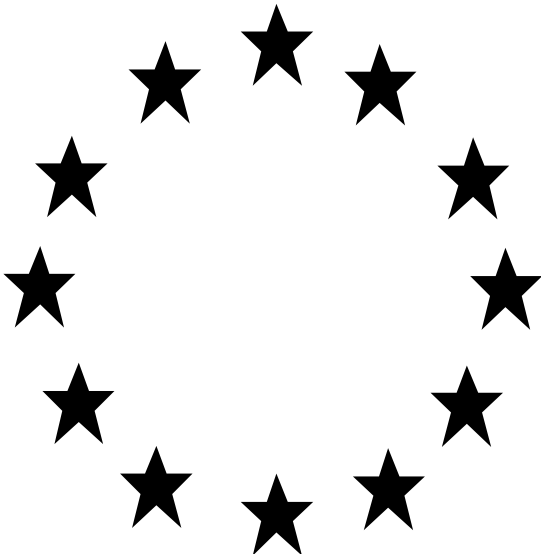

Final addendum to the

Draft Assessment Report (DAR)

- public version -

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

DIFLUBENZURON

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

March 2009

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Corrigendum to the Draft Assessment Report of May 2005

DIFLUBENZURON

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Rapporteur Member State: Sweden

December 2008

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Introduction

This corrigendum was prepared in response to the requirements of the Reporting table rev. 1-0 (20.12.2007). Included herein are also the results on the log P_{ow} of the metabolites which were omitted in the original Annex B.2.

B.2 Physical and chemical properties

B.2.1 Physical and chemical properties of the active substance (IIA 2)

B.2.1.8 Partition coefficient, log P_{ow}

Thus, J. L. G. **1988**

Test Material:	Diflubenzuron technical, batch id. Fun80D21D, purity 97.6 %, 4-chlorophenylurea, 2,6-difluorobenzoic acid
Method:	A modified version of OECD 117 HPLC method (a draft method at the time of the study), where a phenyl modified silica column and a highly salt containing mobile phase buffered at pH 3, were utilized.
Results:	At pH=3.0 and 22 °C ± 0.1 °C: diflubenzuron: log Pow=3.89 ~~at pH=3.0 and 22 °C ± 0.1 °C~~ 4-chlorophenylurea: log P_{ow} =1.14 2,6-difluorobenzoic acid: log P_{ow} =-0.02
Comments:	The measurement was performed with technical grade substance instead of pure substance. However, since the HPLC-method is less sensitive to impurities than the "shake-flask"-method, this should not have affected the result. The measurement was only done at pH 3 and the pH-effect was not examined. Moreover the measurement was not performed in accordance with GLP. Nevertheless, the results from the study show a good relationship between the log P_{ow}-values (literature data) for reference compounds, and the retention data. Moreover the solubility of diflubenzuron in water (see B.2.1.6) was proven to be virtually the same at pH 4 and pH 7, which means that the low pH utilized in this study should not have affected the result significantly. Consequently, the method and the result are acceptable.

B.2.2 Physical, chemical and technical properties of the plant protection product –Water dispersible granules (WG)

Product trade name	Product code number	Concentration of active substance
Dimilin WG-80	-	800 g/kg

B.2.2.8.5.1 Dry sieve test

Reporting table point 1 (21).

Results on dry sieving are available from the shelf-life study and could be presented in B.2.2.8.5.1 even though it is not required for a WG-formulation. RMS to consider a corrigendum.

Not ~~applicable~~ required, since Dimilin WG-80 is not a dustable powder formulation. However a dry sieve test was performed in the shelf-life study and is thus also presented here:

Poel, E. N. **1998**

Test Material:	Dimilin WG-80, batch id. FUN93I21C/FUX024000, concentration of active substance: 79.4% w/w	
Method:	Sieve test (eq. to CIPAC MT 170)	
Results:	Sieve size (mm)	r_x (%)
	> 1	0.03
	0.5-1	30.7
	0.25-0.5	57.5
	0.1-0.25	11.4
	< 0.1 (dust)	0.20
Comments:	The method and the result are acceptable	

Addendum to
Draft Assessment Report

DIFLUBENZURON

Volume 3
Annex B.5
Analytical method

Rapporteur Member State: Sweden

December 2008

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

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Introduction

The Draft Assessment Report on diflubenzuron was finalised and submitted to EFSA in May 2005.

In September 2007 the applicant submitted a new batch analysis and the active ingredient assay method employed in that study was not the same as presented in the original DAR. The method is thus presented in this Addendum.

In addition to this, presented herein are the study aimed to show the applicability of multi-residue methods for analysis of diflubenzuron in plant materials (point of clarification 1.2 in the evaluation table) and the new method for analysis of residues in air (data gap). Addressed herein is also the type of soil used in the validation of the soil method presented in the DAR (open point 1.14). The characteristics of the water used in the validation of the water method (see the original DAR) were provided as supplementary information in January 2007 to address open point 1.14 and it is also presented in this Addendum. Finally, the situation for the analytical method(s) for residues in plant material is clarified in this Addendum as a background for discussions at a meeting of experts (open points 1.13 and 1.16).

B.5 Methods of Analysis

B.5.1 Analytical methods for formulation analysis (Annex IIA, 4.1, Annex IIIA, 5.1)

B.5.1.1 Analytical methods for the determination of the active substance in the active substance as manufactured

In the peer-review a new batch analysis derived from fully validated methods was requested (data gap in the Evaluation table). New batch data was provided in September 2007 and the method used for the analysis of the active substance was not the same as presented in the original DAR. The new method was not specifically requested in the peer-review but as it is a part of the requested batch analysis it is presented below.

Reference:	Goebel, N. (2007). Determination of diflubenzuron in technical and formulated materials by high performance liquid chromatography with internal standardization. Method Number GRL-GM-1066 given as Appendix VI in: Riggs, A.S. (2007) Preliminary analysis of diflubenzuron technical. Final Report Chemtura Canada Co./Cie, Guelph Technology Centre. PO Box 1120, 120 Huron Street Guelph, Ontario, Canada N1H 6N3. Test Facility Study Number: GRL-12508. GLP, Not Published, CONFIDENTIAL
GLP:	Yes (the method GRL-GM-1066 contains a summary of the validation data which is stated to have been derived according to GLP in studies GRL-10796, GRL-11113, GR-12060, GRL-12242 and GRL-12483 which were not submitted to the RMS)

Principle of the method: The technical material is dissolved in dioxane (~90 mL) under heating (70-80°C) and occasional swirling. 10 mL internal standard solution (linuron in acetonitrile) is added and the solution is diluted 1:9 with the eluent (acetonitrile:water:dioxane, 550:550:25). The content of diflubenzuron is determined by HPLC fitted with a Bondapak C18 column employing gradient elution (acetontrile:water:dioxane, 45:45:10→100:0:0) and UV-detection at 254 nm using external calibration relative to the internal standard.

Validation Data:

Specificity: The specificity was checked by means of HPLC-DAD and there was no evidence of peak interference with diflubenzuron or the internal standard from the known impurities in technical diflubenzuron.

Linearity: The linearity was assessed using 5 calibration points in the range 19.2-80.1 mg/1000 ml, corresponding to an actual content of ~40-160% diflubenzuron in the technical material. The curve was found to be linear with a correlation coefficient of 1.000.

Accuracy: The accuracy was assayed as %recovery of added diflubenzuron to technical diflubenzuron. The results are given table B.5.1.1-1

Precision (Repeatability): The method precision was determined by the analysis of six weights of the technical diflubenzuron. The results are given in table B.5.1.1-2

Table B.5.1.1-1: Accuracy data for method GRL-GM-1066 (Riggs, 2007)

Recovery (%)	N	%RSD	F test	Critical F (95% conf.)	t-test	Critical t (99.5% conf.)
101.4%	4	0.17	2.82	9.28	3.83	7.45

Table B.5.1.1-2: Precision data for the analysis of six replicates using method GRL-GM-1066 (Riggs, 2007)

Mean (%w/w)	SD	%RSD	Acceptable %RSD (Horwitz)
96.9	1.01	1.04	1.35

RMS conclusion:

The validation data provided in the method description is considered sufficient even though the primary validation study was not provided. The validation data is in compliance with the criteria in SANCO/3030/99 rev.4 and the batch data derived using the method is thus acceptable. It should be noted that the used method is very similar to the CIPAC method 339/TK/M/-.

B.5.1.2 Analytical methods for the determination of the impurities in the active substance as manufactured

The fully validated method for the impurities, used in the new batch analysis, is considered to be confidential-see Addendum to Annex C

B.5.2 Analytical methods (residue) for plants, plant products, foodstuff of plant and animal origin, feedingstuffs (Annex IIA 4.2.1; Annex IIIA 5.2)

B.5.2.1 Analytical methods for analysis of residues in food of plant origin

Applicability of multiresidue method

In the peer-review it was concluded that the applicability of a multi-residue method for the analysis of diflubenzuron in food of plant origin must be addressed (1.2 point of clarification in the Evaluation table). In January 2007 the applicant submitted a study aiming to analyse diflubenzuron according to the US FDA's multi-residue method. The study is presented below:

Reference:	**Allan, E. and Pouwelse, A. V. (1993)** Determination of diflubenzuron residues according to multiresidue methods described in FDA's pesticide analytical manuals. Solvay Duphar B.V., Analytical Development Department, C.J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands, Laboratory Project ID: C.303.50.019, GLP, Not Published
GLP:	Yes
Principle of the method:	The procedures for multi-residue methods laid down in FDA's Pesticide Analytical Manual Vol. 1 were followed (available at http://www.cfsan.fda.gov/~frf/pami1.html). The guideline describes procedures for GC and HPLC, but the latter seems only to be described for specific classes of substances (i.e. N-methyl carbamates). GC conditions were therefore used for diflubenzuron employing the mildest chromatographic conditions, as diflubenzuron was known to decompose under normal GC-conditions (i.e. hot injection devices). Diflubenzuron calibration solutions with concentrations of 0.107, 1.07, 107 µg/l and 0.107 and 1.07µg/l in acetone and n-hexane respectively were used. Calibration solutions of teradifon, a pesticide usually analysed by GC, with roughly the same concentrations were used as reference check of the performance of the analytical system. A GC-chromatograph fitted with a fused silica 30 m x 0.32 mm capillary column coated with 0.25 µm DB-17, ECD and FID-detectors was used employing cold on-column injection and a column heating programme of 75°C → 250°C (30°C/min). HPLC-UV was also used for verification of the concentration of the injected calibration solutions.
Results:	For all injected solutions, tetradifon was found as a single chromatographic signal, whereas no diflubenzuron was found. When the highest concentrated diflubenzuron solution was analysed a multiple signal was found, probably due to decomposition. Hereby, the full testing of the multi-residue method was not performed.

RMS comments: The study proved that diflubenzuron is not amenable to GC-analysis. Given that the multi-residue method DFG S19 is based on GC, it is also not considered applicable to diflubenzuron. However there are examples in the open literature of multi-residue methods for diflubenzuron using LC-MS/MS (Pihlstrom, T., *et al.*, 2007, Anal. Bioanal. Chem. DOI 10.1007/s00216-007-1425-6; Klein and Alder, 2003, Journal of AOAC International, Vol. 86, No. 5.).

Clarification of the situation of the available method for analysis of residues in apple, pomace and juice

In the peer-review the validation data for the primary validation study for the method in apples, pomace and juice presented in the DAR (Thus and Allan, 1995) was not considered acceptable and not in support of the claimed LOQ of 0.01 mg/kg (reporting table 1(31)).

In addition to this it was questioned if there was any confirmatory method available and if the presented ILV of the method (Rose, 2001) was a ILV or a different method as it appeared that a different detector was used (reporting table 1(41)). These comments resulted in open point 1.13 in the evaluation table stating that "The acceptability of the validation data for the plant residue methods should be discussed by a meeting of experts". As a background for the proposed discussion the RMS has tried to clarify the situation below, by making revisions of the original data presented in the DAR.

Reference:	**1. Thus, J.L.G. and Allan, E. (1995). Diflubenzuron residues in apple, pomace and juice. Report Solvay Duphar B.V., The Netherlands, No. 56835/49/1994, DI – 9320.** ~~**2. Thus, J.L.G. and Allan, E. (1996). Addendum to report diflubenzuron residues in apples, pomac and juice. Report Solvay Duphar B.V., The Netherlands No. 56834/95/1996, DI – 9320.**~~
Method:	Apple matrix Diflubenzuron is extracted from apple homogenates with dichloromethane and the extract is purified on a Florisil cartridge. The amount of diflubenzuron is determined by HPLC using a C8-column and a mixture of tetrehydrofuran/acetonitrile/water (10/40/50, v/v/v) as mobile phase. Diflubenzuron is detected by UV spectrometry at 254 nm. The content of diflubenzuron is determined by comparing the peak height of the sample with that of standard solutions of diflubenzuron (calibration line).
GLP:	Yes

Validation Data:

Specificity:	Control samples of untreated apples (Idared, Elstar, James Grieve varieties) contained no or low traces of diflubenzuron (< 0.003 mg/kg). Jonagold variety contained diflubenzuron in the range 0.004 – 0.011 mg/kg, which was still less than 10% of the residue found in treated samples. No

interfering co-extractive compounds were observed.

Linearity: Analytes in mobile phase (six concentrations in the range 0-1.11 µg/ml) were analysed to determine linearity. The calibration curve was obviously linear to the naked eye, with the linear equation reported (i.e. based on peak heights not peak areas using 6 calibration points each for apples and pommace and juice) ~~(however, the coefficient of correlation or determination was not presented)~~. The correlation coefficient was not reported in the study, but using the calibration data the RMS calculated correlation coefficients of 1.0000 and 0.9997 for whole apples and pomace and juice respectively. ~~This calibration curve corresponded to apple analysis, and a calibration curve of very similar performance was presented when juice/pomace matrices was used in the validation~~

Accuracy: Determined as recovery (see table B.5.2.1-1 below). Mean recoveries, globally and for each fortification level, were within the range 80-110%. More detailed accuracy data is available in the report and it is presented in table B.5.2.1-2 below (also given as supplementary information by the applicant in February 2007).

Precision (Repeatability): ~~Not calculated (se table below) but obviously well ≤ 20% (rsd)~~
Not explicitly reported in the study. However, using the raw data presented the %RSD for each level is calculated by RMS and presented in table B.5.2.1-2 below (also given as supplementary information by the applicant in February 2007).

LOQ: Reported as 0.01 mg/kg in the study. However, the applicant stated during the peer-review that using statistical analysis of the recoveries for the 0.1 mg/kg spikes a LOQ of 0.1 mg/kg is confirmed, which is in line with the lowest fortification level used.
The LOQ is thus 0.1 mg/kg.

LOD: Not reported in the study. However, during the peer-review the applicant submitted a statistical analysis of the recoveries from the 0.1 mg/kg spikes (t-statistics x std deviation), which gives a LOD of 0.038 mg/kg.

~~**Results:**~~

Table B.5.2.1-1: Validation data as presented in original DAR (Thus and Allan, 1995)

Matrix	Fortification level (mg/kg)	Recovery (%)	Global mean recovery (%)	Coefficient of variation (%)
Apples	0.1	70-102 (n=8)	91	Not reported
	1	94-103 (n=8)		Not reported
Apple pomace	0.1	67-88 (n=4)	88	Not reported
	1	95-102 (n=4)		Not reported
Apple juice	0.1	97-103 (n=4)	100	Not reported
	1	97-108 (n=4)		Not reported

Table B.5.2.1-2: More detailed accuracy and precision data (Thus and Allan, 1995)

Matrix	Fortification level (mg/kg)	Individual Recovery (%)	Mean recovery (%)	%RSD
Apples:				
Blank	0	<LOQ, <LOQ, <LOQ, <LOQ	-	-
Idared	0.1	79, 70	82	14
Elstar		93, 102		
Jonagold		86, 86		
James Grieve		70, 71		
Idared	1.0	101, 102	99	3.2
Elstar		98, 98		
Jonagold		96, 94		
James Grieve		103, 101		
Pomace:				
Blank	0	<LOQ, <LOQ	-	-
Jonagold	0.1	84, 88	77	13
James Grieve		67, 70		
Jonagold	1.0	102, 95	98	2.3
James Grieve		98, 98		
Juice:				
Blank	0	<LOQ, <LOQ	-	-
Jonagold	0.1	98, 98	97	2.7
James Grieve		97, 103		
Jonagold	1.0	108, 100	102	4.6
James Grieve		97, 101		

RMS comments (re-evaluation): The validation data is in compliance with the requirements in SANCO/825/00 rev.7, except that only four samples instead of five were used for each fortification level for pomace and juice. However, given the total number of samples used for each fortification level the method is considered sufficiently validated for a LOQ of 0.1 mg/kg. No confirmatory method is presented, but further information is available in the ILV-study (see below).

Independent Laboratory Validation

Reference:	**Rose, J.E. (2001). Independent laboratory validation (ILV) of an analytical method for analysis of diflubenzuron in apple and processed apple matrices. Report PTRL west INC., U.S.A. No.971 W-1 (Uniroyal Chemical Company No. RP-0009), D-11641.**
Method:	Same as above (but supplemented with negative APCI LC-MS confirmation, using a slightly modified mobile phase to increase ionisation). However, the validation data was generated using the exact same method as for the primary validation study (i.e. HPLC-UV).
GLP:	Yes.

Validation Data:

Specificity:	The method is specific, which is supported by LC-MS at 0.10 mg/kg (using the [M-H] of m/z 309 and the [M+formic acid] of m/z 355 but also the [M-H]-HF of m/z 289 is visible).

Linearity: The calibration curve was based on nine concentrations (0.01, 0.02, 0.05, 0.10, 0.20, 0.30, 0.50, 0.75 and 1.00 µg/ml). The linear equation was reported (r^2=0.9995) and the curve appeared nicely linear to the naked eye. The linear range corresponds to 25% (apples) of LOQ to ~90% of 10 x LOQ (juice).

Accuracy: Determined as recovery (see table B.5.2.1-3 below). Mean recoveries were all within the range 80 – 110% (all matrices and all fortification levels).

Precision (Repeatability): Determined as RSD (see table B.5.2.1-3 below). All RSD were < 20%.

LOQ: 0.01 mg/kg.

LOD: Calculated to be 0.005 mg/kg for apples and 0.002 mg/kg for apple juice and pomace.

~~**Results:**~~

Table B.5.2.1-3: Validation data for ILV for apple, pomace and juice (Rose, 2001)

Matrix	Fortification level (mg/kg)	Recovery (%)	Mean recovery (%) (n=5)	RSD (%)
Apples (McIntosh)				
	Blank	<LOQ, <LOQ	-	-
	0.01	75.0 – 106.0	91.6	15.0
	0.1	94.5 – 101.7	97.8	2.7
Apple juice				
	Blank	<LOQ, LOQ	-	-
	0.01	86.7 – 96.9	91.2	5.2
	0.1	79.5 – 84.6	81.9	2.8
Apple pomace				
	Blank	<LOQ, <LOQ	-	-
	0.01	75.0 – 86.0	79.8	6.2
	0.1	75.8 - 105.6	89.2	12.2

RMS comments (re-evaluation): The validation data is in compliance with the requirements in SANCO/825/00 rev.7.

RMS conclusion on the method for residues in apple, pomace and juice: The primary validation is considered acceptable with only a slight deviation in the number of samples for fortification for pomace and juice. However, no confirmatory method was presented. The primary validation indicated a LOQ of 0.1 mg/kg.

The ILV-study was also acceptable and it included a LC-MS procedure for confirmation. The ILV-study was conducted at 0.01 mg/kg and 0.1 mg/kg which gave acceptable accuracy and precision data, whereby this study indicates a LOQ of 0.01 mg/kg. However, in conclusion as the primary validation gives a LOQ of 0.1 mg/kg only this level could be seen to be sufficiently validated by primary validation and ILV. If the LOQ thus is set at 0.1 mg/kg, no ILV is available for >LOQ, so this issue might need to be discussed at a meeting of experts.

It should be noted that the available MRLs for diflubenzuron in pome fruit is 5 mg/kg according to Regulation (EC) No 396/2005. This means that according to SANCO/825/00 rev.7 the validation should have been performed at 0.1 mg/kg (LOQ) and 5 mg/kg (MRL).

Clarification of the situation of the available method for analysis of residues in mushrooms

In the peer-review the validation data for the primary validation study for the method for residues in mushrooms presented in the DAR (Gaydosh, 1998) was not considered acceptable (reporting table 1(32), (43) and (44)).

These comments resulted in open point 1.13 in the Evaluation table stating that "The acceptability of the validation data for the plant residue methods should be discussed by a meeting of experts". As a background for the proposed discussion the RMS has tried to clarify the situation below, by making revisions of the original data presented in the DAR.

Reference:	**Gaydosh, K.A. (1998). Dimilin 25 W and Dimilin 4 L in mushrooms: Magnitude of the residue study. Report Uniroyal Chemical INC., U.S.A. No. RP-97004, DI-11455.**
Method:	~~Mushroom matrix~~ Diflubenzuron Diflubenzuron is extracted with ethyl acetate (2x), evaporated to dryness and re-dissolved in dichloromethane and purified on a Florisil cartridge. The amount of diflubenzuron is determined by reversed phase HPLC (Zorbax C8 column) using gradient elution (acetonitrile:water:1,4-dioxane, 45:45:10 →85:5:10) with UV spectrometric detection at 254 nm. The content of diflubenzuron is determined by comparing the peak ~~height~~ area of the sample with that of standard solutions of diflubenzuron (calibration line). 4-chlrorophenyl urea (CPU) CPU is extracted with ethyl acetate (2x), evaporated to dryness and re-dissolved in acetone:petroleum ether (5:25) and purified on a deactivated silica column. The residue is evaporated to dryness and re-dissolved in acetontrile. The CPU is derivatised using heptafluorobutyric acid anhydride (HFBA) and the derivative is analysed on GC fitted with a DB 5 capillary column and electron capture detector (ECD). The content of CPU is determined by comparing the peak area of the sample with that of derivatised standard solutions of CPU (calibration line). 4-chloroaniline (PCA) PCA is extracted with 0.1 N aqueous HCl and the extract is adjusted to pH > 12 using 50% aqueous NaOH and the PCA is extracted with hexane. The combined hexane extracts are purified on a Florsil column and the eluant is derivatised using heptafluorobutyric acid anhydride (HFBA) and the derivative is analysed on GC fitted with a Supelco SPB 1701 capillary column and MS-detector (SIM mode). The PCA is identified by coincidence of its retention time with the internal standard (^{13}C-PCA), and quantified by integration of the peak areas for ^{12}C-PCA relative to peak areas for ^{13}C-PCA. Additionally, quantitation was achieved by peak area of the ^{12}C-PCA relative to the external standard linearity curve (derivatised PCA). The following fragments are used for quantification and identification m/z 323 (derivatised PCA), 329 (derivatised ^{13}C-PCA),

	126 (PCA) and 132 (^{13}C-PCA).
GLP:	Yes (with documented exceptions)

Validation Data:

Specificity:

Diflubenzuron and CPU

The analyte was identified by the coincidence of its retention time with the reference standards and quantitated by integration of the peak area. Control samples showed no peak areas >LOD. No confirmatory procedure is presented.

PCA

The analyte was identified by the coincidence of its retention time with the internal reference standard and the external reference standards. Control samples showed no peak areas >LOD. Given that quantification/confirmation was based on retention time matching with both internal ^{13}C-standard and external PCA standard as well as the use of two fragments each for the ^{12}C-PCA and the ^{13}C-PCA, the method is considered highly specific.

Linearity:

Diflubenzuron

The calibration curve was based on injections of diflubenzuron standards of the concentrations 0.025, 0.05, 0.1, 0.25, and 0.5 µg/ml. The linear equation of the calibration line was reported (r^2=1.000).

CPU

The calibration curve was based on injections of derivatised CPU standards of the concentrations 0.005, 0.01, 0.05 and 0.1 µg/ml. The linear equation of the calibration line was reported (r^2=0.993).

PCA

The external calibration curve was based on injections of derivatised PCA standards of the concentrations 0.025, 0.05, 0.1 and 0.5 µg/ml. The linear equation of the calibration line was reported (r^2=0.996).

The internal standard calibration curve was based on injections of ^{12}C-PCA:^{13}C-PCA mass ratios of 0.5:1.0, 1.0:1.0, 5.0:1.0 and 10.0:1.0. The linear equation of the calibration line was reported (r^2=1.000).

Accuracy:

Determined as recovery (se table B.5.2.1-4 below). Global mean recovery was within the range 80-100%.

More detailed accuracy data is available in the report and is presented in table B.5.2.1-5 below (also given as supplementary information by the applicant in February 2007). In addition to the duplicate fortifications performed at two levels, a duplicate determination of two fortified samples were performed for each residue trial (QC-sample) meaning a total of 16 fortifications and 32 determinations.

Precision (Repeatability): ~~Not calculated (se table below) but obviously well ≤ 20% (rsd)~~
Not reported in detail in the study. However, using the raw data presented the %RSD for each level is calculated by RMS and presented in table B.5.2.1-5 below.

LOQ: 0.01 mg/kg

LOD: Not reported

~~**Results:**~~

Table B.5.2.1-4: Validation data as presented in original DAR (Gaydosh, 1998)

Matrix	Fortification level (mg/kg)	Recovery (%)	Mean recovery (%)	Coefficient of variation (%)
Mushroom	0.01	not reported	88	SD=11
	0.1 (QC samples)	not reported		
	0.20	not reported		

Table B.5.2.1-5: More detailed accuracy and precision data (Gaydosh, 1998)

Matrix	Analyte	Fortification level (mg/kg)	Recovery range (%)	N	Mean recovery (%)	%RSD
Mushroom	Diflubenzuron	0.01	72-82	2	77	9.2
		0.2	92-97	2	95	3.7
		0.1	80-111	16	97	8.0
	CPU	0.01	88-106	2	97	13
		0.1	86-104	2	95	13
		0.02	70-125	16	97	16
	PCA	5.0 µg/kg	106-117	2	112	7.0
		10 µg/kg	113	2	113	-
		10 µg/kg	89-160	16	106	12

RMS comments (re-evaluation): As the residue definition for mushrooms is under discussion the RMS has presented the available data also for the metabolites. However, no ILV is available for the analysis of the metabolites.

