK 890/053252 (Company file: R-18735). GLP, Unpublished	Y	Makhteshim
IIA, 7.3/08	Chen, Y.S.	1988a	Plant metabolism study of [trichloromethyl-^{14}C] captan. Chevron Chemical Company, Report No. MEF-0009/8808900 (Company file: R-4992/TMN-0394). Not GLP, Unpublished.	Yes	Makhteshim/ Tomen

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection Claimed Y/N	Owner
IIA, 7.3/09	Chen, Y.S.	1988b	Plant metabolism study of [cyclohexene-1,2-^{14}C] captan. Chevron Chemical Company, Report No. MEF-0010/8805420 (Company file: R-4993/TMN-0393). Not GLP, Unpublished.	Yes	Makhteshim/ Tomen
IIA, 7.3/10	DeBaun, J.R., Gruwell, L.A., Menn, J.J.	1975	The fate of captan [carbonyl-^{14}C] on field-grown apple trees. Stauffer Chemical Company, Report No. MRC-B-44 (Company file: TMN-0396). Not GLP, Unpublished.	Yes	Arysta Paris
IIA, 7.3/11	Slesinski, R., S., Wilson, A. E	1992	National Milk Survey. Technical Assessment Systems, Inc., Washington, DC, Report 92-01. (Company file R-6147). GLP; Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/12	Wiebe, L.A.	1991	Captan: Magnitude of the residue of captan metabolites in bovine meat and milk. [redacted] unpublished report No. RR 91-033B (Company file: R-6730/TMN-0355). GLP; Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/13	Kent, S.J., Sankey, S.A., Caunter J.E., Magor, S.E.	1994a	THPI: acute toxicity to rainbow trout (*Oncorhynchus mykiss*). [redacted] Report BL5237/B. (Company file: R-8288/TMN-0025). GLP, Unpublished.	Y	Makhteshim/ Arysta Paris
IIA, 7.3/14	Jenkins, C.A,	2002a	Captan: acute toxicity to rainbow trout. [redacted] Report MAK660/013072. (Company file: R-12335/TMN-0020A). GLP, Unpublished.	Y	Makhteshim/ Arysta Paris