The validation data presented for diflubenzuron and the metabolites CPU and PCA is in compliance with SANCO/825/00 rev.7 with respect to recovery and %RSD. However, the sample set deviates from the requirements as only two samples were used at each fortification level for the normal validation. Further data is available from the control fortification performed for each residue trial so one can argue that the overall number of samples used is acceptable.

Nevertheless, for diflubenzuron the LOQ level has too few samples whereas the 10 x LOQ is acceptable. For CPU the samples at both LOQ and 10 x LOQ is too few whereas the 2 x LOQ is sufficient, whereby it can be argued that LOQ should be set at 0.02 mg/kg. For PCA the situation is similar to that for CPU with too few samples at LOQ and 2 x LOQ in the normal validation (i.e. 2 x LOQ is used instead of 10 x LOQ), but with sufficient samples at 2 x LOQ (i.e. 10 µg/kg) in the additional validation. See further discussion in the overall evaluation below the ILV-study.

Finally, no confirmation method was presented for diflubenzuron and CPU, whereas the method presented for PCA could bee seen as highly specific. Further information is also available in the ILV-study (see below).

Independent Laboratory Validation

Reference:	**Class, T. (2001). Independent laboratory validation (ILV) of an HPLC/UV based analytical method for the determination of diflubenzuron in plant material. Report PTRL Europe GMBH, Germany No.B 451 G (Uniroyal Chemical Company No.RP-00013), DI-11640.**
Method:	Same as above for generating validation data (with documented minor changes), but up-graded with a LC-MS/MS method for confirmation (C18-column, acetonitrile: 0.1% aqueous formic acid, 50:50 → 95:5, negative APCI monitoring the transition m/z 309/311 ([M-H]$^-$, Cl_1 isotopic pattern) → m/z 289 [M-H_2F])
GLP:	Yes

Validation Data:

Specificity:	The method is specific, which is supported by LC-MS/MS. LC-MS/MS chromatograms of calibration solutions, blank controls and a sample fortified at LOQ indicated that the confirmatory method is acceptable. Residues of 35% of LOQ were found in the blanks using the HPLC-UV method (see also accuracy below).
Linearity:	The calibration curve was based on injections of diflubenzuron standards of eight concentrations (0.010 – 1.5 µg/mL). The curve appeared nicely linear to the naked eye and the linear equation was reported (r^2=0.999865). The linear range corresponds to 15% of LOQ to 140% of 10 x LOQ.
Accuracy:	Determined as recovery (see table B.5.3.1-6 below). Mean recoveries, globally and for each fortification level, were within the range 80 -110%. In control sample (blank) 0.0034 mg diflubenzuron/kg was found (ca 35% of LOQ), a value which was used for corrections of the recoveries (below).
Precision (Repeatability):	Determined as RSD (se table B.5.3.1-6 below). All RSD were < 20%.
LOQ:	0.010 mg/kg.
LOD:	Estimated to be 0.005 mg/kg.

Table B.5.2.1-6: Validation data for ILV for mushrooms as presented in the original DAR (Class, 2001)

Matrix	Fortification level (mg/kg)	Recovery (%)	Mean recovery (%) (n=5)	RSD (%)
Mushrooms	0.01	77-109 (corr) 111-143 (uncorr)	92 (cor) 126 (uncorr)	16 (corr) 12 (uncorr)
	0.1	95-104 (corr) 98-107 (uncorr)	99 (corr) 102 (uncorr)	4 (corr) 4 (uncorr)

RMS comments (re-evaluation): The generated validation data corrected for the levels found in the blanks are in compliance with the criteria in SANCO/825/00 rev.7. However, it should be noted that blank levels above 30% is not accepted according to SANCO/825/00 rev.7 whereas levels as high as 38% were found in this study.

RMS conclusion on the method for residues in mushrooms: The validation data generated in the primary validation (Gaydosh, 1998) indicates that the method is acceptable. However, the used sample set was too small (i.e. only two samples per fortification level with additional samples at one more level). Moreover, no confirmatory method was presented for diflubenzuron and the metabolite CPU.

In the ILV-study (Class, 2001) a sufficient sample set was used and the data was in compliance with the criteria in SANCO/825/00 rev.7. However levels of >30% LOQ were found in the blanks, which is not acceptable according to SANCO/825/00 rev.7. Finally an acceptable confirmatory method based on LC-MS/MS was presented for diflubenzuron in the ILV-study.

In conclusion therefore the acceptance of the available data needs to be discussed at a meeting of experts as the primary validation was performed using a too small sample set and as levels >30% of LOQ were found in the blanks in the ILV-study.

It should be noted that the available MRLs for diflubenzuron in cultivated mushrooms is 2 mg/kg according to Regulation (EC) No 396/2005. This means that according to SANCO/825/00 rev.7 the validation should have been performed at 0.1 mg/kg (LOQ) and 2 mg/kg (MRL).

B.5.3 Analytical methods (residue) soil, water, air (Annex IIA 4.2.2 to 4.2.4)

B.5.3.1 Analytical method for the determination of residues in soil (Annex IIA 4.2.2)

In the peer-review it was concluded that details of the type of soil used in the validation of the analytical method for soil is needed (open point 1.14 in the Evaluation table). In the study presented in the original DAR (Faltzynski, 2003a) the used soil was reported as a sandy loam type and no further characteristics were given. However, this information is considered to be sufficient to address the open point 1.14.

B.5.3.2 Analytical method for the determination of residues in water (Annex IIA 4.2.3)

In the peer-review it was concluded that the source and characteristics of the water used in the validation of the water method should be given (open point 1.15 in the Evaluation table). In the study included in the DAR (Faltzynski, 2003b) it is stated that the water used was obtained from a local pond (Winston-Salem, NC, U.S.A.). Furthermore it stated that the water was characterized by Agvise Laboratories and the sample was given the EN-CAS (the company performing the validation) id ES0537.

In January 2007, the applicant submitted a one page document, signed by Robert Deutsch 21.03.2003, which appears to be the characterization report of sample ES0537 performed by Agvise laboratories (see table B.5.3.2-1 below). The open point 1.15 is therefore considered addressed.

Table B.5.3.2-1: Characteristics of the water sample ES0537

pH	6.8
Sodium	6 ppm
Calcium	4 ppm

Magnesium	2 ppm
Hardness mg equivalent $CaCO_3$/L	16 ppm
Conductivity	0.18 mmhos/cm
Sodium Adsorption Ratio (SAR)	0.66
Total Dissolved Solids	52 ppm
Total Suspended Solids	10 ppm
Turbidity	12.5 NTU
Dissolved Organic Carbon	4.4 ppm
Total Organic Carbon	5.0 ppm

B.5.3.4 Analytical method for the determination of residues in air (Annex IIA 4.2.4)

Already in the DAR it was highlighted that the available method for analysis of diflubenzuron in air was not sufficient as it was not highly specific. In May 2006 the RMS received a new method for air and it was proposed in the peer-review that it should be evaluated in an Addendum (reporting table 1(53)), which resulted in the data gap "Analytical method for air" in the Evaluation table. The new method is presented below.

Reference:	**Bacher, R. (2006).** Validation of an analytical confirmatory method for the determination of diflubenzuron in air. Report PTRL Europe GmbH, Germany, No. B 1000 G (Chemtura 2006-001), DI – 11817., GLP, Not Published
GLP:	Yes
Principle of the method:	Air is drawn through XAD adsorption tubes (i.e. stated to retain both particles and aerosols) at about 1.4 L/min for approximately 6 hours (total air sampling volume ≈ 0.5 m^3). Subsequently, the adsorption material is extracted with methanol. The extract is chromatographed on HPLC fitted with a C_{18}-column using gradient elution (0.1% aqueous formic acid: 0.1% methanolic formic acid, 70:30→5:95) and tandem mass spectometry for detection. The method was validated for two transitions: 309→289 (primary) and 309→156 (qualifier).
Validation Data:	
Specificity:	The LC/MS/MS chromatograms of the blank control specimens showed no signals (< 0.12 µg/m^3) at the retention time of diflubenzuron. The method used is highly specific.
Linearity:	Linearity was established over the range 0.50 to 50 ng/mL (20% of LOQ to 200% of 10 x LOQ) using seven calibration points. The correlation coefficient was r^2 = >0.995 for both transitions using a 1/x weighing.
Accuracy:	Determined as recovery (see table B.5.3.4-1 below). The extraction efficiency and storage stability was demonstrated with acceptable average recoveries of 87 % to 109%. The average recoveries for the analyte, for both fortification levels and both

MS/MS transitions after air sampling ranged between 102% to 108% with relative standard deviations ≤6%.

No breakthrough above 5% was observed in the second chamber of the air sampling units.

Precision (Repeatability): Determined as %RSD (se table B.5.3.4-1 below). All RSD were < 20%.

LOQ: The limit of quantification (LOQ) was 0.6 µg/m^3. This is in compliance with the criterion in SANCO/825/00 rev.7 since the LOQ is lower than C, which using an AOEL of 0.0066 mg/kg bw/day, is equal to 1.98 µg/m^{3}air.

LOD: Estimated to be ≤ 0.12 µg/m^3.

Table B.5.3.4-1: Validation data for the air method (Bacher, 2006)

Specimen type	Fortified diflubenzuron (µg)	Average C_{Air} (µg/m^3)	309 m/z →289 m/z			309 m/z →156 m/z			n
			Range recovery	Average recovery	RSD	Range recovery	Average recovery	RSD	
Extraction efficiency	0.30	--	108-109%	109%	--	107-108%	107%	--	2
	3.0	--	83-93%	87%	--	82-91%	87%	--	2
	Overall		83-109%	98%	13%	82-108%	97%	13%	4
Storage stability: overnight, RT	3.0	--	95-102%	99%	--	94-101% 96-99%	97%	--	2
Storage stability: 5 days, RT	3.0	--	97-98%	97%	--	96-99%	98%	--	2
Ambient air 21 °C, 22% relative humidity	0.30	0.63	104-112%	108%	3%	106-111%	108%	2%	5
	3.0	6.1	100-108%	102%	3%	100-107%	102%	3%	5
Warm, humid air 35°C, 99% relative humidity	0.30	0.62	99-114%	107%	5%	97-116%	107%	6%	5
	3.0	5.9	104-110%	107%	2%	105-108%	107%	1%	5

RSD = relative standard deviation
n = number of specimens included in calculation
Average C_{Air} = Average fortified concentration of diflubenzuron in air
RT = room temperature

RMS comments: The method was fully validated and the data generated is in compliance with the criteria in SANCO/825/00 rev.7. The data requirement for a method for air is therefore considered met.

B.5.6 References relied on

Only references not presented in the original DAR included here.

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, 4.1.1/01	Riggs, A. S.	2003	Validation of an analytical method for the determination of organic impurities in technical diflubenzuron using HPLC. Final Report Chemtura Canada Co./Cie, Guelph Technology Centre. PO Box 1120, 120 Huron Street Guelph, Ontario, Canada N1H 6N3. Test Facility Study Number: GRL-12064, Sponsor Project Number: 2003-048 GLP, Not Published CONFIDENTIAL	Y	CRO
IIA 4.2.1/01	Allan, E Pouwelse, A.V.	1993	Determination of diflubenzuron residues according to multiresidue methods described in FDA's pesticide analytical manuals. Solvay Duphar B.V., Analytical Development Department, C.J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands, Laboratory Project ID: C.303.50.019, GLP, Not Published	Y	CRO
IIA 4.2.4/01	Bacher, R.	2006	Validation of an analytical confirmatory method for the determination of diflubenzuron in air. Report PTRL Europe GmbH, Germany, No. B 1000 G (Chemtura 2006-001), DI – 11817., GLP, Not Published	Y	CRO

* *Protection for 5 years claimed from date of decision concerning listing in Annex I - the study report has not been submitted in any of the Member States in support of an application for authorization, or (though the study report has been submitted) has not been used in any of the Member States as the basis for decision on the initial authorization, or to maintain a given authorization, of a plant protection product before the date of submission of the dossier to Rapporteur Member State.*

** *Owners' code identifications and names (Code identification: CRO,, Name: Chemtura Europe Limited previously Crompton Europe B.V)*

Addendum to
Draft Assessment Report

DIFLUBENZURON

Volume 3
Annex B.6
Toxicology

Rapporteur Member State: Sweden

December 2008

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Level 1: Statement of subject matter and purpose for which the monograph was prepared

Level 2: Reasoned statement of the overall conclusions drawn by the Rapporteur Member State

Appendix 1: Standard terms and abbreviations

Appendix 2: Specific terms and abbreviations

Appendix 3: List of endpoints

Level 3: Proposed decision with respect to the application for inclusion of the active substance in Annex I

Level 4: Further information to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in Annex 1

Volume 2

Annex A: List of the tests and studies submitted and of information available

Volume 3

Annex B: RMS summary, evaluation and assessment of the data and information

Annex B.1: Identity

Annex B.2: Phys/chem.

Annex B.3: Data application and further information.

Annex B.4: Proposal for classification and labelling

Annex B.5: Analytical method

Annex B.6: Toxicology and metabolism

Annex B.7: Residues in crop

Annex B.8: Fate and behaviour

Annex B.9: Ecotoxicology

Appendix 1: Standard terms and abbreviations

Appendix 2: Specific terms and abbreviations

Volume 4

Annex C: Confidential information and summary and assessment of information relating to the collective submission of dossiers

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B.6.2 Acute toxicity (Annex IIA 5.2)

Reporting table, mammalian toxicity, 2(2)

EFSA: for some studies the purity level is not mentioned or batches with much lower purity than recommended one have been used. RMS to provide an explanation on the reliability of conclusions drawn.

16 Jan 2007 the RMS received, by e-mail, a document with the purity of the technical diflubenzuron used for the acute toxicity studies. As seen in the table below, all batches had a high purity of Diflubenzuron.

In the skin irritation study by Taylor there are no purity information, however the other skin irritation study by Koopman are prepared with VC-90 which contains 90 % diflubenzuron and in neither of the studies there are any signs of irritation to the skin.

Purity for the diflubenzuron used in the different acute toxicity studies.

Study Name	Author	Study Date	Study Number	Batch Number	Purity %
Acute Oral Studies with DU 112307 in Mice and Rats	Eldik	1973	56645/14/73	309181	>99.6
Acute Toxicity in Rats of DU 112307 Technical After Dermal Application	Keet	1976	56645/2/76	405093	>99.6
Acute Dermal Toxicity Study with DU 112307 Technical in Rats	Koopman	1977	56645/7/77	405093	>99.6
Acute Percutaneous Toxicity to Rabbit of DU112307 Technical	Davies	1974	2171/D175/73	309181	>99.6
Acute Inhalation Toxicity to the Rat of DU 112307 Technical Grade Powder	Berczy	1973	PDR 74/73849	309181	>99.6
Acute Inhalation Toxicity to the Rabbit of DU 112307 Technical Grade Powder	Berczy	1975	PDR 198/74988	405093	>99.6
Primary Skin Irritation Study TH-6040 Technical (Albino Rat)	Taylor	1973			
Irritant Effects of DU 112307 Technical on Rabbit Eye Mucosa	Davies	1973	2170/176D/73	309181	>99.6
Sensitization Study with Diflubenzuron Technical in Guinea Pigs	Prinsen	1992	56645/26/1992	FUN91A10A/ FUX021000	95.6

B.6.3 Short-term toxicity (Annex IIA 5.3)

Reporting table, mammalian toxicity, 2(5)

UK: Derivation of a NOAEL versus NOEL in the 90 day dog study of Greenbough et al, 1985 Justification is required for the assumption that increases in methaemoglobin at 10 mg/kg bw/day, which are statistically significant, are not toxicologically significant.

Chemtura's comments of List of Endpoints and the proposed classification with R48

The 24th of September the RMS received the following e-mail from Chemtura. It contains the Notifier's comments on the changes in the List of Endpoints. The RMS has gone through the List of Endpoint again and some corrections have been made. However we disagree with the notifier and consider increased methaemoglobin as an adverse effect see the section "Toxicological relevance of increased methaemoglobin", after the two papers from Chemtura.

Dear Lena,

Sorry for my late response, but I had other important projects with deadlines to work on.
We were quite surprised by the change in your opinion about methaemoglobin and have to react on it, because we really disagree.
We kindly ask you to send our comments (the attached documents) to EFSA and the members of the expert panel dealing with human toxicology too, so that they are informed of our opinion on the recent changes in the List of Endpoints. In the reporting table send to us by the EFSA recently we didn't had the opportunity to comment on the changes in the List of Endpoints. After asking the EFSA why we couldn't comment on the changes in the list of Endpoints, the EFSA said that this wasn't possible in the current procedure and recommended us to send our comment to you, being the rapporteur.

R48 classification: You are probably refering to the report from Blom (2001, * see reference in red below), but we do not understand why you didn't use the, of more recent date, document
0703a11_NL_haemolytic_anaemia_finalreport. This report is from August 2004, it's the final report from the Working Group on Haemolytic Anaemia, based on the comments from Belgium, Denmark, Germany, Industry, Ireland, The Netherlands and The United Kingdom. This report reflects the opinion of the EU, the Blom-report (2001) is referenced several times in this document and has been used as a source. The report from Blom is the opinion of only 1 Member State and is of an earlier date.

We have assessed the severity of the haemolytic anaemia caused by diflubenzuron using the 2004-document and came to the following conclusion:
Administration of diflubenzuron to laboratory animals does not demonstrate severe anaemia or severe hemolytic anaemic effects. The effects demonstrated are sub-clinical and reversible. Based on the entire toxicological database and especially the long term studies, the

classification of R48 is not warranted. (See the attached file called "R48 Danger of serious damage to health by prolonged exposure" for more details).

Updated list of Endpoints: Not only are we disagreeing with your opinion on the severity of the haemolytic anaemia, but also in the choice of NOEL/NOAEL values from reports that weren't even considered acceptable (for several reasons, mostly old non-GLP-studies) and in one case even not evaluated (present on a list of studies not evaluated, but only mentioned in a list because they had been submitted in the past to the authorities), totally ignoring the results from the acceptable GLP-conform studies. What's the point in doing these GLP-studies then? There are several issues that I want to point out to you, also included is the comment (in black) I've made in the reporting table send lately to the EFSA. I've also attached the updated list of endpoints with my comments on the section Toxicology:

- Short term toxicity (Annex IIA, 5.3): You mention as target/critical effect **chronic hepatitus,** although this wasn't caused by diflubenzuron.

There were 2 experiments in which chronic hepatitis was seen, both in the control & treatment groups and therefore the hepatitis was not caused by the treatment with diflubenzuron, see below.
- Burdock (1980) subchronic (13 weeks) tox in rat: the majority of rats showed chronic hepatitis, also in the control group, but the severity was generally higher at ≥ 2000 ppm (139.1/164.5 mg/kg bw/day M/F).
- Burdock (1980) 90 day –mice: The hepatitis was of variable incidence and also occurred in control animals and this effect was considered to be unrelated to DFB.

- Short term toxicity (Annex IIA, 5.3), relevant oral NOAEL/NOEL: 2-week mouse: the only 2 week mouse study I could find was Keet (1977), this study hasn't been evaluated by you and furthermore the NOEL value was misinterpretated.

The 2 week mouse study (Keet, 1977) is not evaluated by the RMS, but only mentioned as a reference in the DAR because it had been submitted in the past to local authorities The NOEL was established at **40 mg/kg bw/day**. The rapporteur has made a mistake in the NOEL-value, for in the updated list of end-points 2 mg/kg bw/day is mentioned in stead of 40 mg/kg bw/day. This non-GLP study, which hasn't even been evaluated by the rapporteur shouldn't be used for determining end-points.

- Short term toxicity (Annex IIA, 5.3), relevant oral NOAEL/NOEL: oral 90-day and 1 year toxicity - Dog:

We do not agree with the proposed NOEAL of 2 mg/kg bw/day: the study of Greenough (1985) is referring to the 1-year dog study <u>not</u> the 90-day study. An exposure of 1 year in dogs is not a short term exposure (short term: 28 – 90 days), the duration of this study is approximately <u>4 times</u> the 90-day study. The effects seen in both the 90-day and 1-year dog study are not biologically relevant and certainly not adverse.

- In the 90-day study (Versendaal, 1983) the NOEL is 4 mg/kg bw/day and the NOAEL is 50 mg/kg bw/day! The effects at 50 mg/kg bw/day are minor and not adverse: The value of MetHb was < 1% at 50 mg/kg bw/day which is the standard value presented in ECB's document (ECBI/07/03 Add.11).

- In the 1-year dog study (Greenough, 1985) the level of MetHb was < 1% at the NOAEL of 10 mg/kg bw/day. The 2 mg/kg is equal to the NOEL but is not relevant for the NOAEL. The NOAEL should be **10 mg/kg bw/day** based on the increase in spleen weight, which is a secondary effect.

- Short term toxicity (Annex IIA, 5.3), relevant inhalation NOAEL/NOEL: An unacceptable 28-day rabbit study of restricted quality was used for chosing NOAEL/NOEL values.

Value of 1.9 mg DFB/L air is based on Berczy *et al* 1975, 28d rabbit: "Study is of restricted quality". The conclusion of this study was: The dust of technical diflubenzuron has no appreciable sub-acute inhalation toxicity in the rabbit under the conditions described. No NOAEL or NOEL could be established from this study, except that the NOAEL and NOEL were greater than 1.99 mg/L. This study shouldn't be used for determining end-points. The NOAEL/NOEL of the 28 days rat (acceptable study, GLP-compliant) is: **30 mg/L**.

- Long term toxicity and carcinogenicity (Annex IIA, point 5.5): Target/critical effect: You mention "other signs of anemia like haemosiderosis of spleen and liver, marrow, erythroid and thyroid hyperplasia, discoluration of extremites and Heinz body formation", but these are all secondary effects caused by the haemolytic anaemia. Thus no reason to add them as separate effects to the critical effects.

- R48 classification: see also attached file called "R48 Danger of serious damage to health by prolonged exposure", in this document each criterium of the document ECBI/07/03 Add.11 has been adressed.

The toxicology package for diflubenzuron was assessed in association with ECBI/07/03 Add. 11 (Proposal for criteria to be used in the classification of R48 for hemolytic anemia in repeated dose toxicity studies). The treatment related effects seen in the toxicity studies with diflubenzuron are not indicative of serious adverse effects. The assessment concluded that the classification of R48 is not warranted for diflubenzuron. A separate document with our detailed assessment will be sent to the rapporteur (see attached file called.

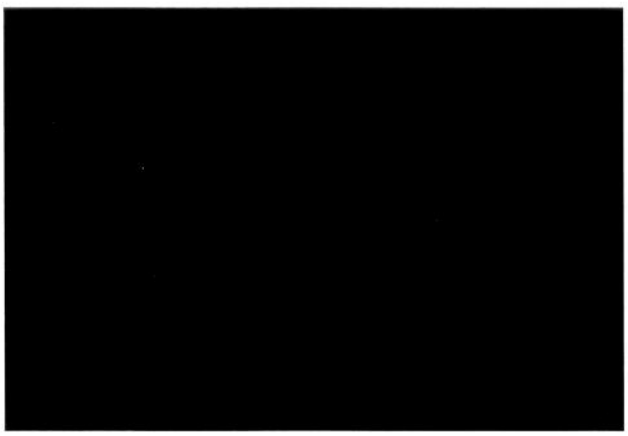
No serious systemic effects were demonstrated in any toxicity studies with diflubenzuron. Repeated dose studies with diflubenzuron in the diet, by oral bolus dose in the form of a capsule, by inhalation or by dermal exposure, have not resulted in any deaths related to treatment. Dietary treatment levels were up to 100,000 ppm for 9 weeks in rats (corresponding to 7801 & 8539 mg/kg bw/day fors males & females, respectively) (Hunter 1979). Clinical signs were not observed during dosing in any study. No decrease in life span for any animal species was noted in any repeated dose study. This demonstrates that the haematological effects as a result of diflubenzuron treatment do not result in a decrease in overall health of the treated animal.

Repeated dose administration of diflubenzuron resulted in sub-clinical expression of anaemia, which was most likely due to extracellular hemolysis. The level of anaemia can be classified as sub-clinical because of the lack of clinical symptoms associated with treatment. The decrease in haemoglobin (Hb) levels was not below the designated adverse level of 10% of in any of the studies. Methemoglobin (MetHb) levels were only above the level of concern (4% in rats, 2% in mice) at extremely high doses (400 ppm in mice and 100,000 ppm in rats). Furthermore, chronic administration of diflubenzuron resulted in a reduction in the expression of anaemia compared to those evident upon sub-chronic treatment.

The increase in liver and spleen weight is a secondary effect which is attributable to the deposition of pigment from damaged erythrocytes. Diflubenzuron affects the circulatory system through mild, subclinical extravascular hemolytic anemia. The effects seen are reversible and compensatable as demonstrated by the toxicological database of diflubenzuron.

- Reproduction target/critical effect: "increase in liver and spleen weight and methaemoglobin" is mentioned again, but these aren't effects on reproduction and should be removed
- Derivation of ADI and AOEL: We do not agree with the NOAEL of 2 mg/kg bw/days as proposed by the RMS for use in the derivation of the ADI and AOEL. The NOAEL used for the ADI & AOEL should be **10 mg/kg bw/day** based on the increase in spleen weight, which is a secondary and certainly not an adverse effect. The effects seen at 10 mg/kg bw/day are minor and not biologically relevant, the values of MetHb are below the 1% value that is mentioned as a standard value in the ECB document (ECBI/07/03 Add.11).
- ARfD: See attached file called "R48 Danger of serious damage to health by prolonged exposure" for the details of the assessment: Methaemoglobinemia is not an acute effect for diflubenzuron, since this effect isn't observed in the acute studies. Only in the short term and chronic studies the levels of methaemoglobinemia are increased. However these effects are mild and are reversible and compensatable, therefore there are certainly no scientifically sound reasons to establish an ARfD!
- Dermal absorption: We do not agree with the 6 % dermal absorption, the Diflubenzuron present in the skin (stratum corneum) is not biologically available and as the skin is renewed every 20 days, it will not be a depot for possible release afterwards.
- All exposure senarios (operator/worker/bystander) have been recalculated by the rapporteur with a new AOEL-value we do not agree with (see above). The NOAEL used for the AOEL should be **10 mg/kg bw/day** and not 2 mg/kg bw/day.

* Blom, M. in RIVM Rapport 601516007 Luttik R ; Raaij MTM van (eds) 2001 Factsheets for the (eco)toxicological risk assessment strategy of the National Institute of Public Health and the Environment (RIVM)



Chemtura

Chemtura's Response to the List of Endpoints for Diflubenzuron Toxicity and Risk Assessment

[redacted]

27 August 2007

Short-term toxicity

Target/Critical Effect:
Critical effects are the main effects seen upon increasing the dose. For diflubenzuron, the critical effect in most studies is the increase in methemoglobin and sulfhemoglobin in the blood and the liver and spleen weight, the other hematological effects mentioned in the updated list of endpoints are not biologically relevant/adverse.

1) The increase in methemoglobin and sulfhemoglobin in the blood is statistically significant, but non-biologically relevant. The increase in liver and spleen weight is a secondary effect which is attributable to the deposition of pigment from damaged erythrocytes.

2) Other signs of anaemia include effects which are secondary and often compensatory.

- Chronic hepatitis is not an effect that is attributable to diflubenzuron treatment.
    - Chronic hepatitis was reported to result in a dose-related increase in the severity of chronic hepatitis in a subchronic dietary rat study conducted in 1980 (Burdock, 1980). Similar findings were not found in a previous subchronic (90 day) studies in rats (Kemp, 1973a), in the 28 day study in rats (Palmer, 1977), in the 9 week study with 4 week withdrawal period in rats (Hunter 1979), in any of the subchronic inhalation or percutaneous absorption studies, or in either of the chronic toxicity/oncogenicity studies in rats (Burdock, 1984 and Hunter, 1976). Doses used in the other studies were comparable or substantially higher than the study in which chronic hepatitis was found. In addition, the study in which chronic hepatitis was found had instances of chronic hepatitis in all animals including controls.
    - Chronic hepatitis was also reported in only one subchronic dietary mouse study (Burdock, 1980). The effect was not demonstrated in a 6 week dietary study in male mice (Hunter, 1974), in the 14 week dietary study in mice (Colley, 1981), or in either of the mouse oncogenicity studies (Hunter, 1975 and Colley, 1976). If this was a true treatment related effect, then it would be seen in other studies, especially ones of chronic duration. Furthermore the hepatitis was of variable incidence and also occurred in control animals, this effect was considered to be unrelated to DFB.

- Chronic hepatitis was not reported in any of the dog studies.

- Mild erythroid hyperplasia in bone marrow is not an adverse effect. The hyperplasia is secondary and in response to the anemia. It does not result in irreversible damage. The bone marrow hyperplasia is a regenerative measure. This effect is not demonstrated in every study, but it occurrence can be attributed secondarily to treatment with diflubenzuron.
- Congestion of the spleen is also secondary to the hemolytic anemia. It has been demonstrated to be reversible upon withdrawal in subchronic studies and compensatable in chronic studies (effect is not present upon chronic treatment).
- Liver haemosiderosis is also secondary to the hemolytic effect. It has been demonstrated to be reversible and does not result in permanent damage.
- Heinz bodies are found in a subchronic mouse study (Colley, 1981) as well as in the mouse chronic toxicity / oncogenicity study by Colley et al, 1984. Otherwise, the identification of heinz bodies was not common finding in the diflubenzuron toxicity database.

Relevant Oral NOAEL/NOEL

NOAEL: 10 mg/kg bw/day; NOEL: 2 mg/kg bw/day (Greenough, 1985)

- The 14 day oral gavage study in male mice demonstrated a NOEL of 40 mg/kg bw/day based on increase in sulfhemoglobin levels. (Keet 1977). NOAEL is > 5000 mg/kg bw/day.
- Short term toxicity should be subchronic (28 – 90 days). An exposure of 1 year in dogs is not a short term exposure. If the endpoint were intermediate exposure, the 1 year dog study would be applicable. The effects seen in the 1 year dog study are not biologically relevant. The 2 mg/kg is equal to the NOEL but is not relevant for the NOAEL. The NOAEL should be 10 mg/kg based on the increase in spleen weight.
- The NOEL in the two week mouse study (Keets, 1977) was 40 mg/kg/day or 5000 ppm and not 2 mg/kg/day.

Relevant Dermal NOAEL/NOEL

NOAEL: > 322 mg/kg bw/day (21.5%); NOEL: 150 mg/kg bw/day (10%) (Davies, 1975)

- Biologically non-relevant changes in MetHb levels. Changes in MetHb levels were not associated with changes in Hb or Hematocrit.
- MetHb levels were not dose related. Statistical Power is low (low number of samples, low statistical significance). If an ANOVA was run with this data, it is highly unlikely that there would be a real difference.

Group	Sex	Met Hb individual values	Met Hb Average
1) Control, intact	Male	0.1,0.1,0.1,0.1,0.1	0.1
	Female	0.1,0.1,0.1,0.1,0.1	0.1

2) Control, abraded	Male	0.1,0.1,0.1,0.1,0.1	0.1
	Female	0.1,0.1,0.1,0.1,0.1	0.1
3) 69.6 mg/kg bw/day (4 64%); intact	Male	0.4,0.5,0.1,0.1,0.3	0.3*
	Female	0.1,0.1,0.2,0.1,0.1	0.1
4) 69.6 mg/kg bw/day (4 64%); abraded	Male	0.1,0.1,0.2,0.2,0.1	0.1
	Female	0.3,0.2,0.1,0.2,0.2	0.2
5) 150 mg/kg bw/day (10%); intact	Male	0.1,0.1,0.2,0.2,0.1	0.1
	Female	0.4,0.2,0.1,0.2,0.1	0.2
6) 150 mg/kg bw/day (10%); abraded	Male	0.3,0.2,0.1,0.2,0.7	0.3*
	Female	0.2,0.1,0.3,0.3,0.1	0.2
7) 322.5 mg/kg bw/day (21 5%); intact	Male	0.3,0.5,0.2,0.4,0.2	0.3*
	Female	0.1,0.3,0.3,0.1,0.4	0.2*
8) 322.5 mg/kg bw/day (21.5%); abraded	Male	0.3,0.2,0.1,0.2,0.1	0.2
	Female	0.3,0.1,0.2,0.4,0.1	0.2*

* Significance at 5%

Relevant Inhalation NOAEL/NOEL

NOAEL: > 30 mg/m3; NOEL: = 30 mg/m3 (Newton 1999). NOEL is based on slightly statistical significant decreases in Hb and Hematocrit.

- The study the NOEL of 1.99 was derived from is an unacceptable non-GLP study (Berczy et al 1975, 28d rabbit). In this study, rabbits were dosed 1 hour a day, 5 days a week for 3 weeks. In addition, the 1.99 mg/m3 was the highest dose tested and no observed effects were demonstrated at this level. No NOAEL or NOEL could be established from this study, except that the NOAEL and NOEL were greater than 1.99 mg/L. This is not an appropriate study for the derivation of an endpoint for inhalation. The Newton 1999 study (rat, 4 weeks) was conducted in accordance with current testing guidelines and is the most appropriate study for the derivation of the inhalation endpoint.

Long-term toxicity

Target/Critical Effect:

1) Blood/increased in methemoglobin and sulfhemoglobin are statistically significant but non-biologically relevant

2) Other signs of anaemia include effects which are secondary and often compensatory. These effects include increased liver and spleen weight which is attributable to the deposition of pigment from damaged erythrocytes.

- Heinz bodies are found in a subchronic mouse study (Colley, 1981) as well as in the mouse chronic toxicity / oncogenicity study by Colley et al,

1984. Otherwise, the identification of heinz bodies was not common finding in the diflubenzuron toxicity database.

- Congestion of the spleen is also secondary to the hemolytic anemia. It has been demonstrated to be reversible upon withdrawal in subchronic studies and compensatable in chronic studies (effect is not present upon chronic treatment).
- Liver haemosiderosis is also secondary to the hemolytic effect. It has been demonstrated to be reversible and does not result in permanent damage.
- Marrow, erythroid and thyroid hyperplasia are not common effects related to treatment with diflubenzuron (erythroid and thyroid hyperplasia) or are compensatory, reversible mechanisms (marrow hyperplasia).
- Discolouration of extremeties is also not a common effect of treatment with diflubenzuron even at treatment levels as high as 1% of the diet. This is not an effect that should be regarded as a critical effect as its occurrence is not typical of the treatment related effects of diflubenzuron.

Lowest relevant NOAEL/NOEL

NOAEL: 6.4 mg/kg/day based on the Mouse 91 week carcinogenicity study.

- Mouse 91 week study: NOAEL: 6.4 mg/kg/day in male mice. NOEL: 1.2 mg/kg/day male mice. The NOEL is based on non-biologically relevant (not adverse) changes in hemaetology.
- Dog 1 year study: The 2 mg/kg is equal to the NOEL but is not relevant for the NOAEL. The NOAEL should be 10 mg/kg based on the increase in spleen weight.

ADI

Value: 0.064	Study: 91 week mouse	Safety Factor: 100

AOEL

Value: 0.033	Study: 1 year dog, 90 day rat, 90 day mouse	Safety Factor: 100 33% oral absorption

Applicability of the R48 Classification to Diflubenzuron

[redacted]

August 21, 2007

The toxicology package for diflubenzuron was assessed in association with ECBI/07/03 Add. 11 (Proposal for criteria to be used in the classification of R48 for hemolytic anemia in repeated dose toxicity studies). The treatment related effects seen in the toxicity studies with diflubenzuron are not indicative of serious adverse effects. The assessment concluded that the classification of R48 is not warranted for diflubenzuron.

No serious systemic effects were demonstrated in any toxicity study with diflubenzuron. Repeated dose studies with diflubenzuron in the diet, by oral bolus dose in the form of a capsule, by inhalation or by dermal exposure, have not resulted in any deaths related to treatment. Dietary treatment levels were up to 100,000 ppm for 9 weeks in rats (7801/8539 mg/kg bw/day male and female respectively) (Hunter 1979). Clinical signs were not observed during dosing in any study. No decrease in life span for any animal species was noted in any repeated dose study. This demonstrates that the hematological effects of diflubenzuron treatment do not result in a decrease in overall health of the treated animal.

Repeated dose administration of diflubenzuron resulted in sub-clinical expression of anaemia, which was most likely due to extracellular hemolysis. The level of anaemia can be classified as sub-clinical because of the lack of clinical symptoms associated with treatment. The decrease in hemoglobin(Hb) levels was not below the designated adverse level of 10% of in any of the studies. Methemoglobin (MetHb) levels were only above the level of concern (4% in rats, 2% in mice) at extremely high doses (400 ppm in mice and 100,000 ppm in rats). Furthermore, chronic administration of diflubenzuron resulted in a reduction in the expression of anaemia compared to those evident upon sub-chronic treatment. This negates the need for classification based on chronic sub-clinical methemoglobinemia.

ECBI/07/03 Add. 11 (Proposal for criteria to be used in the classification of R48 for hemolytic anemia in repeated dose toxicity studies) states that the decision for classification should be based on longest duration study. The longest duration studies in terms of time and percentage of lifespan covered are the combined chronic / carcinogenicity studies in rats and mice. In the rat studies, methaemoglobin levels do not exceed the >4% level of concern. The high dose level in the rat chronic study was 10,000 ppm (1% of the diet). The effects on hematology parameters are decreased or absent at 104 weeks when compared to the 52 week measurement. No clinical effects, deaths or decrease in life span was detected in the rat studies. The percent Hb levels in the chronic rat study were not-dose related. The decreases at 52 weeks of treated ranged from 7 - 8% at the high dose to 12% in females at 2500 ppm and males at 650 ppm at 52 weeks. The percent Hb increased at 104 weeks to 16% in the high dose males. The improvement in Hb levels along with improvements in erythrocyte levels, MCV and reticulocytes demonstrate a successful compensatory mechanism or an alleviation of the hemolytic effect. The increases in relative and absolute liver and spleen weights can be accounted for by the deposition of hemosiderin-like pigment. These are not direct adverse effects but are effects secondary to the hemolytic anaemia. The organs are not irreversibly damaged as shown by the recovery period after 7 weeks of treatment and 4 weeks of non-treatment. The pigment deposition is not accompanied by indications of severe anaemia. The results of the rat chronic/oncogenicity study demonstrate that the classification of R48 is not appropriate.

The chronic/carcinogenicity study in mice was also considered in this assessment. There was no affect on survival. Males in the 10000 ppm treatment group had statistically lower body weight at week 52. The Hb level in the same high dose males was significantly higher than controls at week 78 but were similar among all group at weeks 52 and 91 (termination). The MetHb levels were above the noted 2% of the total Hb level of concern in the male and female treatment groups at 400 ppm. However, as the DAR states, the statistically significant alterations are still within the normal range. Increases in spleen weight that were evident at the interim (52 weeks) were not present at terminal sacrifice. The results of the chronic toxicity/carcinogenicity mouse study furthers the determination that diflubenzuron does not warrant an R48 classification.

Administration of diflubenzuron to laboratory animals does not demonstrate severe anaemia or severe hemolytic anaemic effects. The effects demonstrated are sub-clinical and reversible. Based on the entire toxicological database and especially the long term studies, the classification of R48 is not warranted.

R48 Danger of serious damage to health by prolonged exposure; *Clear functional disturbance or morphological change which has toxicological significance.*

- Particularly important when changes are irreversible
  - Not the case with Diflubenzuron (DFB dietary treatment with recovery period demonstrated a recovery or decrease in severity of all symptoms. Furthermore, chronic studies demonstrated a recovery upon prolonged treatment
- Classification depends on dose level, exposure period and dose route
  - Even at extreme dose levels of DFB (1% of the diet), no clinical signs of anaemia were present
- If studies of multiple durations are available, the study of the longest duration should normally be used
  - For DFB those studies would be the rat chronic/carcinogenicity and mouse oncogenicity studies

1. Substance related death
   - For DFB, no substance related deaths were reported in any study
   - For DFB, no substance related reproductive / developmental toxicity
2. Major Functional Changes in Organ System
   - For DFB, no clinical signs of hypoxia were seen during treatment
3. Changes in clinical biochem/hematology/urinalysis parameters which indicate severe organ dysfunction. Hematological changes are considered to be of particular importance if the evidence suggests that they are due to decreased bone marrow production
   - DFB did not result in a decreased bone marrow production
   - There was no reduction of Hemoglobin at ≥ 20% in any study with DFB at any dose level
   - There was no reduction of functional hemoglobin at ≥ 20% due to a combination of hemoglobin reduction and metHb formation in any study with DFB
   - Hemoglobinuria or hemosiderinuria was not detected in any study with DFB

4. Severe organ damage noted on microscopic examination following autopsy:
   4.1 Widespread or severe necrosis fibrosis etc in organs with regenerative capacity
      - No widespread or severe fibrosis in the spleen, liver or kidney was detected in any study with DFB

   4.2 Severe morphological changes that are potentially reversible but are clear evidence of marked organ dysfunction
      - No severe tubular nephrosis was detected in any study with DFB

   4.3 Evidence of appreciable cell death in vital organs incapable of regeneration or in a stem cell population
      - No appreciable cell death in organs incapable of regeneration or in a stem cell population.

The guidance document also mentions that it is important to consider not only specific severe changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs or severe changes in general health status.

- DFB does not result in any severe changes to the general health status of the treated animals at any dose level or route of administration
- DFB affects the circulatory system through mild, subclinical extravascular hemolytic anemia. The effects seen are reversible and compensatable as demonstrated by the toxicological data.

These effects are relevant when attempting to determine a no-effect level for a chemical substance – irrespective of stat significance.

- Clinical observations or changes in bodyweight gain, food consumption or water intake, which may have some toxicological significance but which do not, by themselves, indicate 'serious damage'
  - DFB does not result in clinical symptoms or significant changes in bodyweight gain, food consumption or water intake. This is relevant when considering the statistically significant but not biologically relevant changes which are not indicative of serious damage.
- Small changes in clinical biochemistry, hematology or urinalysis which are of doubtful or minimal toxicological importance
  - DFB treatment results in sub-clinical expression of anaemia. The changes in hemoglobin levels are less than 10% for the majority of tested doses. MetHb levels are within the 0-4% for rats and usually in the range of 0-2% for the mice. Full recovery was noted after 4 weeks of withdrawal in rats treated for 7 weeks in feed. Compensatory mechanisms begin within 28 days of treatment and chronic treatment demonstrates improvement if not complete reversal of effects.
- Changes in organ weights without evidence of organ dysfunction
  - No or minimal severe histopathology effects were noted in the spleen and liver
- Adaptive responses

- Are present and compensatory. No clinical effects.

- Species specific mechanism of toxicity has been demonstrated
  - All animals responded similarly to DFB. There is no indication that humans would respond any differently to treatment.

Toxicological relevance of increased methaemoglobin (written by the RMS)

Background information of methaemoglobin (MetHb) formation and following reactions

Normally, methaemoglobin levels are <1% of the total haemoglobin.
MetHb binds oxygen more strongly than haemoglobin (Hb) and therefore does not effectively deliver oxygen to tissue.

Spontaneous formation of methaemoglobin is normally counteracted by protective enzyme systems: NADH methaemoglobin reductase (cytochrome-b5 reductase) and NADPH methaemoglobin reductase. The pentose phosphate pathway is a metabolic pathway that supplies energy to the cells and glucose-6-phosphate dehydrogenase (G6PD) is an enzyme in the pentose phosphate pathway that generates NADPH which is thought to be a main source of reducing power. NADPH is primarily used to convert the oxidized glutathione (GSSG) into its reduced form (GSH) in a reaction catalyzed by glutathione reductase. GSH is necessary for avoiding the irreversible oxidation of intracellular proteins, including membrane proteins and enzymes, while the accumulation of GSSG cause protein dysfunction, by creating disulfide bonds between the –SH groups of cysteine and methionine residues. Extended erythrocytic oxidative stress promotes depletion of the antioxidant capacity of the cell, causing dysfunction by reversible interaction between protein thiols and glutathione.

Rat and rabbit (guinea pig and monkey) are less sensitive to MetHb formation and generally show a more effective reduction of MetHb than man and dog (cat) do. Extra sensitive groups are e.g. foetuses and newborns characterized by low NADH and more fluctuating Hb, elderly people with more fluctuating Hb, which is more susceptible to oxidation and people with glucose-6 phosphate dehydrogenase deficiency, with defective NADPH production.

If an effect on MetHb concentration is observed, it is considered an adverse effect because an increase in MetHb levels is possible only when the capacity of the reducing mechanisms is exceeded, the exposure has then already reached such a level that considerable energy will be spent on reduction of MetHb and production of reticulocytes. Any significant increase in MetHb concentration compared to control level is in principle considered an adverse effect if a dose-response relationship is present. An increase in MetHb concentration which is not significant is still considered adverse if dose-response relationship is observed at the consecutive dosage.

Heinz bodies are associated with oxidative damage to the red blood cells and are more persistent than MetHb and therefore their presence may be a more robust indicator of MetHb formation than measurements of blood MetHb concentration. When a macrophage in the spleen "sees" a red blood cell with a Heinz Body, it is removed from the circulation.

Prolonged exposure to MetHb-inducing compounds may bring about several effects, such as the presence of Heinz bodies in red blood cells and changes in the different cell count indicative of anaemia: RBC↓, Hb↓, MCV↑, and reticulocytes↑. In addition, haematopoiesis in liver and spleen, hemosiderins (insoluble iron precipitates) in the liver, and possible (in the beginning of the study) bluing of the skin and/or nose. Increased LDH activity may be an indication of haemolysis.

Howell-Jolly bodies are a histological sign comprising clusters of DNA remaining in red blood cells indicating abnormal mitosis and have been observed in relation to haemolytic anaemia. They have a reduced amount of cell membrane and a hyperchromatic colour. In normal individuals they are removed by the spleen, so that they are not seen in the blood. When the spleen has been removed, or is not functioning properly Howell-Jolly bodies appear in the peripheral blood.

Haemosiderosis is defined as a marked increase in hemosiderin accumulation in organs compared to the normal status, and thereby is a hallmark of secondary iron overload. Haemosiderosis is the deposition of haemosiderin bound iron in several organs, usually the liver, spleen, kidney and bone marrow. Macrophages with dense dark brown (haemosiderin) pigment may occur. Since a low extent of haemosiderosis is a normal age related lesion that may show some degree of individual variation, only clear increases in haemosiderin deposition compared to the internal control group should be considered as treatment-related effects. Marked haemosiderosis in multiple organs is clearly an adverse effect.

Increased spleen weight and enlarged spleen could be indicative of increased degradation of erythrocytes including haemosiderin accumulation, extramedullary haematopoiesis or both.

Increased liver weight could be indicative of extramedullary haematopoiesis or uptake of residues from haemolysed erythrocytes (haemosiderosis). Kupffer cell (macrophage in the liver) activation, increased accumulation of haemosiderin in endothelial (Kupffer) cells may occur in response to haemolytic anaemia. A prominent accumulation of haemosiderin pigment in sinusoidal Kupffer cells and hepatocytes gives an indication of intravascular haemolysis.
Haemosiderin deposition in the liver is a pathological condition.

Normally new blood cells are produced in the bone marrow in adults. However, in foster the haematopoiesis also occurs in the spleen and liver and the splenic and hepatic erythropoiesis can be reactivated in attempt to meet the demand for increased oxygen transport.

Free iron catalyzes autooxidation by Fenton and Haber-Weiss reactions, resulting in the production of reactive oxygen species.

Conclusions

The primary adverse effect caused by diflubenzuron is the formation of methemoglobinemia (caused by oxidative stress) and associated dysfunctions of erythrocytes. The other abnormalities observed could be explained as secondary to this type of hematotoxicity with increased erythrocyte damage and turnover, including red blood cell morphological alterations (e.g. Heinz bodies, Howell-Jolly bodies), discolouration of extremities, effect on the spleen and liver (increased weight, congestion, hemosiderin accumulation and increased hematopoietic cell proliferation) and increased erythroid hyperplasia in the bone marrow.

Main sources of information
Information from RIVM report 601516 007 April 2001
Regular Toxicology and Pharmacology 45 (2006) 299-241

B.6.10 Summary of mammalian toxicology and proposed ADI, AOEL, ARfD and drinking water limit (Annex IIA 5.10)

Reporting table, mammalian toxicity, 2 (5), (9), (10)

Several of the comments in the reporting table are dealing with the effect of increased methaemoglobin and sulfhaemoglobin, seen in almost all studies with diflubenzuron. The question is if the effect should be regarded as adverse or not. When the DAR was first prepared the RMS regarded the effect as not adverse, however after having received the comments from other MS and consulting the literature the RMS now consider increase in methaemoglobin and sulfhaemoglobin as an adverse effect. Even if this is reversible effects it has to be taken seriously when the exposure is repeated many times and signs of anaemia is seen. The changed attitude to these effects has influenced the risk assessment of many of the studies in the Dossier and many NOAELs have been lowered. Therefore this section with the summary of toxicity and the proposed ADI, AOEL and ARfD, has been included to the addendum.

Absorption, distribution, excretion and metabolism (toxicokinetics)

Diflubenzuron is poorly absorbed from the gastro-intestinal tract and, at a dose range of 5-100 mg kg^{-1} used absorption decreases with increased dose level in the rat. High level of non-absorbed diflubenzuron was found in the faeces. The oral absorption was approx. 33 %. Absorbed radioactivity was removed almost completely in 24-48 hours, with the exception of low residues in liver and erythrocytes. In no other part of the rat body do the compound and/or its metabolites accumulate. Excretion takes place *via* bile and urine. The major metabolites of diflubenzuron identified in rat urine were 4-chloroaniline-2-sulfate (45% of urine TTR), and n-(4-chlorophenyl)oxamic acid (13% of urine TRR). About 3% of urine TRR was 2'-hydroxy-diflubenzuron. Other 18 metabolites were accounted and none for more than 2% urine TRR. Diflubenzuron was the only residue found in the faeces. Neither 4-chloroaniline (PCA), 4-chlorophenylurea (CPU) nor their n-hydroxyl derivatives were found in rat urine at a limit of detection of 0.4 ppb. It is suggested that 4-chloroanilin-2-sulfate, an aromatic amine, is responsible for the methaemoglobin formation seen in many studies.

Acute studies

Diflubenzuron had a very low acute mammalian toxicity *via* oral, dermal, inhalation administration. Diflubenzuron was neither irritant nor sensitizer in the animals tested.

The acute oral LD_{50} of diflubenzuron was > 5000 mg kg^{-1} bw in rats and mice. No classification is required in accordance with the provisions of Council Directive 67/548/EEC. The acute dermal LD_{50} of diflubenzuron was > 10000 mg kg^{-1} bw in rats. No classification is required in accordance with the provisions of Council Directive 67/548/EEC.

Short-term toxicity

Oral

The oral short-term toxicity for diflubenzuron has been study in rat, mouse and dog. One 28-day study and three 90-day studies on the rat, two 90-day studies on the mouse, and one 90-day study and one 1-year study on the dog were presented with acceptable quality. The major detected adverse effects were increase of metheamoglobin and sulfhaemoglobin (as % of Hb), variations in organ weights (liver and spleen) and changes in haematological parameters.

In rat, the NOAEL after a 90-day exposure with diflubenzuron was less than less than 160 ppm (M/F < 11/14 mg $kg^{-1}day^{-1}$) based on increase in methaemoglobin, sulfhaemoglobin and spleen weight. In mouse, the lowest NOAEL was 80 ppm (M/F: 7.1 mg $kg^{-1}day^{-1}$), based on increase in methaemoglobin effects on liver, spleen and adrenal weights and changes haematological parameters. In dog, after 90-day of treatment with diflubenzuron the established NOAEL in males was 2 mg $kg^{-1}day^{-1}$ based on increase methaemoglobin (%Hb) in the blood. At higher dose levels an increased liver weight was observed. Therefore, the NOAEL for this study was established to 2 mg $kg^{-1}day^{-1}$ and the value has been considered relevant for the setting of ADI.

In most of the studies there are indications that Diflubenzuron causes anaemia. The RMS therefore suggests that Diflubenzuron should be labelled with R48 “Danger of serious damage to health by prolonged exposure”.

In all studies where, it has been measured, it is an increase in sulfhaemoglobin and methhaemoglobin. There is a RIVM report dealing with Methaemoglobin/Heinz bodies an in summary they conclude that rat/mouse/rabbit/guinea pig/monkey are less sensitive to methhaemoglobin formation and generally show more effective reduction of induced MetHb than do man/dog/cat. If an effect on MetHb concentration is observed, it is by definition considered an adverse effect because an increase in MetHb levels is possible only when the capacity of the reducing mechanisms is exceeded. The exposure in question has then already reached such a level that considerable energy will be spent on reduction of MetHb and production of reticulocytes. This is certainly considered an adverse effect on a long term basis. RIVM (report 601516 007) 2001.

Formation of sulfhaemoglobin, unlike methaemoglobin, is not reversible and therefore considered to be of great toxic significance.
Changes in the blood parameters are seen in most studies: Hb↓, PCV or Hct↓, Erythrocyte counts↓ and RBC ↓ or↑ and also increase in liver and spleen weights which all are indicative of anaemia.

Additional signs of anaemia on top of the ones mentioned above that occurred during exposure of 50 mg/kg bw/ day or less:

6.3.1.2(1) Oral 90-day rat study by Burdock
Dose dependent increased in grading of chronic hepatitis and liver haemosiderosis (incidence: zero for control, 50 % of the animals exposed to 27/34 mg/kg bw (M/F) and 100% of the animals exposed to the highest dose), congestion of the spleen and mild erythroid hyperplasia of the bone marrow.

6.3.1.3(1) Oral 6 week mouse study by Hunter (study used as complementary)
Live necrosis in 3 out of 8 mice exposed to 6 mg/kg bw/day with or without inflammatory cells.

6.3.1.3(2) Oral 90-day mouse study by Burdock
Liver necrosis, haemosiderosis and chronic hepatitis. The severity increased with dose.

6.3.1.3(3) Oral 90-day mouse study by Colley
Heinz bodies, increase in plasma glutamic pyruvic transaminase (indicating liver damage), discolouration and enlargement of the spleen, haemosiderosis in the spleen, liver areas of focal necrosis and /or fibrosis in the parenchyma with or without associated inflammatory cells, dose related increase in grey/blue discolouration of extremities.

6.3.1.4(1) Oral 90-day dog study by Chesterman
Increase in alkaline phosphatise and serum glutamic pyruvic transaminase.

6.3.1.4(3) Oral 90-day dog study by Greenough
Dose related increase in incidence and severity of macrophage and Kupffer cell siderosis, Heinz bodies, increase in LDH (indicating liver damage), and haemosiderosis in the liver.

The effects on haematological parameters were evaluated on the basis of the document presented by ECBI (ECBI/07/03 add.11). Considering the change in blood parameters, increased methaemoglobin and sulfhaemoglobin together with pathological effects like haemosiderosis and necrosis in the liver, enlargement and congestion of the spleen and effect of the boon marrow the RMS suggest R48 to be an appropriate classification.

Inhalation short-term toxicity

One 28-day inhalation study on rat and one on rabbit have been preformed with acceptable quality. In the rat study the NOAEL was 0.1 mg/L based on change in haematological parameters. In the rabbit study no adverse effects was observed up to a dose of 1.9 mg diflubenzuron/L air. RMS consider that since diflubenzuron has a low vapour pressure (< 1.2 x 10-7 Pa at 25ºC) and the exposure to operators during normal agricultural use is anticipated to be very low, the toxicity of diflubenzuron *via* inhalation doesn't need to be further investigated.

Dermal short-term toxicity

One 21-day and one 28-day in both rat and rabbit dermal studies, with acceptable quality, have been preformed. In rat, the NOAEL was established to 500 mg $kg^{-1}day^{-1}$ based on increase in methaemoglobin and in rabbit the NOAEL was 150 mg $kg^{-1}day^{-1}$ based on increased sulfhaemoglobin

Genotoxicity

Four *in vitro* studies were presented to predict the genotoxic potential of diflubenzuron. The systems used were: Ames Salmonella/microsome assay, malignant transformation in BAL/3T3 cells, cytogenetic assay for measuring chromosome aberration in Chinese hamster and primary culture of rat hepatocytes. All the assays were negative under the study conditions.

One *in vivo* micronucleus test in mice treated with diflubenzuron was presented with acceptable quality. Diflubenzuron was not mutagenic under the study conditions. One *in vivo* dominat lethal test in albino mice was presented and concluded as negative, however no positive control was presented and concluded as negative, however no positive control was included in the test and RMS judge the study as supplementary.

Long-term toxicity and carcinogenicity

Three studies (one in rat, mouse and dog) with acceptable quality have been evaluated. **No tumour induction related to diflubenzuron was observed in these three studies.**

In rat, the NOAEL was 156 ppm (7.8 mg kg^{-1} day^{-1}) based on increased methaemoglobin and sulfhaemoglobin at 625 followed by increased spleen weight (absolute and relative) in both sexes and increased liver weight (relative) in females at 2 500 ppm. In mouse, a NOAEL of 16 ppm (1.24/1.44 mg kg^{-1} day^{-1} M/F) can be derived from this study based on increased Methaemoglobin and sulfhaemoglobin seen in both sexes at 80 ppm. After 1-year treatment the NOAEL in dog was 2 mg $kg^{-1}day^{-1}$ in both sexes, based on increased Methaemoglobin at 10 mg $kg^{-1}day^{-1}$ followed by changes on liver, spleen and brain weights changes in and blood parameters.
The NOAEL established for the mouse, 1.2 mg $kg^{-1}day^{-1}$ was considered relevant for the setting of ADI.

In most of the studies there are indications that Diflubenzuron causes anaemia. The RMS therefore suggests that Diflubenzuron should be labelled with R48 "Danger of serious damage to health by prolonged exposure".

In all studies, where it has been measured, it is an increase in sulfhaemoglobin and methaemoglobin. There is a RIVM report dealing with Methaemoglobin/Heinz bodies an in summary they conclude that rat/mouse/rabbit/guinea pig/monkey are less sensitive to methaemoglobin formation and generally show more effective reduction of induced MetHb than do man/dog/cat. If an effect on MetHb concentration is observed, it is by definition considered an adverse effect because an increase in MetHb levels is possible only when the capacity of the reducing mechanisms is exceeded. The exposure in question has then already reached such a level that considerable energy will be spent on reduction of MetHb and production of reticulocytes. This is certainly considered an adverse effect on a long term basis. RIVM (report 601516 007) 2001.

Formation of sulfhaemoglobin, unlike methaemoglobin, is not reversible and therefore considered to be of great toxic significance.
Changes in the blood parameters are seen in most studies: Hb↓, PCV or Hct↓, Erythrocyte counts↓ and RBC ↓ or↑ and also increase in liver and spleen weights which all are indicative of anaemia.

Additional signs of anaemia on top of the ones mentioned above that occurred during exposure of 50 mg/kg bw/ day or less:

6.5.2(1) Carcinogenicity study in rat by Burdock
Compound-related increase in haemosiderosis of spleen and liver, marrow hyperplasia, erythroid hyperplasia and distended marrow spaces (males) and thyroid hyperplasia (female) at al dose levels.

6.5.4(1) Chronic toxicity and carcinogenicity study on mouse by Colley
Discolouration of extremities, Heinz bodies, increased extra medullary haemopoesis in spleen, siderocytosis in spleen and hepatocytes enlargement.

The effects on haematological parameters were evaluated on the basis of the document presented by ECBI (ECBI/07/03 add.11). Considering the change in blood parameters, increased methaemoglobin and sulfhaemoglobin together with pathological effects like haemosiderosis in liver and spleen, and effect of the boon marrow the RMS suggest R48 to be an appropriate classification.

Reproduction toxicity

Multigeneration

One two-generation study in rat of acceptable quality was presented. The LOAEL was established to 30 mg $kg^{-1}day^{-1}$ based on increased of liver and spleen weight in correlation with histopatological changes and variations in blood parameters. No NOAEL could be established in the study. However, no treatment related reprotoxic effects were observed.
In most of the studies there are indications that Diflubenzuron causes anaemia. The RMS therefore suggests that Diflubenzuron should be labelled with R48 “Danger of serious damage to health by prolonged exposure”.

In all studies, where it has been measured, it is an increase in sulfhaemoglobin and methaemoglobin. There is a RIVM report dealing with Methaemoglobin/Heinz bodies an in summary they conclude that rat/mouse/rabbit/guinea pig/monkey are less sensitive to methaemoglobin formation and generally show more effective reduction of induced MetHb than do man/dog/cat. If an effect on MetHb concentration is observed, it is by definition considered an adverse effect because an increase in MetHb levels is possible only when the capacity of the reducing mechanisms is exceeded. The exposure in question has then already reached such a level that considerable energy will be spent on reduction of MetHb and production of reticulocytes. This is certainly considered an adverse effect on a long term basis. RIVM (report 601516 007) 2001.

Formation of sulfhaemoglobin, unlike methaemoglobin, is not reversible and therefore considered to be of great toxic significance.
Changes in the blood parameters are seen in most studies: Hb↓, PCV or Hct↓, Erythrocyte counts↓ and RBC ↓ or↑ and also increase in liver and spleen weights which all are indicative of anaemia.

Additional signs of anaemia on top of the ones mentioned above that occurred during exposure of 50 mg/kg bw/ day or less:

6.6.1.3(1) Two-generation reproductive toxicity in rat by Brooker
Polychromasia, Howell-Jolly bodies, macroscopic changes in the spleen (enlargement, congestion, increased fluid-filled cysts), haemosiderosis in the spleen, centrilobular hepatocytes enlargement, pigmented Kuppfer cells.

The effects on haematological parameters were evaluated on the basis of the document presented by ECBI (ECBI/07/03 add.11). Considering the change in blood parameters, increased methaemoglobin and sulfhaemoglobin together with pathological effects like haemosiderosis in liver and spleen, and effect of the boon marrow the RMS suggest R48 to be an appropriate classification.

Teratogenicity
Two teratogenicity studies of acceptable quality, one in rat and one in rabbit, were presented. The NOAELs were ≥ 1 000 mg kg^{-1} day^{-1}. No maternal toxicity or any evidence of embryo toxicity was found.

Delayed neurotoxicity
Diflubenzuron is neither an organophosphorous nor a carbamate compound. Therefore, specific neurotoxicity testing is not deemed necessary. In all acute, sub-acute, semi-chronic and chronic toxicity studies no effect whatsoever indicative for or related to neurotoxic properties was found.

Table B.6.10-1: Summary of diflubenzuron repeated dose toxicity studies with acceptable quality

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
ORAL:					
28-day in rat					
Palmer *et al.* 1977	0, 81/87, 430/420, 2 000/2 100 and 10 500 mg kg^{-1} day^{-1} (M/F) 0, 800, 4 000, 20 000 and 100 000 ppm	Oral via dietary mixture	**M/F:81/87 mg kg^{-1} day^{-1}** **800 ppm**	**M/F:430/420 mg kg^{-1} day^{-1}** **4 000 ppm**	**↑ MetHb** **↑ SulfHb** **↑ Spleen weight** **↑ Liver weight (100 000 ppm)** **Haematological changes (100 000 ppm)**
90-day in rat					
Kemp, *et al* 1977; Offringa, 1977	0, 0.3/0.4, 1.1/1.6, 4.2/6.3 and 17/26 mg kg^{-1} day^{-1} (M/F) 0, 3.125, 12, 50 and 200 ppm	Oral via dietary mixture	**NOAEL:** **M/F:≥ 17/26 mg kg^{-1} day^{-1}** **≥ 200 ppm** NOEL: M/F:≥ 4.2/6.3 mg kg^{-1} day^{-1} 50 ppm	**LOAEL:** **M/F:≥ 17/26 mg kg^{-1} day^{-1}** **≥ 200 ppm** LOEL: M/F: 17/26 mg kg^{-1} day^{-1} 200 ppm	Organ weights of testis and adrenals Haemological parameters
Burdock *et al* 1980; Goodman 1980	0, 11/14, 27/34, 140/160, 690/890 and 3 700/4 400 mg kg^{-1} day^{-1} (M/F) 0, 160, 400, 2 000, 10 000 and 50 000 ppm	Oral via dietary mixture	**NOAEL:** **M/F:<11/14 mg kg^{-1} day^{-1}** **160 ppm**	**LOAEL:** **M/F:27/34 mg kg^{-1} day^{-1}** **400 ppm**	**↑ MetHb** **↑SulfHb** **↑Spleen weight**
Hunter *et al* 1979	0, 1 000 and 10 000 mg kg^{-1} day^{-1} 0, 10 000 and 100 000 ppm	Oral via dietary mixture	**<1 000 mg kg^{-1} day^{-1}** **<10 000 ppm**	**<1 000 mg kg^{-1} day^{-1}** **<10 000 ppm**	**↑ MetHb** **↑Spleen weight** **Histophatological changes in spleen** **Changes in haematological parameters**
90-day in mouse					
Burdock *et al* 1980	0, 2.3, 7.1, 57, 290, 1 400 and 7 100 mg kg^{-1} day^{-1} 0, 16, 50, 400,	Oral via dietary mixture	**NOAEL** **M/F:7.1 mg kg^{-1} day^{-1}** **M/F: 50 ppm**	**LOAEL** **M/F:290/1 400 mg kg^{-1} day^{-1}** **M/F: 2 000/10 000 ppm**	**↑ MetHb in both sexes** **↑ Organ weights: liver, spleen and adrenals** **Histophatological changes in liver**

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
	2 000, 10 000 and 50 000 ppm				
Colley *et al* 1981	0/0, 9.7/11, 51/55, 240/290, 1 200/1 400, 6 000/7 500 mg kg^{-1} day^{-1} (M/F) 0, 80, 400, 2 000, 10 000 and 50 000 ppm	Oral via dietary mixture	**NOAEL** **M/F: 9.7/11 mg kg^{-1} day^{-1}** **80 ppm**	**LOAEL** **M/F: 51/55 mg kg^{-1} day^{-1}** **400 ppm**	**↑Increase in MetHb (%Hb)** **↑Increase in SulfHb (%Hb** **↑ Organ weights: liver and spleen (2 000 ppm)** **Histophatological changes in liver and spleen (2 000 ppm)** ↑ spleen weights (80 ppm)
90-day in dog					
Versendaal *et al* 1983	0, 2, 4, 50 and 250 mg $kg^{-1}day^{-1}$	Oral *via* gavage/ gelatine capsules	**NOAEL** **4 mg $kg^{-1}day^{-1}$**	**LOAEL** **50 mg $kg^{-1}day^{-1}$**	**↑Increase in MetHb (%Hb)** **↑ M: liver weight (250 mg $kg^{-1}day^{-1}$)**
1-year in dog					
Greenough *et al* 1985	0, 2, 10, 50 and 250 mg $kg^{-1}day^{-1}$	Oral *via* gavage/ gelatine capsules	**NOAEL** **2 mg $kg^{-1}day^{-1}$**	**LOAEL** **10 mg $kg^{-1}day^{-1}$**	**↑Increase in MetHb (%Hb)** **Changes on organ weights and** **Histopatological changes (50 mg $kg^{-1}day^{-1}$)**
INHALATION: ***28-day in rat***					
Newton *et al* 1999	0, 11.6, 34 and 109 mg/L air	Inhalation	**NOAEL** **109 mg/L air**	**LOAEL** **≥ 109 mg/L air**	Changes in haematological parameters
28-day in rabbit					
Berczy *et al* 1975 **"Study used of restricted quality"**	0, 015, 0.75 and 1.9 mg/L air	Inhalation	**NOAEL** **≥ 1.9 mg/L air**	**LOAEL** **≥ 1.9 mg/L air**	

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
DERMAL: ***21-day in rat***					
Goldenthal, E.I (1996) **21-day dermal toxicity study in rats**	0, 20, 500, 1 000 kg^{-1}bw day^{-1}	Dermal	**NOAEL** **500 kg^{-1}bw day^{-1}**	**LOAEL** **1 000 kg^{-1}bw day^{-1}**	**Increased methaemoglobin** **Increased sulfhaemoglobin**
28-day in rabbit					
Davies *et al.* (1975b)	0, 70, 150 and 322 mg kg^{-1}bw day^{-1}	Dermal	**NOAEL** **150** **mg kg^{-1} day^{-1}**	**LOAEL** **322** **mg kg^{-1}day^{-1}**	**Increased sulfhaemoglobin**
ORAL ***Rat 1-year***					
104 weeks **(2 years) in rat** Burdock *et al.* 1984	0, 7.8, 31, 120 and 500 mg kg^{-1} day^{-1} 0, 156, 625, 2 500 and 10 000 ppm	Oral *via* the diet	**NOAEL/NOEL: 7.8 mg kg^{-1} day^{-1}** **156 ppm**	**LOAEL/LOEL: 120 mg kg^{-1} day^{-1}** **2 500 ppm**	**Increased methaemoglobin** **Increased sulfhaemoglobin** **Increased spleen weight (30-61%) at 2 500 ppm, both sexes** **Increased adjusted liver weight (28%) at 2500 ppm, females** **No tumour induction related to diflubenzuron was observed.**
Mouse					
91 weeks Colley, et al. 1984	0, 1.2/1.4, 6.4/7.2, 32/35, 160/190 and 835/958 mg kg^{-1} day^{-1} (M/F) 0, 16, 80, 400, 2 000 and 10 000 ppm	Oral *via* the diet	**NOAEL** **M/F:1.24/1.44 mg kg^{-1} day^{-1}** **16 ppm**	**LOAEL** **M/F:6.4/7.2 mg kg^{-1} day^{-1}** **80 ppm**	**Increased methaemoglobin** **Increased sulfhaemoglobin** **Methaemoglobinemia >2% associated with Heinz bodies at 400 ppm, both sexes** **No tumour induction related to diflubenzuron was observed.**
Dog					

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
1-year **Greenough *et al* 1985** **104 weeks** **(2 years) in rat** Burdock *et al.* 1984	0, 2, 10, 50 and 250 mg $kg^{-1}day^{-1}$ 0, 7.8, 31, 120 and 500 mg kg^{-1} day^{-1} 0, 156, 625, 2 500 and 10 000 ppm	Oral *via* gavage/ gelatine capsules Oral *via* the diet	**NOAEL** **2 mg $kg^{-1}day^{-1}$**	**LOAEL** **10 mg $kg^{-1}day^{-1}$**	**Increased methaemoglobin** **Changes on organ weights** **Histopatological changes at 50 mg $kg^{-1}day^{-1}$**
MULTI-GENERATION: ***Two generation/rat***					
Brooker 1995	0, 30, 300 and 3 200 mg kg^{-1} day^{-1} 0, 500, 5 000 and 50 000 ppm	Oral via dietary mixture	**<30 mg kg^{-1} day^{-1}** **500 ppm**	**≤ 30 mg kg^{-1} day^{-1}** **500 ppm**	**Increased methaemoglobin** **Increase of liver and spleen weights and histopatological changes** **Non effect on reproduction was observed in this study.**
TERATOGENICITY: ***Rat***					
Kavanagh *et al.* 1987	0, 1 000 mg kg^{-1} day^{-1}	Orally by gavage	**NOAEL/NOEL** **≥ 1 000 mg kg^{-1} day^{-1}**	**LOAEL/LOEL** **≥ 1 000 mg kg^{-1} day^{-1}**	**No maternal or any evidence of embryotoxicity**
Rabbit					
Kavanagh *et al.* 1987b	0, 1 000 mg kg^{-1} day^{-1}	Orally by gavage	**NOAEL/NOEL** **≥ 1 000 mg kg^{-1} day^{-1}**	**LOAEL/LOEL** **≥ 1 000 mg kg^{-1} day^{-1}**	**No maternal toxicity or any evidence of embryo toxicity**
M = male; F = female					

B.6.10.8 Acceptable daily intake (ADI)

The chronic studies in rat, mice, and dog were considered appropriate studies to use as a basis for the ADI. See Table B.6.10.8-1 for a summary of the NOAEL/NOELs observed in these studies.

The observed effects after diflubenzuron treatment in rats, mouse and dogs were increase in methaemoglobin and sulfhaemoglobin, changes in other blood parameters, increased organ weights (liver and spleen in rat and dog and brain in dog). The most sensitive species was the male mouse showing increased met- and sulfhaemoglobin at a dose of 1.2 mg kg^{-1} day^{-1} (Colley *et al.*, 1984) followed by changes in other blood parameters, formation of Heinz bodies, increased siderocytosis and extramedullary haemopoesis in spleen, hepatocytes enlargement and pigmented Kupffer cell pigmentation in higer concentrations. **The NOEL was established to 1.2 mg $kg^{-1}day^{-1}$ from the mouse 91 weeks study. Therefore, by applying a 100-fold safety factor to 1.2 mg $kg^{-1}day^{-1}$, the proposed ADI is 0.012 mg $kg^{-1}day^{-1}$.**

The notifier disagreed with the setting of ADI and had the opinion that the NOAEL of 2 mg/kg bw/day, from the dog study, should be used.

B.6.10.8-1. Summary of the NOAEL/NOEL observed in the chronic studies

Study	Dose levels	Administration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
Rat					
104 weeks (2 years) in rat Burdock *et al.* 1984	0, 7.8, 31, 120 and 500 mg kg^{-1} day^{-1} 0, 156, 625, 2 500 and 10 000 ppm	Oral *via* the diet	**NOAEL/NOEL: 7.8 mg kg^{-1} day^{-1}** **156 ppm**	**LOAEL/LOEL: 120 mg kg^{-1} day^{-1}** **2 500 ppm**	**Increased methaemoglobin** **Increased sulfhaemoglobin** **Increased spleen weight (30-61%) at 2 500 ppm, both sexes** **Increased adjusted liver weight (28%) at 2500 ppm, females** **No tumour induction related to diflubenzuron was observed.**
Mouse					
91 weeks Colley, et al. 1984	0, 1.2/1.4, 6.4/7.2, 32/35, 160/190 and 835/958 mg kg^{-1} day^{-1} (M/F) 0, 16, 80, 400, 2	Oral *via* the diet	**NOAEL** **M/F:1.24/1.44 mg kg^{-1} day^{-1}** **16 ppm**	**LOAEL** **M/F:6.4/7.2 mg kg^{-1} day^{-1}** **80 ppm**	**Increased methaemoglobin** **Increased sulfhaemoglobin** **Methaemoglobinemia >2% associated with Heinz bodies at 400 ppm, both**

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
	000 and 10 000 ppm				**sexes** **No tumour induction related to diflubenzuron was observed.**
Dog					
1-year **Greenough *et al* 1985**	0, 2, 10, 50 and 250 mg $kg^{-1}day^{-1}$	Oral *via* gavage/ gelatine capsules	**NOAEL** **2 mg $kg^{-1}day^{-1}$**	**LOAEL** **10 mg $kg^{-1}day^{-1}$**	**Increased methaemoglobin** **Changes on organ weights** **Histopatological changes at 50 mg $kg^{-1}day^{-1}$**
M = male; F = female					

B.6.10.9 Acceptable operator exposure level (AOEL).

Table B.6.10.9-1 Summary of repeated toxicity studies suitable for setting AOEL

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
ORAL: ***28-day in rat***					
Palmer *et al.* 1977	0, 81/87, 430/420, 2 000/2 100 and 10 500 mg kg^{-1} day^{-1} (M/F) 0, 800, 4 000, 20 000 and 100 000 ppm	Oral via dietary mixture	**M/F:81/87 mg kg^{-1} day^{-1}** **800 ppm**	**M/F:430/420 mg kg^{-1} day^{-1}** **4 000 ppm**	**↑ MetHb** **↑ SulfHb** **↑ Spleen weight** **↑ Liver weight (100 000 ppm)** **Haematological changes (100 000 ppm)**
90-day in rat					
Kemp, *et al* 1977; Offringa, 1977	0, 0.3/0.4, 1.1/1.6, 4.2/6.3 and 17/26 mg kg^{-1} day^{-1} (M/F) 0, 3.125, 12, 50 and 200 ppm	Oral via dietary mixture	**NOAEL:** **M/F:≥ 17/26 mg kg^{-1} day^{-1}** **≥ 200 ppm** NOEL: M/F:≥ 4.2/6.3 mg kg^{-1} day^{-1} 50 ppm	**LOAEL:** **M/F:≥ 17/26 mg kg^{-1} day^{-1}** **≥ 200 ppm** LOEL: M/F: 17/26 mg kg^{-1} day^{-1} 200 ppm	Organ weights of testis and adrenals Haemological parameters

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
Burdock *et al* 1980; Goodman 1980	0, 11/14, 27/34, 140/160, 690/890 and 3 700/4 400 mg kg^{-1} day^{-1} (M/F) 0, 160, 400, 2 000, 10 000 and 50 000 ppm	Oral via dietary mixture	**NOAEL:** **M/F:<11/14 mg kg^{-1} day^{-1}** **160 ppm**	**LOAEL:** **M/F:27/34 mg kg^{-1} day^{-1}** **400 ppm**	**↑ MetHb** **↑SulfHb** **↑Spleen weight**
Hunter *et al* 1979	0, 1 000 and 10 000 mg kg^{-1} day^{-1} 0, 10 000 and 100 000 ppm	Oral via dietary mixture	**<1 000 mg kg^{-1} day^{-1}** **<10 000 ppm**	**<1 000 mg kg^{-1} day^{-1}** **<10 000 ppm**	**↑ MetHb** **↑Spleen weight** **Histophatological changes in spleen** **Changes in haematological parameters**
90-day in mouse					
Burdock *et al* 1980	0, 2.3, 7.1, 57, 290, 1 400 and 7 100 mg kg^{-1} day^{-1} 0, 16, 50, 400, 2 000, 10 000 and 50 000 ppm	Oral via dietary mixture	**NOAEL** **M/F:7.1 mg kg^{-1} day^{-1}** **M/F: 50 ppm**	**LOAEL** **M/F:290/1 400 mg kg^{-1} day^{-1}** **M/F: 2 000/10 000 ppm**	**↑ MetHb in both sexes** **↑ Organ weights: liver, spleen and adrenals** **Histophatological changes in liver**
Colley *et al* 1981	0/0, 9.7/11, 51/55, 240/290, 1 200/1 400, 6 000/7 500 mg kg^{-1} day^{-1} (M/F) 0, 80, 400, 2 000, 10 000 and 50 000 ppm	Oral via dietary mixture	**NOAEL** **M/F: 9.7/11 mg kg^{-1} day^{-1}** **80 ppm**	**LOAEL** **M/F: 51/55 mg kg^{-1} day^{-1}** **400 ppm**	**↑Increase in MetHb (%Hb)** **↑Increase in SulfHb (%Hb** **↑ Organ weights: liver and spleen (2 000 ppm)** **Histophatological changes in liver and spleen (2 000 ppm)** ↑ spleen weights (80 ppm)
90-day in dog					
Versendaal *et al* 1983	0, 2, 4, 50 and 250 mg $kg^{-1}$$day^{-1}$	Oral *via* gavage/ gelatine capsules	**NOAEL** **4 mg $kg^{-1}$$day^{-1}$**	**LOAEL** **50 mg $kg^{-1}$$day^{-1}$**	**↑Increase in MetHb (%Hb)** **↑ M: liver weight (250 mg $kg^{-1}$$day^{-1}$)**
1-year in dog					
Greenough *et al* 1985	0, 2, 10, 50 and 250 mg $kg^{-1}$$day^{-1}$	Oral *via* gavage/ gelatine	**NOAEL** **2 mg $kg^{-1}$$day^{-1}$**	**LOAEL** **10 mg $kg^{-1}$$day^{-1}$**	**↑Increase in MetHb (%Hb)** **Changes on organ**

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
		capsules			**weights and** **Histopatological changes (50 mg $kg^{-1}day^{-1}$)**
INHALATION: ***28-day in rat***					
Newton *et al* 1999	0, 11.6, 34 and 109 mg/L air	Inhalation	**NOAEL** **109 mg/L air**	**LOAEL** **≥ 109 mg/L air**	Changes in haematological parameters
28-day in rabbit					
Berczy *et al* 1975 **"Study used of restricted quality"**	0, 015, 0.75 and 1.9 mg/L air	Inhalation	**NOAEL** **≥ 1.9 mg/L air**	**LOAEL** **≥ 1.9 mg/L air**	
DERMAL: ***21-day in rat***					
Goldenthal, E.I (1996)	0, 20, 500, 1 000 mg kg^{-1}bw day^{-1}	Dermal	**NOAEL** **500 mg kg^{-1}bw day^{-1}**	**LOAEL** **1 000 mg kg^{-1}bw day^{-1}**	**↑Increase in MetHb and sulfHb (%Hb)**
28-day in rabbit					
Davies *et al.* (1975b)	0, 70, 150 and 322 mg kg^{-1}bw day^{-1}	Dermal	**NOAEL** **150** **mg kg^{-1} day^{-1}**	**LOAEL** **322** **mg $kg^{-1}day^{-1}$**	
MULTI-GENERATION: ***Two generation/rat***					
Brooker 1995	0, 30, 300 and 3 200 mg kg^{-1} day^{-1} 0, 500, 5 000 and 50 000 ppm	Oral via dietary mixture	**<30 mg kg^{-1} day^{-1}** **500 ppm**	**≤ 30 mg kg^{-1} day^{-1}** **500 ppm**	**Increased methaemoglobin** **Increase of liver and spleen weights and histopatological changes** **Non effect on reproduction was observed in this study.**

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
TERATOGENICITY: ***Rat***					
Kavanagh *et al.* 1987	0, 1 000 mg kg^{-1} day^{-1}	Orally by gavage	**NOAEL/NOEL ≥ 1 000 mg kg^{-1} day^{-1}**	**LOAEL/LOEL ≥ 1 000 mg kg^{-1} day^{-1}**	**No maternal or any evidence of embryotoxicity**
Rabbit					
Kavanagh *et al.* 1987b	0, 1 000 mg kg^{-1} day^{-1}	Orally by gavage	**NOAEL/NOEL ≥ 1 000 mg kg^{-1} day^{-1}**	**LOAEL/LOEL ≥ 1 000 mg kg^{-1} day^{-1}**	**No maternal toxicity or any evidence of embryo toxicity**
M = male; F = female					

According to the guideline of setting the AOEL[1], the NOAEL for effects in the long-term studies (including 1 year dog) should be considered in AOEL setting if there are indicators that effects only become evident in chronic studies but might be initiated by shorter term exposure. Metabolism studies demonstrated that diflubenzuron is poorly absorbed from the intestinal tract, high levels of non-absorbed diflubenzuron was found in the faeces. The oral absorption was approx. 33%. In the subchronic studies, the lowest relevant NOAEL was 2 mg $kg^{-1}day^{-1}$ in dog after an oral administration of diflubenzuron. The proposed AOEL is 2 mg $kg^{-1}day^{-1}$, applying a 100-fold safety factor to the relevant dose and an oral absorption of 33%.

$$\text{AOEL} = \frac{\text{NOAEL x oral absoption}}{\text{Safety factor}} \qquad \frac{2 \text{ mg kg}^{-1}\text{day}^{-1} \times 33\%}{100} = 0.0066 \text{ mg kg}^{-1}\text{day}^{-1}$$

The major effect observed at the Lowest Observed Adverse Effect Level (LOAEL) was increase in methaemoglobin and sulfhaemoglobin.

The notifier disagreed with the setting of AOEL and had the opinion that the NOAEL of 20 mg/kg bw/day, from the dermal rat study (Goldenthal 1996), should be used, as operators will not be exposed to diflubenzuron every day of the year. The notifier expect fewer than 28 exposures per year for operators and in most situations fewer than 5 exposures per day.

[1] *AOEL* Guideline for setting of acceptable operator exposure levels (AOELs). Draft. Sanco/xxx/2005 rev.8, 27 January 2005

B.6.10.10 Acute reference dose (ARfD)

Reporting table, mammalian toxicity, 2(11)

Methaemoglobin can be an acute effect. However, Diflubenzurone has very low acute toxicity when given by various routs (oral, dermal, inhalation). There are recovery systems for increase in methaemoglobin so most likely one single acute dose is not critical but it is the repeated doses that overwhelm the reducing system and affects the whole body that is critical. Thus according to the toxicological profile of Diflubenzuron the RMS suggest that establishing an ARfD is unnecessary.

However, if an ARfD have to be set; the most striking effect of Diflubenzuron is increase in methaemoglobin and sulfhaemoglobin. In the 28-day study in rat by Palmer et al 1977 these effects were seen in both sexes at around 80 mg kg^{-1} day^{-1} = LOAEL. Applying a safety factor for inter- and intraspecies differences of 100 and a factor 2 for extrapolation from LOAEL to NOAEL results in an ARfD of 0.4 mg kg^{-1} day^{-1}.

The Notifier's opinion is that no ARfD has to be set and the 24th of February 2007 RMS received a document by e-mail from Chemtura with the title "Rationale in Support of the Removal of the Acute Reference Dose (ARfD)", see below.

PRODUCT
Diflubenzuron

STUDY TITLE
Rationale in Support of the Removal of the Acute Reference Dose (ARfD)

AUTHOR
[redacted]

PERFORMING INSTITUTION
Chemtura Corporation

STUDY NUMBER
EF002

DATE
05 February 2007

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STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA 10 (d) (1) (A), (B) or (C).

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

The information complied herein is not a study as defined in FR 54 (158): 34068, and therefore a Good Laboratory Practice Compliance Statement is not required.

Submitter/Sponsor/Approver

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PURPOSE

To provide rationale in support of the removal of the acute reference dose (ARfD) for diflubenzuron.

SUMMARY

Chemtura contends that an Acute Reference Dose (ARfD) is not warranted for diflubenzuron. This position is supported by both the US EPA and the FAO/WHO. Diflubenzuron is not acutely toxic. Exposure to diflubenzuron via food or water will not result in any biological relevant change in methaemoglobinemia (MetHb) levels, even in sensitive populations. There should not be an ARfD for diflubenzuron.

RATIONALE FOR THE REMOVAL OF THE ACUTE REFERENCE DOSE (ARfD) FOR DIFLUBENZURON

I. The Decision of the US EPA FIFRA in regards to the ARfD for diflubenzuron.

Diflubenzuron is not acutely toxic (LD50s > 4640 mg/kg orally, >10000 mg/kg dermally, > 3.7 mg/L inhalation). According to the US EPA RED document, one day single dose oral studies in rats and mice indicated only marginal effects on methaemoglobinemia (MetHb) levels at a dose level of 10000 mg/kg of a 25% wettable powder formulation (2500 mg/kg bw of diflubenzuron).[1,2] Sulfhaemoglobin levels and Heinz bodies were not affected. Therefore according to the EPA assessment, there is no acute dietary endpoint and a risk assessment for acute dietary exposure is not necessary.[3]

II. The Decision of the FAO/WHO in regards to the ARfD for diflubenzuron.

FAO/WHO has also concluded that the ARfD is not necessary. The Meeting concluded that, although MetHb is potentially an acute effect, the overall

toxicological profile of diflubenzuron indicates that establishment of an ARfD is unnecessary. The absorption of diflubenzuron declined with increasing doses, and its excretion was relatively rapid, which would tend to limit systemic concentrations after high acute doses. The meeting also concluded that MetHb and sulfhaemoglobinemia occurred only after saturation of reduction processes in the toxicological database.

Diflubenzuron has very low acute toxicity when given by various routes (oral, dermal and inhalation). The results of acute toxicity studies show that diflubenzuron (purity, 99.6%) has little acute toxicity when given by the oral, inhalation or dermal route. The LD_{50} in mice and rats given diflubenzuron in 1% tragacanth by gavage was > 4600 mg/kg bw (van Eldik, 1973). In rats treated dermally for 24 h, the LD_{50} was > 10,000 mg/kg bw (Koopman, 1977), and in rats treated by whole-body inhalation of a preparation with a mass median aerodynamic diameter < 5 µm, the LC_{50} was > 2.9 mg/l of air (Berczy et al., 1973). No clinical signs were seen in these studies. Only marginal increases (less than doubling) in MetHb concentrations were seen in mice and rats given 10,000 mg/kg bw of a formulation of diflubenzuron, equivalent to 2500 mg/kg bw, which is above the limit doses used in toxicological tests.[1,2] No developmental toxicity was seen when diflubenzuron was given at up to a limit dose of 1000 mg/kg bw per day. There was no evidence of neurotoxicity in routine studies of toxicity.[4]

III. General Considerations on the derivation of an ARfD

Chemtura's position is that humans will not be exposed via food and water in one day to the amounts of diflubenzuron required to produce the minimal effects seen in the rat and mouse acute studies.[1,2] In addition to the extremely high levels of diflubenzuron required to be consumed to make even a non-relevant change in MetHb levels, the metabolism of diflubenzuron must also be considered in the evaluation for the need of an ARfD. Diflubenzuron is poorly absorbed from the gastrointestinal tract and, at a dose range of 5-100 mg/kg, absorption decreased with increased dose in the rat. High level of non-absorbed diflubenzuron was found in the faeces. The oral absorption was approximately 0.33% and absorbed radioactivity was almost completely removed by 24-48 hours. Taking the

absorption, distribution, metabolism and excretion of diflubenzuron into consideration along with the toxicological database, there is no need for an ARfD. The doses required to result in even non-significant changes of MetHb will not be achieved upon acute exposure.

IV. Sensitive Populations

There are increased levels of MetHb over background levels (normal background levels are 1-2%) that do not elicit any clinical effects. Clinical symptoms are proportional to the level of MetHb; less than 10% MetHb is associated with no clinical symptoms.[6] This is in accordance with the JMPR Guideline for setting an ARfD which states that increased levels of MetHb in humans will not produce a biologically significant effect until over 6% MetHb, which is the threshold for the occurrence of clinical signs due to MetHb formation in sensitive individuals.[7] Understandably, the concern that the most sensitive population, those deficient in enzyme responsible for the reformation of haemoglobin from MetHb, should be protected. This is not a concern with diflubenzuron because the levels of MetHb produced by diflubenzuron will never be of clinical significance, even in a sensitive population.

CONCLUSION

In conclusion, Chemtura Corporation is in agreement with both US EPA and the FAO/WHO in that the assignment of an ARfD is not warranted for diflubenzuron. This is based on the lack of effects seen in toxicological testing, the non-biological relevance of the change in MetHb levels, as well as the metabolism and the limited potential exposure to diflubenzuron via food and water.

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B.6.10.11 Drinking water limit

Assuming that exposure through drinking water should not account for more than 10% of the ADI, an average consumption of 2 L of water per person per day and a body weight of 60 kg, the proposed drinking water limit for diflubenzuron is:

0.012 mg $kg^{-1}day^{-1}$ x 0.1 x 60 kg ÷ 2 L = 0.06 mg/L = 36 µg/L

The maximum permissible concentration laid down by Council Directive 80/778/EEC is 0.1µg/L for pesticide active substances.

Classification with R48

As stated in section 6.10, diflubenzuron should be classified with R48 according to the RMS. The Notifier does not agree with this classification and RMS has received the following document from Chemtura called "Applicabillity of the R48 Classification to diflubenzuron".

Chemtura

Applicability of the R48 Classification to Diflubenzuron

[redacted]

August 21, 2007

The toxicology package for diflubenzuron was assessed in association with ECBI/07/03 Add. 11 (Proposal for criteria to be used in the classification of R48 for hemolytic anemia in repeated dose toxicity studies). The treatment related effects seen in the toxicity studies with diflubenzuron are not indicative of serious adverse effects. The assessment concluded that the classification of R48 is not warranted for diflubenzuron.

No serious systemic effects were demonstrated in any toxicity study with diflubenzuron. Repeated dose studies with diflubenzuron in the diet, by oral bolus dose in the form of a capsule, by inhalation or by dermal exposure, have not resulted in any deaths related to treatment. Dietary treatment levels were up to 100,000 ppm for 9 weeks in rats (7801/8539 mg/kg bw/day male and female respectively) (Hunter 1979). Clinical signs were not observed during dosing in any study. No decrease in life span for any animal species was noted in any repeated dose study. This demonstrates that the hematological effects of diflubenzuron treatment do not result in a decrease in overall health of the treated animal.

Repeated dose administration of diflubenzuron resulted in sub-clinical expression of anaemia, which was most likely due to extracellular hemolysis. The level of anaemia can be classified as sub-clinical because of the lack of clinical symptoms associated with treatment. The decrease in hemoglobin(Hb) levels was not below the designated adverse level of 10% of in any of the studies. Methemoglobin (MetHb) levels were only above the level of concern (4% in rats, 2% in mice) at extremely high doses (400 ppm in mice and 100,000 ppm in rats). Furthermore, chronic administration of diflubenzuron resulted in a reduction in the expression of anaemia compared to those evident upon sub-chronic treatment. This negates the need for classification based on chronic sub-clinical methemoglobinemia.

ECBI/07/03 Add. 11 (Proposal for criteria to be used in the classification of R48 for hemolytic anemia in repeated dose toxicity studies) states that the decision for classification should be based on longest duration study. The longest duration studies in terms of time and percentage of lifespan covered are the combined chronic / carcinogenicity studies in rats and mice. In the rat studies, methaemoglobin levels do not exceed the >4% level of concern. The high dose level in the rat chronic study was 10,000 ppm (1% of the diet). The effects on hematology parameters are decreased or absent at 104 weeks when compared to the 52 week measurement. No clinical effects, deaths or decrease in life span was detected in the rat studies. The percent Hb levels in the chronic rat study were not-dose related. The decreases at 52 weeks of treated ranged from 7 - 8% at the high dose to 12% in females at 2500 ppm and males at 650 ppm at 52 weeks. The percent Hb increased at 104 weeks to 16% in the high dose males. The improvement in Hb levels along with improvements in erythrocyte levels, MCV and reticulocytes demonstrate a successful compensatory mechanism or an alleviation of the hemolytic effect. The increases in relative and absolute liver and spleen weights can be accounted for by the deposition of hemosiderin-like pigment. These are not direct adverse effects but are effects secondary to the hemolytic anaemia. The organs are not irreversibly damaged as shown by the recovery period after 7 weeks of treatment and 4 weeks of non-treatment. The pigment deposition is not accompanied by indications of severe anaemia. The results of the rat chronic/oncogenicity study demonstrate that the classification of R48 is not appropriate.

The chronic/carcinogenicity study in mice was also considered in this assessment. There was no affect on survival. Males in the 10000 ppm treatment group had statistically lower body weight at week 52. The Hb level in the same high dose males was significantly higher than controls at week 78 but were similar among all group at weeks 52 and 91 (termination). The MetHb levels were above the noted 2% of the total Hb level of concern in the male and female treatment groups at 400 ppm. However, as the DAR states, the statistically significant alterations are still within the normal range. Increases in spleen weight that were evident at the interim (52 weeks) were not present at terminal sacrifice. The results of the chronic toxicity/carcinogenicity mouse study furthers the determination that diflubenzuron does not warrant an R48 classification.

Administration of diflubenzuron to laboratory animals does not demonstrate severe anaemia or severe hemolytic anaemic effects. The effects demonstrated are sub-clinical and reversible. Based on the entire toxicological database and especially the long term studies, the classification of R48 is not warranted.

R48 Danger of serious damage to health by prolonged exposure; *Clear functional disturbance or morphological change which has toxicological significance.*

- Particularly important when changes are irreversible
  - Not the case with Diflubenzuron (DFB dietary treatment with recovery period demonstrated a recovery or decrease in severity of all symptoms. Furthermore, chronic studies demonstrated a recovery upon prolonged treatment
- Classification depends on dose level, exposure period and dose route
  - Even at extreme dose levels of DFB (1% of the diet), no clinical signs of anaemia were present
- If studies of multiple durations are available, the study of the longest duration should normally be used
  - For DFB those studies would be the rat chronic/carcinogenicity and mouse oncogenicity studies

1. Substance related death
   - For DFB, no substance related deaths were reported in any study
   - For DFB, no substance related reproductive / developmental toxicity
2. Major Functional Changes in Organ System
   - For DFB, no clinical signs of hypoxia were seen during treatment
3. Changes in clinical biochem/hematology/urinalysis parameters which indicate severe organ dysfunction. Hematological changes are considered to be of particular importance if the evidence suggests that they are due to decreased bone marrow production
   - DFB did not result in a decreased bone marrow production
   - There was no reduction of Hemoglobin at ≥ 20% in any study with DFB at any dose level
   - There was no reduction of functional hemoglobin at ≥ 20% due to a combination of hemoglobin reduction and metHb formation in any study with DFB
   - Hemoglobinuria or hemosiderinuria was not detected in any study with DFB

4. Severe organ damage noted on microscopic examination following autopsy:
   4.1 Widespread or severe necrosis fibrosis etc in organs with regenerative capacity
      - No widespread or severe fibrosis in the spleen, liver or kidney was detected in any study with DFB
   4.2 Severe morphological changes that are potentially reversible but are clear evidence of marked organ dysfunction
      - No severe tubular nephrosis was detected in any study with DFB
   4.3 Evidence of appreciable cell death in vital organs incapable of regeneration or in a stem cell population
      - No appreciable cell death in organs incapable of regeneration or in a stem cell population.

The guidance document also mentions that it is important to consider not only specific severe changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs or severe changes in general health status.

- DFB does not result in any severe changes to the general health status of the treated animals at any dose level or route of administration
- DFB affects the circulatory system through mild, subclinical extravascular hemolytic anemia. The effects seen are reversible and compensatable as demonstrated by the toxicological data.

These effects are relevant when attempting to determine a no-effect level for a chemical substance – irrespective of stat significance.

- Clinical observations or changes in bodyweight gain, food consumption or water intake, which may have some toxicological significance but which do not, by themselves, indicate 'serious damage'
  - DFB does not result in clinical symptoms or significant changes in bodyweight gain, food consumption or water intake. This is relevant when considering the statistically significant but not biologically relevant changes which are not indicative of serious damage.
- Small changes in clinical biochemistry, hematology or urinalysis which are of doubtful or minimal toxicological importance
  - DFB treatment results in sub-clinical expression of anaemia. The changes in hemoglobin levels are less than 10% for the majority of tested doses. MetHb levels are within the 0-4% for rats and usually in the range of 0-2% for the mice. Full recovery was noted after 4 weeks of withdrawal in rats treated for 7 weeks in feed. Compensatory mechanisms begin within 28 days of treatment and chronic treatment demonstrates improvement if not complete reversal of effects.
- Changes in organ weights without evidence of organ dysfunction
  - No or minimal severe histopathology effects were noted in the spleen and liver
- Adaptive responses

- Are present and compensatory. No clinical effects.

- Species specific mechanism of toxicity has been demonstrated
  - All animals responded similarly to DFB. There is no indication that humans would respond any differently to treatment.

The RMS has read the paper by Freeman E and still has the opinion that diflubenzuron should be classified as R48 “Danger of serious damage to health by prolonged exposure”.
Diflubenzuron oxidises haemoglobin to methaemoglobin. This is seen in most of the studies with diflubenzuron together with formation of sulfhaemoglobin.

Normally methaemoglobin is rapidly reduced back to haemoglobin and if an increase in methaemoglobin can be measured it is because the reducing capacity has been exceeded. The exposure has then already reached such a level that considerable energy will be spent on reduction of methaemoglobin and production of new reticulocytes. This is considered an adverse toxicological effect on a long term basis (RIVM report 061516 007, 2001). In the same report it is stated that rat, mouse, rabbit, guinea pig and monkey are less sensitive to methaemoglobin formation and generally show more effective reduction of methaemoglobin than man and dog do.

Unlike methaemoglobin the formation of sulfhaemoglobin is not reversible and is therefore also considered to be of toxic significance.

The increased formation of methaemoglobin and sulfhaemoglobin seems to cause an increased turn over of erythrocytes. Normally the blood cells are produced in the bone marrow but under extreme conditions the blood cells can also be produced in the liver and spleen, as during the foetal period, and this is observed during diflubenzuron exposure. The increased turnover of erythrocytes also causes an increased accumulation of iron. In healthy individuals small amounts of haemosiderin can occur in the spleen (and it increases with age) but haemosiderin present in liver and kidney is a pathologic condition and can cause damage to the organs. In several studies with diflubenzuron damage to the liver has also been observed.

The RMS has listed the studies with the above-mentioned effects indicative of anaemia that was seen during diflubenzuron exposure and that occurred during repeated exposure of 50 mg/kg bw/day or less. Other effects observed in most studies with diflubenzuron were changes in blood parameters: Hb↓, PCV or Hct↓, erythrocyte counts↓ and RBC↓ o r↑ and also increase in liver and spleen weights which all are indicative of anaemia.

6.3.1(3) Oral 6 week mouse study by Hunter (study used as complementary)
Live necrosis in 3 out of 8 mice exposed to 6 mg/kg bw/day with or without inflammatory cells.

6.3.1 (3) Oral 90-day mouse study by Colley (study of restricted quality)
Heinz bodies (sine of methaemoglobin formation but more stable), increase in plasma glutamic pyruvic transaminase (indicating liver damage). Discolouration and enlargement of spleen, haemosiderosis in the spleen, liver areas of focal necrosis and/or fibrosis in the parenchyma with or without associated inflammatory cells, dose related increase in grey/blue discolouration of extremities.

6.4.1(3) Oral 90-day mouse study by Burdock

Liver necrosis, haemosiderosis and chronic hepatitis. The severity increased with dose.

6.4.1(2) Oral 90-day rat study by Burdock
Dose dependent increased in grading of chronic hepatitis and liver haemosiderosis (incidence: zero for control, 50 % of the animals exposed to 27/34 mg/kg bw (M/F) and 100% of the animals exposed to the highest dose), congestion of the spleen and mild erythroid hyperplasia of the bone marrow.

6.4.1(5) Oral 90-day dog study by Chesterman (study of restricted quality)
Increase in alkaline phosphatise and serum glutamic transaminase.

6.4.1(6) Oral 90-day dog study by Greenough
Dose related increase in incidence and severity of macrophage and Kupffer cell siderosis, Heinz bodies, increase in LDH (indicating liver damage), and haemosiderosis in the liver.

The effects on haematological parameters were evaluated on the basis of the document presented by ECBI (ECBI/07/03 add.11). Considering the change in blood parameters, increased methaemoglobin and sulfhaemoglobin together with pathological effects like haemosiderosis and necrosis in the liver, enlargement and congestion of the spleen and the effect on the boon marrow RMS suggest R48 to be an appropriate classification.

B.6.12 Dermal absorption (Annex IIIA 7.3)

Reporting table 2(14)
In the dermal absorption study the animals were killed immediately after 1, 4 or 10 h of exposure. At these time points a significant amount of label was still present in the exposed skin. Furthermore, for the low dose label was still excreted in urine at the end of the 10 h exposure period.
Based on this study the dermal absorption should be about 6% as the amount remaining in the skin after 10 hours could be absorbed.

B.6.14 Exposure data (Annex IIIA 7.2)

Dimilin WG-80 is a water-dispersible granular (WG) formulation containing 800 g diflubenzuron/kg recommended for use in pome fruit, mushrooms and forestry. Dimilin WG-80 is applied to pome fruit by tractor-mounted or hand-held spray equipment, to mushrooms by hand-held spray equipment or automatic sprayer, and to forestry by aerial application. A summary of the application methods and the recommended "worst case" application rates are provided in the following table:

Table B.6.14-1: Summary of application methods and rates of Dimilin WG-80 relevant for the operator exposure assessment

Field of use	Method of application	Max. application rate	Spray volume	Max. application concentration
Pome fruit	Tractor-mounted sprayer; spray directed upwards and sideways	180 g a.s./ha	1 500 L/ha	0.12 g a.s./L
	Hand-held sprayer; spray directed upwards and sideways			
Forestry	Aerial application - ultra low volume (ULV)	48 g a.s./ha	3 - 5 L/ha in oil	16 g a.s./L
	Aerial application - low volume (LV)		30 - 50 L/ha in water	1.6 g a.s./L
Mushrooms	Automatic sprayer	1 g a.s./m^2 (=10 000 g a.s./ha)	1 - 1.5 L/m^2	1 g a.s./L
	Hand-held sprayer; high volume spray directed downwards			

B.6.14.1 Operator exposure

B.6.14.1.1 Estimation of operator exposure in orchards

Estimation of operator exposure in orchards using UK POEM and the German model

The estimates of total diflubenzuron exposure predicted by UK POEM[2](Predictive operator exposure model) and the German model[3] were calculated as a proportion of the proposed AOEL for the active ingredient. Two different application techniques are used: Tractor-mounted sprayer (spray directed upwards and sideways) and hand-held sprayer (spray directed upwards and sideways).

Additional assumptions/data utilised in the models are as follows:

Area Treated in One Day:	8 ha/day for tractor-mounted sprayer 1 ha for hand-held treatment
Application Rate:	180 g as./ha
Inhalation Exposure for Mixer/Loader:	0.01 ml/hr
Application Volume – Groundboom Application:	1 500 l/ha
Inhalation absorption	100%
Dermal absorption	6 %

Tractor-mounted and hand-held sprayer in orchards

The estimated operator exposure values for tractor-mounted sprayer and hand-held sprayer in orchards, determined on the basis of the model scenarios without or with minimum acceptable protective clothing, were set

[2] *Scientific Subcommittee on Pesticides and British Agrochemicals Joint Medical Panel., Estimation of Exposure and Absorption of Pesticides by Spray Operators (UK MAFF) 1986 and the Predictive Operator Exposure Model (POEM – UK MAFF) 1992*

[3] *Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem, no. 277, 1992*

out in Table B.6.14.1.1-1. Systemic exposure was taken into consideration in relation to the AOELsystemic. Total systemic exposure was calculated from the addition of dermal and inhalation exposure (see also calculation in Appendix 1, A-J).

Table B.6.14.1.1-1: Estimations of operator exposure to Dimilin WG-80 and comparison in relation to the systemic AOEL in orchards

DIMILIN WG-80		
Tractor-mounted sprayer		
PPE	**Operator total exposure (**mg kg^{-1} bw day^{-1}**)**	**% of AOEL[1)]**
	UK POEM	
Without	0.0292	**442 %**
With gloves and PRE (FFP3) during mixing and loading and gloves during spraying	0.0112	**170 %**
	German model	
Without	0.0201	**304 %**
With gloves during mixing and loading and gloves, coverall and sturdy footwear during spraying	0.00308	**47 %**
Hand-held sprayer		
	Operator total exposure (mg kg^{-1} bw day^{-1}**)**	**% of AOEL[1)]**
PPE	**UK POEM**	
Without	0.0400	**607 %**
With gloves during mixing and loading and gloves during spraying	0.00629	**95 %**
With gloves during mixing and loading and gloves and impermeable coverall during spraying	0.00260	**39 %**
	German model	
Without	0.0120	**182 %**
With gloves during mixing and loading and gloves during spraying	0.00638	**97 %**
With gloves during mixing and loading and gloves, coverall and sturdy footwear during spraying	0.00211	**32 %**

$AOEL_{sys}$=0.0066 mg kg^{-1} bw day^{-1}; Dermal exposure 6%

Conclusion:

The modelling data based on UK POEM and the German model for tractor-mounted and hand-held spraying in orchards showed that exposure to diflubenzuron does involve a significant risk to the health of the operators concerned. **Using tractor-mounted sprayer, the German model predicted a value of 47 % of the AOEL when maximum PPE was used. However, with the same conditions in the UK POEM 170 % of AOEL was reached. Using hand-held sprayer 95 and 97 % of AOEL was reached using gloves during mixing, loading and spraying.**

B.6.14.1.2 Estimation of operator exposure in forestry

The scenario for application Dimilin WG-80 in forestry is either by aerial application using fixed-wing aircraft or helicopters with enclosed cockpits or by ground application by tractor-mounted or hand –held spray. All the applications are done by specialist companies who are licensed by local government bodies. The intended use of Dimilin WG-80 in forestry is dependent on the biological cycle of the pest but no more than one application per crop and year. The applications are made in spring or autumn. Treatments are not sprayed routinely but if an infestation of the pest is present. For aerial application separate operators do the mixing/loading and the applications.

Aerial application by aircraft or helicopter
Mixing and loading is done in the same way as for applications by tractor-mounted equipment. The appropriate weight of product is mixed with the required volume of water for low volume (LV) applications or with water plus mineral oil or crop oil for ultra-low volume (ULV) applications. Sufficient product is mixed to apply up to 200 ha per flight.

Applications by air are generally made in early morning (four to five hours spraying time) and/or late afternoon (two to three hours spraying time) to reduce drift and evaporation of the droplets during windy or hot weather conditions. For ULV applications, the nozzles are designed to apply droplets of between 80 and 120 µm to give good crop coverage and to reduce drift. Each flight takes approximately one hour for application to 200 ha. Based on a working day of 8 hours, assuming 0.5 hours for mixing/loading and 4 times taking off and landing the airplane (5 x 0.5 hour = 2.5 hours), the maximum flying time would be 5 hours per day. Therefore, the maximum area that could be treated in a day is 1 000 ha. This can be considered to represent the worst-case use for the assessment of operator exposure.

'Ground markers' or 'flaggers', i.e. persons on the ground who direct the pilots to the correct location for spraying, are not used in forestry. The crop canopy is high and such persons would not be visible from the air. Modern forest plantations are set out in separate blocks allowing the pilot to locate the correct target area. The potential exposure of operators during aerial application is therefore limited to persons involved in mixing/loading and to the pilots of the aircraft or helicopters.

Ground application by tractor-mounted or hand-held spray
The application of Dimilin WG-80 could be done by tractor-mounted spray or hand –held spry equipment, "high" crop application.

Estimation of mixing/loading and application based on the German model during aerial and ground application
Exposure during mixing prior to application by air can be estimated using the German model as the product is prepared in the same way as for application by tractor-mounted equipment. The exposure was 1.024 mg kg^{-1} bw day^{-1} without PPE and 0.0104 mg kg^{-1} bw day^{-1} with gloves and A1P2, corresponding to 15515 % respective 157

% of the AOEL already during the mixing and loading step, indicating a risk during forest treatment by aircraft. No further calculations on the application from aircraft were therefore done. (For calculations se Appendix 1 K-L)

Total systemic exposure was calculated for Dimilin WG-80: application to forest with tractor-mounted or hand – held spray equipment, from the addition of dermal and inhalation exposure (see also calculation in Appendix 1). Without the use of PPE the exposure was 0.00535 and 0.00320 mg kg^{-1} bw day^{-1} respectively which corresponds to 81 and 49 % of the AOEL. (For calculations se Appendix 1 M-N)

Additional assumptions/data utilised in the models are as follows:

	Application from air	Ground application Tractor-mounted spray	Ground application Hand-held spray
Area Treated in One Day:	1 000 ha	8 ha	1 ha
Application Rate:	48 g as./ha	48 g as./ha	48 g as./ha
Inhalation absorption	100%	100%	100%
Dermal absorption	6 %	6 %	6 %

Table B.6.14.1.2-1: Estimations of operator exposure during mixing/loading and application to Dimilin WG-80 with and without PPE and comparison in relation to the systemic AOEL in aerial and ground application

DIMILIN WG-80 Application-Forest		
PPE		**% of AOEL[1)]**
	Aerial application	
	Exposure during mixing and loading (mg kg^{-1} bw day^{-1}**)**	
	German model mixing and loading	
Without	1.024	**15515 %**
With gloves and A1P2	0.0104	**157 %**
	Ground application	
PPE	**Operator total exposure (**mg kg^{-1} bw day^{-1}**)**	
	Tractor-mounted sprayer (German model)	
Without	0.00535	**81 %**
	Hand-held sprayer(German model)	
Without	0.00320	**49 %**

[1] *$AOEL_{sys}$=0.0066 mg kg^{-1} bw day^{-1}; Dermal exposure 6%*

Conclusion

The exposure of the operators to diflubenzuron during mixing/loading in the scenario of aircraft application has been calculated from the German model; the exposure already during mixing and loading, using PPE was 157% of the AOEL and it is not acceptable. However, ground application using either tractor-mounted or hand-held sprayer resulted in exposure 81 % and 49 % of the AOEL respectively, without the use of PPE. This application is considered acceptable use.

B.6.14.1.3 Estimation of operator exposure in greenhouse using mushrooms grower

Mushrooms are grown in insulated houses and planted in compost in wooden trays or aluminium shelves stacked in tiers on either side of a central aisle. The compost consists of peat and is pasteurised prior to use. Mushroom spawn (mycelium culture) is incorporated into the compost and this is subsequently covered with casing medi, which is typically a mixture of peat and sugar beet lime. Mushroom farms vary in size and an average area of production would be approximately 300 to 400 m^2 with the largest farms growing a total of up to 1 500 m^2, i.e. 0.15 ha, in three to four mushroom houses. Applications are made routinely to the casing media as a high volume low pressure sprays drench. There is one application of Dimilin WG-80 per cropping cycle (which takes 6 to 8 weeks) and up to five cycles per year. Cycles start at different times within a mushroom house to provide continuous cropping and so an application of Dimilin WG-80 could be made once a week with each application taking approximately one hour. The same operators do the mixing/loading and the applications. Product is prepared and used by each mushroom grower and applications are not made at several mushroom farms by spray contractors.

Applications are made automatically through the irrigation system in many modern houses. Alternatively, applications are made using hand-held equipment. The product is mixed and loaded prior to application by both methods but application by hand-held equipment involves the higher potential for exposure of operators. Sprays are applied at high volume (up to 1.5 L/m^2, equivalent to 15 000 L/ha) and the spray is directed downwards to the casing media. The water volume incorporates the active substance into the casing media.

Additional assumptions/data utilised in the models are as follows:

Area Treated in One Day:	1 ha
Application Rate:	10 kg a.s./ha
Application volume:	15 000 L/ha
Inhalation absorption	100 %
Dermal absorption	6 %

Estimation of operator exposure in greenhouse for growing mushrooms during mixing and loading

The operator exposure during mixing and loading is estimated using the German model. It is assumed that a maximum of 0.15 ha/day can be treated as the farmers are not bigger (see above). Based on a maximum use rate of 1 g a.s./m^2 (10 kg a.s./ha), this will result in the following estimated exposure of spray operators to diflubenzuron without or with personal protective equipments (see also Appendix 1, O-R):

Table B.6.14.1.3-1: Estimations of operator exposure during mixing/loading to Dimilin WG-80 with and without PPE and comparison in relation to the systemic AOEL in greenhouse using mushrooms grower

DIMILIN WG-80 **Aerial application-mushroom**		
PPE	**Operator total exposure (**mg kg^{-1} bw day^{-1}**)**	**% of AOEL[1)]**
	German model automatic spraying (only mixing and loading)	
Without	0.032	**484%**
With gloves	0.000815	**12 %**
	German model hand-held spraying	
Without	0.1001	**1571 %**
With gloves and A1P2 during mixing and loading and Hood, visor, gloves, coverall and sturdy footwear during spraying	0.0102	**155 %**

[1] *$AOEL_{sys}$=0.0066 mg kg^{-1} bw day^{-1}; Dermal exposure 6%*

No calculations have been presented by the notifier on the operator exposure during spraying in greenhouse. The arguments are that the application in greenhouse is comparable to "high" crops in orchards. RMS doesn't agree with this argument since the greenhouses are closed rooms and the operator exposure could be higher than outside. However, the operator exposure during spraying automatically is consider as acceptable, the exposure during mixing/loading is low when gloves is used (12 % of AOEL) and since the operator doesn't need to be in the greenhouse during spraying and the exposure during spraying should be negligible. The operator exposure with hand-held sprayer is not acceptable even if maximum PPE is used (155 %). **In conclusion, the operator exposure to diflubenzuron in greenhouse using mushrooms grower is considered as acceptable using automatic sprayer with gloves during mixing and loading. Hand–held spraying is not acceptable-**

B.6.14.1.4 Summary of operator exposure

The proposed AOEL for diflubenzuron is 0.0066 mg kg^{-1} day^{-1} using 100 as safety factor and correlated with an oral absorption of 33%. Skin absorption value of 6 % for the concentrated product and the spray solution is used.

The operator exposure of diflubenzuron for pome fruit using tractor-mounted sprayer and hand-held sprayer was calculated using the German model and the UK POEM. The outcome exposure was below the systemic AOEL when maximum PPE was used according to the German model, but according to the UK POEM it was above AOEL and not acceptable. In forestry and greenhouse, the operator exposure during mixing/loading was also calculated using the German model. Furthermore, no appropriate calculations were presented by the notifier for the exposure during spraying in forestry and mushrooms. However, during the forest application the exposure was too high already in the mixing and loading step even when maximum PPE was used. Thus the forest application is not accepted. In greenhouse, the operator exposure during automatic spraying was considered as negligible and accepted if gloves were used during mixing and loading. During hand-held sprayer the operator exposure was considered as not acceptable, not even when all possible PPE was worn.

The overall exposure modelling assessments is presented in Table below:

Table B.6.14.1.4-1: Summary of the predicted operator exposure using Dimilin WG-80 in pome fruit, forestry and mushrooms

Field of use	Method of application	Dose (kg a.s./ha) Work rate (ha/day)	Exposure mg kg^{-1} day^{-1}	% AOEL[1]	PPE
Pome fruit	Tractor-mounted sprayer; spray directed upwards and sideways	0.18 8	0.0031[2] 0.0112[3]	**47 %** **>100 %**	yes[4] yes
	Hand-held sprayer; spray directed upwards and sideways	0.18 1	0.0063[3] 0.0064[2]	**95 %** **97 %**	yes yes
Forestry	Aerial application - ultra low volume (ULV) Aerial application - low volume (LV)	0.048 1000	Mix/loading: 0.014[2]	**>100 %**	yes
	Ground application Tractor-mounted sprayer Hand-held sprayer		0.00535[2] 0.00320[2]	**81 %** **49 %**	no no
Mushrooms	Automatic sprayer	10 1	Mix/loading: 0.00082[2] Spraying: negligible	**12 %**	yes
	Hand-held sprayer; high volume spray directed downwards		Mix/loading: 0.00082[2]	**12 %**	no
			Spraying: not calculated	**>100%**	yes[4]

[1]*AOEL= 0.0066 mg $kg^{-1}day^{-1}$;* [2]*German model;* [3]*UK POEM;* [4] *gloves and overall during spraying*

In conclusion, the operator exposure of diflubenzuron in pome fruit with tractor mounted and hand-held application is acceptable when PPE are used. The forest aerial application with aircraft or helicopters is not accepted but the ground application with tractor-mounted or hand-held sprayer is accepted without PPE. Fore mushroom grower the application with automatic sprayer is accepted when PPE is used. The hand-held sprayer is not accepted.

B.6.14.2 Bystander exposure

Bystanders are not expected to be present in mushroom houses during application. Bystanders will not be present in forests during application as specific precautions are taken to exclude the public from forests that are being sprayed.

Bystanders could be exposed to spray drift if they were walking next to an orchard being treated with Dimilin WG-80. However, the bystander can always be expected to be several metres away from the spray boom. At 10 m from the sprayer, estimates that for pome fruit the maximum drift estimate (90th percentile data, single application; late application for pome fruit) is 3.60%[4].

[4]*Rautmann, D., Streloke, M., Winkler, R. (2001) New basic drift values in the authorisation procedure for plant protection products. In: Workshop on risk assessment and risk mitigation measures in the context of the authorisation of plant protection products (WORMM; Forster, R., Streloke, M. Eds.), 27-29 September, 1999, Heft 383, Biologischen Bundesanstalt für Land - und Fortwirtschaft, Berlin and Braunschweig, Germany.*

Based on the maximum application rate for diflubenzuron to pome fruit of 0.18 kg/ha and assuming a bystander is located 10 m from the sprayer, they could receive 3.6% drift, i.e. 0.65 mg diflubenzuron/m^2. Assuming that 50% of a body surface, assumed to be 2 m^2 in total (US EPA[5]), is covered with clothing and that dermal exposure is reduced to 50 % with long shirt and trousers, direct deposition on the skin could be 0.975 mg diflubenzuron. Using 6 % skin absorption, the absorbed dose of diflubenzuron would be 0.0585 mg.

As a worst case scenario the inhalation value can be assumed to be the same as for the operator and can be taken from the German model, tractor-mounted sprayer which is 0.01152 mg/day.

Taken together the dermal and inhalation exposure is 0.07 mg and assuming a 60 kg body weight (as appropriate for adult men and women), the systemic exposure would be 0.001167 mg kg^{-1} day^{-1}.

Compared with the AOEL for diflubenzuron of 0.066 mg kg^{-1} day^{-1}, the potential exposure of bystanders is 18 % of systemic AOEL. Therefore, the bystander exposure during the use of Dimilin WG-80 is considered as acceptable.

B.6.14.3 Worker exposure

B.6.14.3.1 Estimation of worker exposure in orchards

Worker exposure to diflubenzuron during re-entering the application area in orchards has been estimated using the coefficients from EUROPOEM[6]. Table below shows the calculation of the potential dermal exposure:

Table B.6.14.3.1-1: Worker exposure of Dimilin 80WG in orchards

Dimilin 80WG in orchards

Worker exposure=	(AR/LAI)*TF*T) * DA/bw		
Application rate (AR)	180	g a.s./ha	(pome fruit)
Leaf area index (LAI)	1	µg/cm2	
Transfer Factor (TF)	4500	cm2/h	
Exposure duration (T)	8	h	
Dermal abs (DA):	6	%	
Body weight (bw)	60	kg	
Worker exposure of *Dimilin 80 WG* Pome fruit =		0.0648	mg kg-1 day-1
%AOEL (0.0066 mg $kg^{-1}day^{-1}$)		**982 %**	

[5] *Central estimate for adults. The EPA Exposure Factors Handbook (1997)*
[6] *EUROPOEM-the developmenta, maintenance and dissemination of generic european databases and predictive exposure models to plant protection products. Final report December 2002*

The systemic exposure for workers harvesting pome fruit or carrying out maintenance operations such as pruning without PPE is 0.0648 mg kg^{-1} day^{-1}, equivalent to 982 % of the AOEL of 0.0066 mg kg^{-1} day^{-1}. **If the workers wear gloves, the dermal absorption could be reduced to 0.6 % and give an exposure of 0.00648 mg kg^{-1} day^{-1}, equivalent to 98 % of the AOEL. In conclusion, the worker exposure of Dimilin WG-80 is acceptable in orchards for pome fruit under the conditions that PPE is used. This assumption assume that the trees only are sprayed once as the concentrations on the fruits and leafs other vice could be built up to a concentration that gloves can not reduce to an acceptable level.**

B.6.14.3.2 Estimation of worker exposure in forestry

Workers are not expected to handle treated trees and so exposure following use of Dimilin WG-80 in forests is not considered further.

B.6.14.3.3 Estimation of worker exposure in greenhouse using mushrooms grower

A study to measure the exposure of workers handling treated compost, which is relevant to harvesting mushrooms treated with Dimilin WG-80 is summarised below.

REFERENCE 01:	BELCHER,T. (1997). **GREENHOUSE WORKER REENTRY EXPOSURE TO ETRIDIAZOLE**
Formulation/a.s.	Terrazole 35%WP/ Etridiazole or Truban 5g Granular fungicide/4.58%etridiazole
Guideline/GLP:	OPPTS Harmonised Test Guideline Series 875 (875.2200, 875.1200 and 875.1400)/yes
Acceptability:	**Yes**
Test system:	The exposure of workers to etridiazole residues when handling soil media treated with 'Terrazole 35% Wettable Powder' (a WP formulation containing 33.39% etridiazole) or 'Truban 5G Granular Fungicide' (a G formulation containing 4.58% etridiazole) was measured under greenhouse conditions in California, USA. The results with 'Terrazole 35% Wettable Powder' are considered to be applicable to Dimilin WG-80 as a WP formulation type is similar to a WG, whereas a G formulation is designed to release active substance more slowly over time. The results with 'Truban 5G Granular Fungicide' are therefore not considered further. Soil media consisting of bark, peat moss and sand was treated evenly with 'Terrazole 35% Wettable Powder' at a nominal rate of 37.2 g a.s./m3. At 4 hours, 12 hours and 24 hours after application (re-entry times), four workers each filled 12 plastic pots (10 cm diameter) by scooping them into the treated soil media with their bare hands. They then brushed off excess soil media so that the media was level with the top of the pot, and placed the full pot in a pot holder. All workers were observed and actions such as brushing their faces with their hands noted. Dermal exposure was measured using whole body dosimeters (worn over workers underwear and under cotton trousers and shirt), facial and neck swabs of cotton gauze and hand washings. Inhalation exposure was measured using personal air sampling tubes clipped to the shirt collar and fitted to a personal sampling pump on the workers belt. Monitoring took place over approximately a 4-hour period at each interval. Samples of treated and untreated soil media were also collected and 'dislodged' 0, 4, 8, 12, 24, 48 and 72 hours after treatment for measurement of residue decline. Samples were analysed for etridiazole after extraction from the matrices using gas chromatography with electron capture detection. Field fortifications were made for all matrices.

Findings:

Etridiazole residues in the soil media declined from 14.4 µg/g immediately after application to 11.3 4 µg/g after 72 hours (Table B.6.14.3.3-1). The data were used to construct a decline curve using linear regression. The dislodgeable soil residues at 4, 12 and 24 hours were calculated from the regression line.

Table B.6.14.3.3-1: Dislodgeable residues of etridiazole in soil following application of 'Terrazole 35% WP'

Sampling interval (hours)	Dislodgeable etridiazole residues in soil media (µg/g)
0	14.3
4	14.6
8	9.83
12	9.57
24	9.05
48	10.8
72	11.3

Etridiazole residues were found in sections of the cotton whole body dosimeters and all inhalation tubes at all re-entry times. Residues in facial swabs were absent with the exception of one worker at the 12-hour re-entry time. Residues in hand washings were found in the 4-hour re-entry time but not in other samplings. The residues found were used to calculate total dermal and inhalation exposure. From these values, total exposure for an 8-hour working day and the total exposure rate were calculated. Transfer factors were calculated by dividing the exposure rate by the dislodgeable soil residues at each re-entry time. Transfer factors for the 4, 12 and 24-hour time intervals were 9.15, 5.45 and 8.62 g/hour, respectively (Table B.6.14.3.3-2). The worst case value for the transfer factor was 9.15 g/hour and was found after 4 hours. The mean transfer factor was 7.74 g/hour.

Table B.6.14.3.3-2: Measured exposure of etridiazole residues and calculated transfer factors from soil dislodgeable residues

Parameter	4 hours	12 hours	24 hours
Dermal exposure over 8 hours (µg)	249.6	143.3	177.9
Inhalation exposure over 8 hours (µg)	595.5	352.8	591.2
Dermal plus inhalation exposure over 8 hours (µg)	845.1	496.1	769.1
Total exposure rate (µg/hour)	105.6	62.0	96.1
Dislodgeable soil residues (µg/g)*	11.54	11.38	11.15
Transfer factor (g/hour)	9.15	5.45	8.62
Worst case/Mean transfer factor (g/hour)	9.15/7.74		
** Calculated from regression line from decline curve.*			

For workers handling soil media treated with etridiazole, a mean soil transfer factor of 7.74 g/hour from dislodgeable soil residues to human exposure was calculated.

Dimilin WG-80 is recommended for application to the casing media at 1 g diflubenzuron/m^2. The active substance is incorporated into the casing media by the high volume of water applied. Assuming the active substance is incorporated evenly to a depth of 15 cm, the concentration of diflubenzuron in the casing media would be 6.67 g a.s./m^3.

In the study with 'Terrazole 35% Wettable Powder', etridiazole was applied to soil media at 37.2 g a.s./m^3. Assuming that the density of the soil media in the study and the casing media used in mushroom growing in the EU are the same, the concentration of etridiazole was approximately 5.6 times the expected concentration of diflubenzuron. Dislodgeable residues of etridiazole in soil media 0 and 4 hours after application were 14.3 and 14.6 µg/g (mean 14.5 µg/g). The mean of the values at 0 and 4 hours can be used as surrogates for diflubenzuron. Residues of etridiazole at later samplings are not applicable as levels declined and this decline is likely to be specific to etridiazole. Thus, the application of 'Terrazole 35% Wettable Powder' at a rate of active substance 5.6 times higher than Dimilin WG-80 led to dislodgeable residues in soil media of 14.5 µg/g. Therefore, at the recommended rate of Dimilin WG-80, dislodgeable residues of diflubenzuron can be expected to be 2.6 µg/g a.s.

In the worker exposure study, workers scooped treated soil media into plastic pots and brushed off the excess with their hands. These tasks are considered to be a suitable surrogate for workers harvesting mushrooms by hand. Harvesting involves leaning over the mushroom beds to pick the ripe crop and this would involve contact with diflubenzuron treated casing media. In the study with etridiazole, a worst case soil transfer factor of 9.15 g/hour was calculated.

Therefore, the daily exposure to diflubenzuron for an 8-hour working day and a worker of body weight 60 kg is calculated as follows:

Exposure without PPE = 0.0026 mg/g x 9.15 g/hour x 8 hours/day ÷ 60 kg = 0.0032 mg kg^{-1} day^{-1}

The systemic exposure for workers harvesting mushrooms without PPE and without taking the dermal absorption into consideration was 48 % of the AOEL. The exposure of workers carrying out other tasks in mushroom houses is likely to be lower than during harvesting as contact with the casing media would be lower. Therefore, the risk to workers is considered to be acceptable and it is not necessary to set a re-entry period before workers can re-enter mushroom houses to harvest the crop or handle the treated casing media after applications of Dimilin WG-80, and it is not necessary for workers to wear personal protective equipment.

B.6.14.3.4 Summary of worker exposure

The worker exposure of Dimilin WG-80 in pome fruits, forestry and mushrooms are considered as acceptable under the conditions studied. PPE are needed for the workers using Dimilin WG-80 in the orchards.

Appendix 1

A. UK POEM: tractor-mounted, orchard without PPE using Dimilin WG-80

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM) WITH GERMAN MODEL MIX/LOAD DATA (75th PERCENTILE)

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha			
Product	**Dimilin WG80**	Active substance	**diflubenzuron**	
Formulation type	WG or SG	a.s. concentration	**800**	mg/g
Dermal absorption from product	**6** %	Dermal absorption from spray	**6**	%
PPE during mix/loading	None	PPE during application	None	
Dose	**0,225** kg product/ha	Work rate/day	**8**	ha
Application volume	**1500** l/ha	Duration of spraying	**6**	h
AOEL	**0,0066** mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	5,72	mg/kg a.s.
Hand contamination/day	8,2368	mg/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to a.s.	8,2368	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,242	mg/kg a.s.
Inhalation exposure/day	0,34848	mg/day
RPE	None	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,34848	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha			
Application volume	1500	spray/ha		
Volume of surface contamination	400	ml/h		
Distribution	Hands	Trunk	Legs	
	10%	65%	25%	
Clothing	None	Permeable	Permeable	
Penetration	100%	2%	5%	
Dermal exposure	10	5,2	5	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	121,2	ml/day		
Concentration of a.s. in spray solut	0,12	mg/ml		
Dermal exposure to a.s.	14,544	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure to spray	0,05	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0,12	mg/ml
Inhalation exposure to a.s.	0,036	mg/day
Percent absorbed	100	%
Absorbed dose	0,036	mg/day

ABSORBED DOSE

	Mix/load		Application		
Dermal exposure to a.s.	8,2368	mg/day		14,544	mg/day
Percent absorbed	6	%		6	%
Absorbed dose (dermal route)	0,494208	mg/day		0,87264	mg/day
Inhalation exposure to a.s.	0,34848	mg/day		0,036	mg/day
Absorbed dose	0,842688	mg/day		0,90864	mg/day

PREDICTED EXPOSURE

Total absorbed dose	1,751328	mg/day
Operator body weight	60	kg
Operator exposure	**0,0291888**	**mg/kg bw/day**
Operator exposure % of AOEL	**442,2545455**	**%**

B. UK POEM: tractor-mounted, orchard with PPE using Dimilin WG-80

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM) WITH GERMAN MODEL MIX/LOAD DATA (75th PERCENTILE)

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha			
Product	**Dimilin WG80**	Active substance	**diflubenzuron**	
Formulation type	WG or SG	a.s. concentration	**800**	mg/g
Dermal absorption from product	**6** %	Dermal absorption from spray	**6**	%
PPE during mix/loading	Gloves and RPE (FFP3)	PPE during application	Gloves	
Dose	**0,225** kg product/ha	Work rate/day	**8**	ha
Application volume	**1500** l/ha	Duration of spraying	**6**	h
AOEL	**0,0066** mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	5,72	mg/kg a.s.
Hand contamination/day	8,2368	mg/day
Protective clothing	Gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,082368	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,242	mg/kg a.s.
Inhalation exposure/day	0,34848	mg/day
RPE	RPE (FFP3)	
Transmission through RPE	5	%
Inhalation exposure to a.s.	0,017424	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha			
Application volume	1500	spray/ha		
Volume of surface contamination	400	ml/h		
Distribution	Hands	Trunk	Legs	
	10%	65%	25%	
Clothing	Gloves	Permeable	Permeable	
Penetration	10%	2%	5%	
Dermal exposure	4	5,2	5	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	85,2	ml/day		
Concentration of a.s. in spray solut	0,12	mg/ml		
Dermal exposure to a.s.	10,224	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure to spray	0,05	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0,12	mg/ml
Inhalation exposure to a.s.	0,036	mg/day
Percent absorbed	100	%
Absorbed dose	0,036	mg/day

ABSORBED DOSE

	Mix/load		Application		
Dermal exposure to a.s.	0,082368	mg/day		10,224	mg/day
Percent absorbed	6	%		6	%
Absorbed dose (dermal route)	0,00494208	mg/day		0,61344	mg/day
Inhalation exposure to a.s.	0,017424	mg/day		0,036	mg/day
Absorbed dose	0,02236608	mg/day		0,64944	mg/day

PREDICTED EXPOSURE

Total absorbed dose	0,67180608	mg/day
Operator body weight	60	kg
Operator exposure	**0,011196768**	**mg/kg bw/day**
Operator exposure % of AOEL	**169,648**	**%**

C. German model: tractor-mounted, orchard without PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**0,225** kg product/ha		Work rate/day		**8** ha
AOEL	**0,0066** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2	mg/kg a.s.
Hand contamination/day	2,88	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	2,88	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,008	mg/kg a.s.
Inhalation exposure/day	0,01152	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,01152	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Tractor-mounted/trailed broadcast air-assisted sprayer

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	1,2	0,7	9,6	
Dermal contamination/day	1,728	1,008	13,824	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	16,56	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,018	mg/kg a.s.
Inhalation exposure/day	0,02592	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,02592	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	2,88	mg/day	16,56	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,1728	mg/day	0,9936	mg/day
Inhalation exposure to a.s.	0,01152	mg/day	0,02592	mg/day
Total systemic exposure	0,18432	mg/day	1,01952	mg/day

PREDICTED EXPOSURE

Total systemic exposure	1,20384	mg/day
Operator body weight	60	kg
Operator exposure	**0,020064**	**mg/kg bw/day**
Operator exposure % of AOEL	**304**	**%**

D. German model: tractor-mounted, orchard with PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	Gloves				
PPE during application: Head	None	Hands	Gloves	Body	Coverall and sturdy footwear
Dose	**0,225** kg product/ha		Work rate/day		**8** ha
AOEL	**0,0066** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2	mg/kg a.s.
Hand contamination/day	2,88	mg/day
Protective clothing	gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,0288	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,008	mg/kg a.s.
Inhalation exposure/day	0,01152	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,01152	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Tractor-mounted/trailed broadcast air-assisted sprayer

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	1,2	0,7	9,6	
Dermal contamination/day	1,728	1,008	13,824	
Protective clothing	none	gloves	coverall and sturdy footwear	
Transmission to skin	100	1	5	%
Total dermal exposure to a.s.	2,42928	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,018	mg/kg a.s.
Inhalation exposure/day	0,02592	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,02592	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	0,0288	mg/day	2,42928	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,001728	mg/day	0,1457568	mg/day
Inhalation exposure to a.s.	0,01152	mg/day	0,02592	mg/day
Total systemic exposure	0,013248	mg/day	0,1716768	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0,1849248	mg/day
Operator body weight	60	kg
Operator exposure	**0,00308208**	**mg/kg bw/day**
Operator exposure % of AOEL	**47**	**%**

E. UK POEM: hand-held, orchard without PPE using Dimilin WG-80

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM) WITH GERMAN MODEL MIX/LOAD DATA (75th PERCENTILE)

Application method	Hand-held rotary atomiser equipment (2.5 l tank). Outdoor, high level target				
Product	**Dimilin WG80**		Active substance	**diflubenzuron**	
Formulation type	WG or SG		a.s. concentration	**800**	mg/g
Dermal absorption from product	**6**	%	Dermal absorption from spray	**6**	%
PPE during mix/loading	None		PPE during application	None	
Dose	**0,225**	kg product/ha	Work rate/day	**1**	ha
Application volume	**1500**	l/ha	Duration of spraying	**6**	h
AOEL	**0,0066**	mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	171,4	mg/kg a.s.
Hand contamination/day	30,852	mg/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to a.s.	30,852	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,0628	mg/kg a.s.
Inhalation exposure/day	0,011304	mg/day
RPE	None	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,011304	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Hand-held rotary atomiser equipment (2.5 l tank). Outdoor, high level target			
Application volume	1500	spray/ha		
Volume of surface contamination	50	ml/h		
Distribution	Hands	Trunk	Legs	
	10%	65%	25%	
Clothing	None	Permeable	Permeable	
Penetration	100%	15%	20%	
Dermal exposure	5	4,875	2,5	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	74,25	ml/day		
Concentration of a.s. in spray solut	0,12	mg/ml		
Dermal exposure to a.s.	8,91	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure to spray	0,01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0,12	mg/ml
Inhalation exposure to a.s.	0,0072	mg/day
Percent absorbed	100	%
Absorbed dose	0,0072	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	30,852	mg/day	8,91	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	1,85112	mg/day	0,5346	mg/day
Inhalation exposure to a.s.	0,011304	mg/day	0,0072	mg/day
Absorbed dose	1,862424	mg/day	0,5418	mg/day

PREDICTED EXPOSURE

Total absorbed dose	2,404224	mg/day
Operator body weight	60	kg
Operator exposure	**0,0400704**	**mg/kg bw/day**
Operator exposure % of AOEL	**607,1272727**	**%**

F. UK POEM: hand-held, orchard with PPE using Dimilin WG-80

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM) WITH GERMAN MODEL MIX/LOAD DATA (75th PERCENTILE)

Application method	Hand-held rotary atomiser equipment (2.5 l tank). Outdoor, high level target			
Product	**Dimilin WG80**	Active substance	**diflubenzuron**	
Formulation type	WG or SG	a.s. concentration	**800**	mg/g
Dermal absorption from product	**6** %	Dermal absorption from spray	**6**	%
PPE during mix/loading	Gloves	PPE during application	Gloves	
Dose	**0,225** kg product/ha	Work rate/day	**1**	ha
Application volume	**1500** l/ha	Duration of spraying	**6**	h
AOEL	**0,0066** mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	171,4	mg/kg a.s.
Hand contamination/day	30,852	mg/day
Protective clothing	Gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,30852	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,0628	mg/kg a.s.
Inhalation exposure/day	0,011304	mg/day
RPE	None	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,011304	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Hand-held rotary atomiser equipment (2.5 l tank). Outdoor, high level target			
Application volume	1500	spray/ha		
Volume of surface contamination	50	ml/h		
Distribution	Hands	Trunk	Legs	
	10%	65%	25%	
Clothing	Gloves	Permeable	Permeable	
Penetration	10%	15%	20%	
Dermal exposure	0,5	4,875	2,5	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	47,25	ml/day		
Concentration of a.s. in spray solut	0,12	mg/ml		
Dermal exposure to a.s.	5,67	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure to spray	0,01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0,12	mg/ml
Inhalation exposure to a.s.	0,0072	mg/day
Percent absorbed	100	%
Absorbed dose	0,0072	mg/day

ABSORBED DOSE

	Mix/load		Application		
Dermal exposure to a.s.	0,30852	mg/day		5,67	mg/day
Percent absorbed	6	%		6	%
Absorbed dose (dermal route)	0,0185112	mg/day		0,3402	mg/day
Inhalation exposure to a.s.	0,011304	mg/day		0,0072	mg/day
Absorbed dose	0,0298152	mg/day		0,3474	mg/day

PREDICTED EXPOSURE

Total absorbed dose	0,3772152	mg/day
Operator body weight	60	kg
Operator exposure	**0,00628692**	**mg/kg bw/day**
Operator exposure % of AOEL	**95,25636364**	**%**

G. UK POEM: hand-held, orchard with PPE using Dimilin WG-80

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM) WITH GERMAN MODEL MIX/LOAD DATA (75th PERCENTILE)

Application method	Hand-held rotary atomiser equipment (2.5 l tank). Outdoor, high level target			
Product	**Dimilin WG80**	Active substance	**diflubenzuron**	
Formulation type	WG or SG	a.s. concentration	**800**	mg/g
Dermal absorption from product	**6** %	Dermal absorption from spray	**6**	%
PPE during mix/loading	Gloves	PPE during application	Gloves and impermeable coveralls	
Dose	**0,225** kg product/ha	Work rate/day	**1**	ha
Application volume	**1500** l/ha	Duration of spraying	**6**	h
AOEL	**0,0066** mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	171,4	mg/kg a.s.
Hand contamination/day	30,852	mg/day
Protective clothing	Gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,30852	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,0628	mg/kg a.s.
Inhalation exposure/day	0,011304	mg/day
RPE	None	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,011304	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Hand-held rotary atomiser equipment (2.5 l tank). Outdoor, high level target			
Application volume	1500	spray/ha		
Volume of surface contamination	50	ml/h		
Distribution	Hands	Trunk	Legs	
	10%	65%	25%	
Clothing	Gloves	Impermeable	Impermeable	
Penetration	10%	5%	5%	
Dermal exposure	0,5	1,625	0,625	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	16,5	ml/day		
Concentration of a.s. in spray solut	0,12	mg/ml		
Dermal exposure to a.s.	1,98	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure to spray	0,01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0,12	mg/ml
Inhalation exposure to a.s.	0,0072	mg/day
Percent absorbed	100	%
Absorbed dose	0,0072	mg/day

ABSORBED DOSE

	Mix/load		Application		
Dermal exposure to a.s.	0,30852	mg/day		1,98	mg/day
Percent absorbed	6	%		6	%
Absorbed dose (dermal route)	0,0185112	mg/day		0,1188	mg/day
Inhalation exposure to a.s.	0,011304	mg/day		0,0072	mg/day
Absorbed dose	0,0298152	mg/day		0,126	mg/day

PREDICTED EXPOSURE

Total absorbed dose	0,1558152	mg/day
Operator body weight	60	kg
Operator exposure	**0,00259692**	**mg/kg bw/day**
Operator exposure % of AOEL	**39,34727273**	**%**

H. German model: hand-held, orchard without PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**0,225** kg product/ha		Work rate/day		**1** ha
AOEL	**0,0066** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	3,78	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	3,78	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,0036	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,0036	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	0,864	1,908	4,5	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	7,272	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,054	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,054	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	3,78	mg/day	7,272	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,2268	mg/day	0,43632	mg/day
Inhalation exposure to a.s.	0,0036	mg/day	0,054	mg/day
Total systemic exposure	0,2304	mg/day	0,49032	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0,72072	mg/day
Operator body weight	60	kg
Operator exposure	**0,012012**	**mg/kg bw/day**
Operator exposure % of AOEL	**182**	**%**

I. German model: hand-held, orchard with PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	Gloves				
PPE during application: Head	None	Hands	Gloves	Body	None
Dose	**0,225** kg product/ha		Work rate/day		**1** ha
AOEL	**0,0066** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	3,78	mg/day
Protective clothing	gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,0378	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,0036	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,0036	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	0,864	1,908	4,5	
Protective clothing	none	gloves	none	
Transmission to skin	100	1	100	%
Total dermal exposure to a.s.	5,38308	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,054	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,054	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	0,0378	mg/day	5,38308	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,002268	mg/day	0,3229848	mg/day
Inhalation exposure to a.s.	0,0036	mg/day	0,054	mg/day
Total systemic exposure	0,005868	mg/day	0,3769848	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0,3828528	mg/day
Operator body weight	60	kg
Operator exposure	**0,00638088**	**mg/kg bw/day**
Operator exposure % of AOEL	**97**	**%**

J. German model: hand-held, orchard with PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	Gloves				
PPE during application: Head	None	Hands	Gloves	Body	Coverall and sturdy footwear
Dose	**0,225** kg product/ha		Work rate/day		**1** ha
AOEL	**0,0066** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	3,78	mg/day
Protective clothing	gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,0378	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,0036	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,0036	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	0,864	1,908	4,5	
Protective clothing	none	gloves	coverall and sturdy footwear	
Transmission to skin	100	1	5	%
Total dermal exposure to a.s.	1,10808	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,054	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,054	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	0,0378	mg/day	1,10808	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,002268	mg/day	0,0664848	mg/day
Inhalation exposure to a.s.	0,0036	mg/day	0,054	mg/day
Total systemic exposure	0,005868	mg/day	0,1204848	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0,1263528	mg/day
Operator body weight	60	kg
Operator exposure	**0,00210588**	**mg/kg bw/day**
Operator exposure % of AOEL	**32**	**%**

K. German model: Estimated dermal and inhalation exposure during mixing/loading with aerial application in forestry using Dimilin WG-80 without PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**0,06** kg product/ha		Work rate/day		**1000** ha
AOEL	**0,0066** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	1008	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	1008	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,96	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,96	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	230,4	508,8	1200	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	1939,2	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	14,4	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	14,4	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	1008	mg/day	1939,2	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	60,48	mg/day	116,352	mg/day
Inhalation exposure to a.s.	0,96	mg/day	14,4	mg/day
Total systemic exposure	61,44	mg/day	130,752	mg/day

PREDICTED EXPOSURE

Total systemic exposure	192,192	mg/day
Operator body weight	60	kg
Operator exposure	**3,2032**	**mg/kg bw/day**
Operator exposure % of AOEL	**48533**	**%**

Operator exposure =1.024 mg/kg bw/day

L. German model: Estimated dermal and inhalation exposure during mixing/loading with aerial application in forestry using Dimilin WG-80 with PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target					
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**	
Formulation type	WG		a.s. concentration		**800**	g/kg
Dermal absorption from product	**6**	%	Dermal absorption from spray		**6**	%
RPE during mix/loading	A1P2		RPE during application		None	
PPE during mix/loading	Gloves					
PPE during application: Head	None	Hands	None	Body	None	
Dose	**0,06**	kg product/ha	Work rate/day		**1000**	ha
AOEL	**0,0066**	mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	1008	mg/day
Protective clothing	gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	10,08	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,96	mg/day
RPE	A1P2	
Transmission through RPE	2	%
Inhalation exposure to a.s.	0,0192	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	230,4	508,8	1200	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	1939,2	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	14,4	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	14,4	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	10,08	mg/day	1939,2	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,6048	mg/day	116,352	mg/day
Inhalation exposure to a.s.	0,0192	mg/day	14,4	mg/day
Total systemic exposure	0,624	mg/day	130,752	mg/day

PREDICTED EXPOSURE

Total systemic exposure	131,376	mg/day
Operator body weight	60	kg
Operator exposure	**2,1896**	**mg/kg bw/day**
Operator exposure % of AOEL	**33176**	**%**

Operator exposure =0.0104 mg/kg bw/day
% of AOEL = 157 %

M. German model: tractor-mounted, forestry, without PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/ trailed broadcast air-assisted sprayer				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**0,06** kg product/ha		Work rate/day		**8** ha
AOEL	**0,0066** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2	mg/kg a.s.
Hand contamination/day	0,768	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	0,768	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,008	mg/kg a.s.
Inhalation exposure/day	0,003072	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,003072	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Tractor-mounted/trailed broadcast air-assisted sprayer

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	1,2	0,7	9,6	
Dermal contamination/day	0,4608	0,2688	3,6864	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	4,416	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,018	mg/kg a.s.
Inhalation exposure/day	0,006912	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,006912	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	0,768	mg/day	4,416	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,04608	mg/day	0,26496	mg/day
Inhalation exposure to a.s.	0,003072	mg/day	0,006912	mg/day
Total systemic exposure	0,049152	mg/day	0,271872	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0,321024	mg/day
Operator body weight	60	kg
Operator exposure	**0,0053504**	**mg/kg bw/day**
Operator exposure % of AOEL	**81**	**%**

N. German model: hand-held, orchard without PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration	**800**	g/kg
Dermal absorption from product	**6**	%	Dermal absorption from spray	**6**	%
RPE during mix/loading	None		RPE during application	None	
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**0,06**	kg product/ha	Work rate/day	**1**	ha
AOEL	**0,0066**	mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	1,008	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	1,008	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,00096	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,00096	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	0,2304	0,5088	1,2	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	1,9392	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,0144	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,0144	mg/day

ABSORBED DOSE

	Mix/load		Application		
Dermal exposure to a.s.	1,008	mg/day	1,9392	mg/day	
Percent absorbed	6	%	6	%	
Absorbed dose (dermal route)	0,06048	mg/day	0,116352	mg/day	
Inhalation exposure to a.s.	0,00096	mg/day	0,0144	mg/day	
Total systemic exposure	0,06144	mg/day	0,130752	mg/day	

PREDICTED EXPOSURE

Total systemic exposure	0,192192	mg/day
Operator body weight	60	kg
Operator exposure	**0,0032032**	**mg/kg bw/day**
Operator exposure % of AOEL	**49**	**%**

O. German model: Estimated dermal and inhalation exposure during mixing/loading for mushroom grower in greenhouse using automatic spraying of Dimilin WG-80 without PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**12,5** kg product/ha		Work rate/day		**0,15** ha
AOEL	**0,0066** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	31,5	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	31,5	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,03	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,03	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	7,2	15,9	37,5	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	60,6	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,45	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,45	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	31,5	mg/day	60,6	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	1,89	mg/day	3,636	mg/day
Inhalation exposure to a.s.	0,03	mg/day	0,45	mg/day
Total systemic exposure	1,92	mg/day	4,086	mg/day

PREDICTED EXPOSURE

Total systemic exposure	6,006	mg/day
Operator body weight	60	kg
Operator exposure	**0,1001**	**mg/kg bw/day**
Operator exposure % of AOEL	**1517**	**%**

Operator exposure =0.032 mg/kg bw/day
% of AOEL = 484 %

P. German model: Estimated dermal and inhalation exposure during mixing/loading for mushroom grower in greenhouse using automatic spraying of Dimilin WG-80 with PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target					
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**	
Formulation type	WG		a.s. concentration		**800**	g/kg
Dermal absorption from product	**6**	%	Dermal absorption from spray		**6**	%
RPE during mix/loading	None		RPE during application		None	
PPE during mix/loading	Gloves					
PPE during application: Head	Hood and visor	Hands	Gloves	Body	Coverall and sturdy footwear	
Dose	**12,5**	kg product/ha	Work rate/day		**0,15**	ha
AOEL	**0,0066**	mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	31,5	mg/day
Protective clothing	gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,315	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,03	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,03	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target			
	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	7,2	15,9	37,5	
Protective clothing	hood and visor	gloves	coverall and sturdy footwear	
Transmission to skin	5	1	5	%
Total dermal exposure to a.s.	2,394	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,45	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,45	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	0,315	mg/day	2,394	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,0189	mg/day	0,14364	mg/day
Inhalation exposure to a.s.	0,03	mg/day	0,45	mg/day
Total systemic exposure	0,0489	mg/day	0,59364	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0,64254	mg/day
Operator body weight	60	kg
Operator exposure	**0,010709**	**mg/kg bw/day**
Operator exposure % of AOEL	**162**	**%**

Operator exposure =0.000815 mg/kg bw/day
% of AOEL = 12 %

Q. German model: Estimated dermal and inhalation exposure during mixing/loading for mushroom grower in greenhouse using Dimilin WG-80 and hand-held sprayer without PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**12,5** kg product/ha		Work rate/day		**0,15** ha
AOEL	**0,0066** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	31,5	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	31,5	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,03	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,03	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	7,2	15,9	37,5	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	60,6	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,45	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,45	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	31,5	mg/day	60,6	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	1,89	mg/day	3,636	mg/day
Inhalation exposure to a.s.	0,03	mg/day	0,45	mg/day
Total systemic exposure	1,92	mg/day	4,086	mg/day

PREDICTED EXPOSURE

Total systemic exposure	6,006	mg/day
Operator body weight	60	kg
Operator exposure	**0,1001**	**mg/kg bw/day**
Operator exposure % of AOEL	**1517**	**%**

R. German model: Estimated dermal and inhalation exposure during mixing/loading for mushroom grower in greenhouse using Dimilin WG-80 and hand-held sprayer with PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method		Hand-held sprayer: hydraulic nozzles. Outdoor, high level target					
Product		**Dimilin WG-80**			Active substance		**diflubenzuron**
Formulation type		WG			a.s. concentration		**800** g/kg
Dermal absorption from product		**6** %			Dermal absorption from spray		**6** %
RPE during mix/loading		A1P2			RPE during application		None
PPE during mix/loading		Gloves					
PPE during application:	Head	Hood and visor	Hands	Gloves		Body	Coverall and sturdy footwear
Dose		**12,5** kg product/ha			Work rate/day		**0,15** ha
AOEL		**0,0066** mg/kg bw/day					

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	31,5	mg/day
Protective clothing	gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,315	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,03	mg/day
RPE	A1P2	
Transmission through RPE	2	%
Inhalation exposure to a.s.	0,0006	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	7,2	15,9	37,5	
Protective clothing	hood and visor	gloves	coverall and sturdy footwear	
Transmission to skin	5	1	5	%
Total dermal exposure to a.s.	2,394	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,45	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,45	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	0,315	mg/day	2,394	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,0189	mg/day	0,14364	mg/day
Inhalation exposure to a.s.	0,0006	mg/day	0,45	mg/day
Total systemic exposure	0,0195	mg/day	0,59364	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0,61314	mg/day
Operator body weight	60	kg
Operator exposure	**0,010219**	**mg/kg bw/day**
Operator exposure % of AOEL	**155**	**%**

Addendum to
Draft Assessment Report

DIFLUBENZURON

Volume 3
Annex B.7
Residue data

Rapporteur Member State: Sweden

December 2008

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Volume 1

Level 1: Statement of subject matter and purpose for which the monograph was prepared

Level 2: Reasoned statement of the overall conclusions drawn by the Rapporteur Member State

Appendix 1: Standard terms and abbreviations

Appendix 2: Specific terms and abbreviations

Appendix 3: List of endpoints

Level 3: Proposed decision with respect to the application for inclusion of the active substance in Annex I

Level 4: Further information to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in Annex 1

Volume 2

Annex A: List of the tests and studies submitted and of information available

Volume 3

Annex B: RMS summary, evaluation and assessment of the data and information

Annex B.1: Identity

Annex B.2: Phys/chem.

Annex B.3: Data application and further information.

Annex B.4: Proposal for classification and labelling

Annex B.5: Analytical method

Annex B.6: Toxicology and metabolism

Annex B.7: Residues in crop

Annex B.8: Fate and behaviour

Annex B.9: Ecotoxicology

Volume 4

Annex C: Confidential information and summary and assessment of information relating to the collective submission of dossiers

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B.7 Residue data

B.7.6 Residues resulting from supervised residue trials (Annex IIA 6.3; Annex IIIA 8.2)

Reporting table point 3 (15)

RMS to report the US trials on mushrooms in an addendum for considering in expert meeting

Reference:	**Report 04:** Gaydosh K.A (1998) Dimilin 25W and Dimilin 4L in Mushrooms: Magnitude of the Residue Study. Report Uniroyal chemical Inc., USA NO RP-97004 DI - 11455
Test Material:	Mushroom
Guideline:	US EPA Pesticide Assessment Guidelines:
GLP:	Yes

Material and methods:

Test concentration:	The application rates for the casing treatment in this study were similar to the rate proposed within the E.U. (*i.e.* 4 g Dimilin WP-25/m^2 or 2 g Dimilin 4L/m^2, equivalent to 1 and 0.8 g a.s./m^2, respectively).
Test system:	Dimilin WP-25 and Dimilin 4L can be used to control larvae of sciarid flies in mushroom growing medium, preventing damage to the developing mushrooms. Either formulation may be applied to the compost, between filling and spawning, and/or to the casing in the U.S.A In this study, the magnitude of the residues of diflubenzuron and its possible metabolites, 4-chlorophenylurea and 4-chloroaniline, were determined in mushrooms after application of either Dimilin WP-25 (containing 25 % w/w diflubenzuron) or Dimilin 4L (containing 40.4 % w/w diflubenzuron) according to the U.S. maximum label rates for mushrooms. The plots were located at 2 commercial mushroom production facilities and the crops were grown and maintained under conditions typical of the cultural practice in a commercial facility.
Sampling time points:	The mushrooms were harvested according to commercial practice at 4 flushes (breaks) and the samples were shipped to the analytical testing facility for analysis.
Method of analysis:	Separate methods were used to analyse the mushrooms for each of the three analytes, diflubenzuron (DFB), 4-chlorophenylurea (CPU), and 4-chloroaniline (PCA). The methods for diflubenzuron and CPU used external standards, while the method for PCA used an internal standard.

The accuracy, reliability, and reproducibility of each method was demonstrated through acceptable recoveries of the fortified analytes during a method of verification conducted prior to sample analysis, and through procedural recoveries conducted concurrently with sample analysis. The limit of quantification (LOQ) were established at 0.01 ppm for Diflubenzuron and CPU, and 0.0050 ppm for PCA. The time from harvest to latest analysis was for Pennsylvania for DFB 37-39 days, CPU 29-39 days, and PCA 43-78 days. The time from harvest to latest analysis was for California for DFB 64-76 days, CPU 64-71 days, and PCA 57-146 days.

Date of experiment: 1997-1998

Table 6.3-6: Residues in mushrooms after casing treatment with Dimilin WP-25 or Dimilin 4L

Trial	Analyte	Residue mg/kg*			
Formulation		Dimilin WP-25		Dimilin 4L	
California	DFB	< 0.01 0.04 0.02 0.09	< 0.01 0.06 0.02 0.09	0.01 0.05 <0.01 0.05	0.02 0.04 <0.01 0.05
	CPU	< 0.01 < 0.01 0.01 0.01	< 0.01 < 0.01 < 0.01 < 0.01	< 0.01 < 0.01 < 0.01 < 0.01	< 0.01 < 0.01 < 0.01 < 0.01
	PCA	<0.0050 <0.0050 0.0051 0.0235	<0.0050 <0.0050 <0.0050 0.0148	<0.0050 <0.0050 0.0100 0.0154	<0.0050 <0.0050 0.0100 0.0154
Pennsylvania	DFB	0.07 0.06 0.04 <0.01	0.06 0.07 0.04 <0.01	0.14 0.05 0.03 0.02	0.14 0.05 0.03 0.02
	CPU	0.02 0.02 0.02 <0.01	0.02 0.03 0.02 <0.01	0.04 0.03 0.03 0.02	0.04 0.03 0.03 0.02

	PCA	<0.0050 <0.0050 0.0051 <0.0050	<0.0050 <0.0050 <0.0050 0.0059	<0.0050 <0.0050 <0.0050 0.0065	<0.0050 <0.0050 <0.0050 0.0100
**Figures represent duplicate values from 4 flushes (breaks)*					

Comment:
Residues for diflubenzuron (DFB) ranged from < 0.01 to 0.14 mg/kg, for 4-chlorophenylurea (CPU) from < 0.01 to 0.04 mg/kg and for 4-chloroaniline (PCA) from <0.0050 to 0.0235mg/kg. The levels of residues from DFB, CPU and PCA were higher than residues reported from European residue trials (DAR B.7.6).

The time from harvest to storage is adequate for DFB, and CPU as data show that these substances are stable for 18-19 months (DAR, Tables 6.2.2 and 6.2.3). However PCA is not stable during time from harvest to analysis in the experiment (DAR, table 6.2-3) after 30 days of storage 14% of PCA was recovered, and after 18 months 27% of PCA was recovered. Mushrooms analysed for PCA should best be analysed directly after harvest as the metabolite is degraded or binds to plant tissue under storage conditions. However, the result for PCA shows the concentration of available PCA residues in mushrooms with the available analytical method.

Corrigendum to the Draft Assessment Report of May 2005

DIFLUBENZURON

Volume 3
Annex B.7
Residue data

December 2008

KEMI
Kemikalieinspektionen

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Introduction

This corrigendum was prepared in response to the requirements of the Reporting table rev. 1-0 (20.12.2007);

B.7.2 Metabolism, distribution and expression of residues in livestock

Reporting table point 3 (2).
For the laying hen study, information should be given on the evolution of the residue levels in eggs, reflecting the accumulation capacity of diflubenzuron. RMS to consider a corrigendum.

B.7.2.1 Metabolism studies on laying hen

Reference: Report 01a	Gifford, L.J. Dunsire, J.P. (1994). The disposition of [^{14}C]-Diflubenzuron in the laying hen. Report Inveresk Research International, Scotland No. 56354/19/1993. D1-8935
Report 01b	Cnubben N., H., P., Bie, A.,T.,M., J. De, Ommen B.van (1996) Extraction, quantification, storage stability, metabolite profiling and metabolite identification of ^{14}C-Diflubenzuron and its metabolites in edible tissues of the laying hen. Report TNO Nutrition and Food Research institute, the Netherlands. V94.426. DI - 8935
Test Material:	**[^{14}C]-Diflubenzuron** uniformly labelled in both phenyl rings, batch number AO189K30A, purity 99,8%, AIS9247AA purity 99%, A0188K034A purity 97,5%. **[^{14}C]-4-chloroaniline PCA** (batch number CFQ5464, specific radioactivity 22.4 mCi/g), **[^{14}C]-4-chlorophenylurea CPU** (batch number AIS9112AAspecific radioactivity 11.0 mCi/g) and **[^{14}C]-4-chloroacetanilide PCAA** (batch number AIS9223AB), specific radioactivity 15.3 mCi/g) for the determination of recoveries.
Guideline:	US EPA-FIFRA guideline 171-4.
GLP:	Yes

Material and methods:

Test concentration:	1 mg/kg bw/day (11.15 mg/kg feed/day) and 10 mg/kg bw/day (101.26 mg/kg feed/day).
Test system:	Oral administration twice daily for 10 days. Doses were administrated as a suspension in 1% gum tragacanth. Group 1 (control group 1% gum tragacanth only) Group 2

	(1mg/kg/day), Group 3 (10 mg/kg/day).
Duration:	20 days
Sampling time points:	Eggs were collected when laid. Excreta were collected prior to each dose and at sacrifice. Skin, liver, kidney, muscle, bone marrow and fat were sampled at sacrifice.
Method of analysis:	Samples of each commodity were extracted and fractionated to determine the quantity and qualitative nature of residue. Radioactive residues were quantified with combustion analysis and liquid scintillation analysis. The qualitative analysis were performed with HPLC, LC-MS-MS and GC-MS.
Number of animals:	Group 1 three hens, group 2 six hens and group 3 three hens
Date of experiment:	October 1992 - March 1993

Group 2: low dose level: 1 mg/kg/day: Analysis of eggs indicated low levels of radioactivity associated with egg whites (table 6). Mean levels of radioactivity in egg whites plateau at 24 ng equiv.g^{-1} after the fifth dose (2.5 days) and thereafter only increased slightly until mean of 28 ng equiv.g^{-1} at post dose 19. Higher levels of radioactivity were detected in egg yolk (table 7). An increase from a mean of 1 ng equiv.g^{-1} post dose 1 to 769 ng equiv.g^{-1} post dose 15 (7.5 days) and thereafter a small increase until a mean of 819 ng equiv.g^{-1} post dose 19.

TABLE 6

Group 2 (Low Dose)

Level of Total Radioactivity in Egg White Following 20 Twice Daily Oral Administrations of [^{14}C]-diflubenzuron to Laying Hens Target Dose Level 1 mg.kg^{-1}.day^{-1}

Time Point (h)	13♀		14♀		15♀		**Mean ng equiv.g^{-1}**
	ng equiv.g^{-1}	% Dose	ng equiv.g^{-1}	% Dose	ng equiv.g^{-1}	% Dose	
Predose 1	2	0.00	1	0.00	1	0.00	
0-8	1	0.00	0**	0.00**	0*	0.00*	
8-24	NS	NS	NS	NS	NS	NS	
24-32	17	0.00	19	0.00	16	0.00	
32-48	NS	NS	NS	NS	NS	NS	
48-56	23	0.00	25	0.01	24	0.00	17.3
56-72	NS	NS	NS	NS	NS	NS	
72-80	26	0.00	33	0.01	24	0.00	24
80-96	NS	NS	NS	NS	NS	NS	
96-104	26	0.00	34	0.01	24	0.00	27
104-120	NS	NS	NS	NS	NS	NS	
120-128	28	0.00	32	0.01	24	0.00	28
128-144	NS	NS	NS	NS	NS	NS	
144-152	29	0.01	32	0.01	24	0.00	28
152-168	NS	NS	NS	NS	NS	NS	
168-176	30	0.01	31	0.01	24	0.00	
176-192	NS	NS	NS	NS	NS	NS	28
192-200	32	0.01	27	0.00	36	0.01	
200-216	NS	NS	NS	NS	NS	NS	28
216-224	27	0.00	32	0.01	24	0.00	
224-226	NS	NS	NS	NS	NS	NS	

* = Results based on data <30 d.p.m. above background
** = Results based on data <10 d.p.m. above background
NS = No sample

TABLE 7

Group 2 (Low Dose)

Levels of Total Radioactivity in Egg Yolk Following 20 Twice Daily Oral Administrations of [^{14}C]-diflubenzuron to Laying Hens Target Dose Level 1 mg.kg^{-1}.day^{-1}

Time Point (h)	13♀		14♀		15♀	
	ng equiv.g^{-1}	% Dose	ng equiv.g^{-1}	% Dose	ng equiv.g^{-1}	% Dose
Predose 1	0**	0.00**	1*	0.00*	0**	0.00**
0-8	1*	0.00*	2	0.00	0**	0.00**
8-24	NS	NS	NS	NS	NS	NS
24-32	33	0.00	41	0.00	41	0.00
32-48	NS	NS	NS	NS	NS	NS
48-56	124	0.01	145	0.01	169	0.01
56-72	NS	NS	NS	NS	NS	NS
72-80	228	0.02	262	0.02	254	0.02
80-96	NS	NS	NS	NS	NS	NS
96-104	331	0.03	440	0.03	357	0.03
104-120	NS	NS	NS	NS	NS	NS
120-128	444	0.04	608	0.05	481	0.04
128-144	NS	NS	NS	NS	NS	NS
144-152	542	0.05	666	0.06	571	0.05
152-168	NS	NS	NS	NS	NS	NS
168-176	683	0.06	854	0.07	670	0.06
176-192	NS	NS	NS	NS	NS	NS
192-200	940	0.08	746	0.06	662	0.06
200-216	NS	NS	NS	NS	NS	NS
216-224	773	0.07	967	0.08	697	0.06
224-226	NS	NS	NS	NS	NS	NS

* = Results based on data <30 d.p.m. above background
** = Results based on data <10 d.p.m. above background
NS = No sample

TABLE 7 (continued)

Time Point (h)	16♀		17♀		18♀		Mean	
	ng equiv.g^{-1}	% Dose	ng equiv.g^{-1}	% Dose	ng equiv.g^{-1}	% Dose	ng equiv.g	% Dose
Predose 1	1*	0.00*	0**	0.00**	0**	0.00**	0	0.00
0-8	0**	0.00**	1*	0.00**	1*	0.00*	1	0.00
8-24	NS	NS	NS	NS	NS	NS	NS	NS
24-32	40	0.00	41	0.00	41	0.00	40	0.00
32-48	NS	NS	NS	NS	NS	NS	NS	NS
48-56	141	0.01	156	0.01	135	0.01	145	0.01
56-72	NS	NS	NS	NS	NS	NS	NS	NS
72-80	254	0.02	299	0.02	261	0.02	260	0.02
80-96	NS	NS	NS	NS	NS	NS	NS	NS
96-104	387	0.03	462	0.04	390	0.03	394	0.03
104-120	NS	NS	NS	NS	NS	NS	NS	NS
120-128	545	0.04	596	0.05	505	0.04	530	0.04
128-144	NS	NS	NS	NS	NS	NS	NS	NS
144-152	697	0.06	770	0.06	635	0.05	647	0.06
152-168	NS	NS	NS	NS	NS	NS	NS	NS
168-176	819	0.07	861	0.07	724	0.06	769	0.07
176-192	NS	NS	NS	NS	NS	NS	NS	NS
192-200	864	0.07	832	0.07	747	0.07	799	0.07
200-216	NS	NS	NS	NS	NS	NS	NS	NS
216-224	845	0.07	849	0.07	782	0.07	819	0.07
224-226	NS	NS	NS	NS	NS	NS	NS	NS

* = Results based on data <30 d.p.m. above background
** = Results based on data <10 d.p.m. above background
NS = No sample

Group 3: high dose level: 10 mg/kg.day: Analysis of eggs indicated low levels of radioactivity associated with egg whites (table 13). Mean levels of radioactivity reached a plateau of 0.2 µg equiv. g^{-1} following administration of the fifth dose (2.5 days). Higher levels of radioactivity were detected in egg yolks (table 14). An increase from a mean of 0.3 µg equiv. g^{-1} post dose 3 to 7.3 µg equiv. g^{-1} post dose 15 (7.5 days) was observed, thereafter the levels remained constant. Thus, a plateau was reached at dose 15 (7, 5 days) which also was observed in the low dose administration (table 7). 8

TABLE 13

Group 3 (High Dose)

Levels of Total Radioactivity in Egg White Following 20 Twice Daily Oral Administrations of [^{14}C]-diflubenzuron to Laying Hens
Target Dose Level 10 mg.kg^{-1}.day^{-1}

Time (h)	Animal Number						Mean	
	10♀		11♀		12♀			
	µg equiv.g^{-1}	Total % Dose	µg equiv.g^{-1}	Total % Dose	µg equiv.g^{-1}	Total % Dose	µg equiv.g^{-1}	Total % Dose
Predose 1	0.0**	0.00**	0.0**	0.00**	0.0**	0.00**	0.0	0.00
0-8	0.0**	0.00**	0.0*	0.00*	0.0**	0.00**	0.0	0.00
8-24	0.1	0.00	NS	NS	NS	NS	0.1	0.00
24-32	NS	NS	0.1	0.00	0.1	0.00	0.1	0.00
32-48	NS	NS	NS	NS	NS	NS	NS	NS
48-56	0.2	0.00	0.3	0.00	NS	NS	0.2	0.00
56-72	NS	NS	NS	NS	NSϕ	NSϕ	NS	NS
72-80	0.2	0.00	0.3	0.00	NS	NS	0.2	0.00
80-96	NS	NS	NS	NS	NS	NS	NS	NS
96-104	0.2	0.00	0.2	0.00	0.3	0.01	0.2	0.00
104-120	NS	NS	NS	NS	NS	NS	NS	NS
120-128	0.2	0.00	0.2	0.00	0.3	0.01	0.2	0.00
128-144	NS	NS	NS	NS	NS	NS	NS	NS
144-152	0.1	0.00	0.2	0.00	0.3	0.01	0.2	0.00
152-168	NS	NS	NS	NS	NS	NS	NS	NS
168-176	0.2	0.00	0.2	0.00	0.2	0.01	0.2	0.00
176-192	NS	NS	NS	NS	NS	NS	NS	NS
192-200	0.2	0.00	0.2	0.00	0.2	0.01	0.2	0.00
200-216	NS	NS	NS	NS	NS	NS	NS	NS
216-224	0.2	0.00	0.2	0.00	0.2	0.01	0.2	0.00
224-226	NS	NS	NS	NS	NS	NS	NS	NS

* = Results based on data <30 d.p.m. above background
** = Results based on data <10 d.p.m. above background
ϕ = Egg laid at this time was broken, therefore analysed with excreta
NS = No sample

TABLE 14

Group 3 (High Dose)

Levels of Total Radioactivity in Egg Yolk Following 20 Twice Daily Oral Administrations of [^{14}C]-diflubenzuron to Laying Hens Target Dose Level 10 mg.kg^{-1}.day^{-1}

Time (h)	Animal Number						Mean	
	10♀		11♀		12♀			
	µg equiv.g^{-1}	Total % Dose	µg equiv.g^{-1}	Total % Dose	µg equiv.g^{-1}	Total % Dose	µg equiv.g^{-1}	Total % Dose
Predose 1	0.0**	0.00**	0.0*	0.00*	0.0**	0.00**	0.0	0.00
0-8	0.0*	0.00*	0.0*	0.00*	0.0*	0.00*	0.0	0.00
8-24	0.2	0.00	NS	NS	NS	NS	0.2	0.00
24-32	NS	NS	0.3	0.00	0.3	0.00	0.3	0.00
32-48	NS	NS	NS	NS	NS	NS	NS	NS
48-56	0.7	0.01	1.5	0.01	NS	NS	1.1	0.01
56-72	NS	NS	NS	NS	NSϕ	NSϕ	NS	NS
72-80	1.7	0.01	3.1	0.03	NS	NS	2.4	0.02
80-96	NS	NS	NS	NS	NS	NS	NS	NS
96-104	2.7	0.03	4.8	0.04	4.8	0.04	4.1	0.04
104-120	NS	NS	NS	NS	NS	NS	NS	NS
120-128	3.9	0.04	6.2	0.05	6.9	0.05	5.7	0.05
128-144	NS	NS	NS	NS	NS	NS	NS	NS
144-152	4.9	0.05	7.3	0.06	7.2	0.06	6.5	0.06
152-168	NS	NS	NS	NS	NS	NS	NS	NS
168-176	5.6	0.05	7.9	0.06	8.5	0.07	7.3	0.06
176-192	NS	NS	NS	NS	NS	NS	NS	NS
192-200	5.9	0.05	8.2	0.06	8.3	0.07	7.5	0.06
200-216	NS	NS	NS	NS	NS	NS	NS	NS
216-224	5.9	0.05	7.8	0.06	8.2	0.06	7.3	0.06
224-226	NS	NS	NS	NS	NS	NS	NS	NS

* = Results based on data <30 d.p.m. above background
** = Results based on data <10 d.p.m. above background
ϕ = Egg laid at this time was broken, therefore analysed with excreta
NS = No sample

Comment: The study shows an accumulation of radioactive residues in egg yolks. Levels reached a plateau after the fifteenth dose following 20 twice daily oral administrations of [^{14}C]-Diflubenzuron at 1 mg/kg bw/day (table 7) and 10 mg/kg bw/day (table 14). 769 ng equiv.g^{-1} $_{and}$ 7.3 µg equiv. g^{-1} respectively.

Reporting table point 3 (5) and 3(6).

It is not stated whether results in table reflect the 1mg/kg bw/d or 10 mg/kg bw/d dose. RMS to consider a corrigendum.

The target doses for the study were 1 and 10 mg/kg bw/day. As there was insufficient radioactive material, the high doses were reduced from about 10 mg/kg bw (doses 1-5) to about 9 mg/kg bw (doses 6-11) to about 8 mg/kg bw (doses 12-20). Since the levels in the tissues will be mainly determined by the doses at the end of the treatment period, the high dose is taken to be 8 mg/kg bw/day.

Table B.7.2.1-5. Amounts of parent compound and metabolites in tissue sample from Laying hen taken 2 hours after the last oral dose of diflbenzuron HPLC system 2*

Sample	Dose level mg/kg bw/day	^{14}C, diflubenzuron equvivalents mg/kg and (% of total radioactivity in sample)				Sum of residues as % of total ^{14}C in sample	Total residues, mg/kg diflubenzuron equivalents
		CPU	PCAA	PCA	diflubenzuron		
Liver	1 8	0.12 (20) 0.79 (22)	0.015 (2.6) nd	0.018 (3.1) 0.048 (1.3)	0.20 (34) 1.8 (49)	59 72	0.67 4.0
Kidney	1 8	0.089 (23) 0.5 (28)	nd nd	0.014 (3.6) nd	0.048 (12) 0.40 (22)	38 50	0.44 2.0
Muscle	1 8	0.020 (14) 0.14 (15)	nd nd	nd nd	0.10 (71) 0.72 (76)	85 91	0.15 1.0
Fat	1 8	0.008 (0.8) 0.051 (0.6)	0.005 (0.5) 0.026 (0.3)	nd nd	0.99 (98) 7.9 (99)	99 100	1.0 8.1
Skin	1 8	0.016 (3.8) 0.082 (2.6)	nd nd	nd nd	0.38 (90) 3.0 (94)	94 96	0.42 3.3
Egg-yolk (post-dose)	1 8	nd 0.56 (11)	nd nd	nd nd	0.26 (75) 4.2 (80)	75 91	0.81 5.6
Egg white (post-dose)	1 8	nd nd	0.007 (37) nd	nd nd	0.001 (5.3) nd	42 nd	0.024 0.29

nd = not detected.
*= The figures have been calculated with the aid of JMPRs evaluation of diflubenzuron from 2002

Reporting table point 3 (7).

Storage stability data in the tables should not only be given in mg/kg but also in percentage of the starting value. RMS to consider a corrigendum.

Table: B.7.2.1-7: Storage stability of egg yolk, spiked control homogenate from Laying hen

Identity	Spike µg/g*	Amount in fraction (in mg/kg) after storage					
		10 months -195°C		12 months - 80°C		10 months - 20°C	
CPU	0.040	0.034	85%	0.032	80%	0.032	80%
PCAA	0.040	0.036	90%	0.034	85%	0.034	85%
PCA	0.020	0.017	85%	0.018	106%	0.018	106%
diflubenzuron	0.040	0.036	90%	0.033	92%	0.033	92%

* The amounts are expressed as µg/g of tissue instead of µg/g of homogenate

Table: B.7.2.1-8: Storage stability of liver, spiked control homogenate from Laying hen

Identity	Spike µg/g*	Amount in fraction (in mg/kg) after storage					
		10 months -195°C		12 months - 80°C		15 months - 20°C	
CPU	0.040	0.037	93%	0.033	83%	0.053	133%
PCAA	0.040	0.057	143%	0.032	80%	0.023	58%
PCA	0.020	0.007	35%	0.016	80%	0.005	25%
diflubenzuron	0.040	0.039	98%	0.032	80%	0.032	80%

* The amounts are expressed as µg/g of tissue instead of µg/g of homogenate.

Table: B.7.2.1-9: Storage stability of muscle, spiked homogenate

Identity	Spike µg/g*	Amount in fraction (in mg/kg) after storage					
		10 months -195°C		12 months - 80°C		15 months - 20°C	
CPU	0.040	0.036	90%	0.036	90%	0.031	86%
PCAA	0.040	0.068	170%	0.067	168%	0.048	120%
PCA	0.020	<LLO**	0%	<LLO**	0%	0.005	25%
diflubenzuron	0.040	0.035	88%	0.037	93%	0.036	90%

* The amounts are expressed as µg/g of tissue instead of µg/g of homogenate.
** <LLOQ means below lower limit of quantification.

Comment: The storage stability of the three tissues (muscle, liver and egg yolk) was studied at different storage conditions varying in temperature as well as time. For the spiked egg yolk, the metabolite profile remains similar at the different storage conditions, with high recovery for all metabolites including 4-chloroaniline (PCA). In the spiked liver and muscle the recover of 4-chlorophenylurea (CPU) and 4-chloroacetanilide (PCAA) were sometime above theoretical maximum while 4-chloroaniline. PCA however, was only recovered from 0-25% at all storage conditions.

B.7.3 Residue definitions in plants and animals

Reporting table point 3 (11).

***Open point**: RMS should provide an evaluation of the existing data from available reports and publication on metabolites of diflubenzuron (CPU, DFBA and PCA) and suggest which end-points could be used to characterise their toxicological properties (same end points as diflubenzuron or other end points). On the basis of that evaluation, the residue definition for risk assessment should be re-examined in particular for mushrooms MS to discuss residue definition for plants commodities in an expert meeting.*

Residue definition for plants commodities will be discussed in an expert meeting, see Evaluation table

Reporting table point 3 (12).

Open point*: For ruminants it is difficult to conclude on a residue definition as residues were identified only in milk and liver. Meat and fat were not investigated although the metabolism in hens demonstrated a lipophilic behaviour of diflubenzuron. A new metabolism study should be requested unless clear evidence can be supported that the exposure of ruminants leads to a no-residue situation in ruminant tissues or unless based on expert judgment it could be considered that the residue definition proposed by the RMS, including parent and CPU is safe for the consumer. MS to discuss residue definition for animals commodities in an expert meeting.*

Residue definition for plants commodities will be discussed in an expert meeting, see Evaluation table

Reporting table point 3 (17).

Data requirement

Notifier to submit further residue data in mushrooms taking into account the storage stability of compounds to be determined.

RMS has asked Notifier to submit further residue trials 080122.

No new studies have been submitted, see Evaluation table data gap:

Reporting table point 3 (21 and 22).

Table B.7.5.1 Identification of critical GAPs. The rate per treatment for the application in mushrooms must be 1 g as /m2 (the value 0.25 is incorrect). The spray volume in forestry for ULV should be 3-5 "water + oil" in stead of "oil" (the oil is added to the water to prevent evaporation). RMS to consider a corrigendum.

Table B.7.5-1. Critical EU-GAP information for diflubenzuron in Europe

Crop	Country	Formulation	Application						PHI (days)
		type (code) & content of a.i. (g/kg)	Method	Kg as/ha/ treatment	Rate kg as/ha	Spray conc., kg as/hl	Number maxi	BBCH stages	

Apples and Pears	Northern and Southern Europe	Dimilin WG-80 F	Spray, Directed air-assisted spray equipment	0.18	0.15-0.18	0.01 - 0.12	2 14-28 days intervals between	Spring or autumn application dependant on the pest to be controlled	14
Mushrooms	Northern and Southern Europe	Dimilin WG-80 I	Spray boom/ lance		1 g as/m^2	N.A	1	Course spray, immediate after casing	na
Forestry	Northern and Southern Europe	Dimilin WG-80 F	Spray, ariel and ground application including ULV	0.048	0.8	3-5 water + oil	1	Dependant on the pest to be controlled	na

na= Not applicable

B.7.7 Effects of industrial processing and/or household preparation (Annex IIA 6.5; Annex IIIA 8.4)

Reporting table point 3 (27).

For mushrooms, apparently one processing study for canned mushrooms is available (study AF/6263/UR/1). In the list of end points it is mentioned that 5 studies are available, this should be corrected. RMS to consider a corrigendum.

Four residue trials were conducted on mushrooms during 2002, two in UK (AF/6263/UR1 and 2) and two in the Netherlands (AF/6263/UR 3 and 4). All these trials are reported as residue trials in DAR table B. 7.6-3. At trial AF/ 6263/UR/1 specimens were also taken for processing into canned mushrooms. This study is reported below.

B.7.7.2 Effects of processing on the nature of residue in mushrooms

Reference: Gilles, N. (2004)
To determine the magnitude of diflubenzuron residues at harvest in the raw agricultural commodity mushrooms and processed fractions resulting from a single application of Dimilin SC-48 or Dimilin WG-80 in the UK and The Netherlands
Interim Report Agrisearch Uk Ltd, England No.AF/6263/UR
DI – 11748 (Final report was submitted after the dossier was delivered).

Test Material: Mushrooms from residue trials. The trials have been reported in DAR B.7.6

Guideline: 7029/VI/95 rev.5 and the guideline; Processing Phase Plane for Processing mushroom into canned mushrooms, established by CCRA Technology Limited.

GLP: Yes

Material and methods:

Test concentration:	At trial AF/6263/UR/1 a single application of DIMILIN SC-48 (480g/L diflubenzuron) - treatment 2 or DIMILIN WG-80 (80%w/w diflubenzuron) - treatment 3 was applied at 0.96grams a.s./m^2, diluted with water immediately prior to application to a spray volume similar to commercial practice.
Test system:	At trial AF/6263/UR/1 specimens were also taken for processing into canned mushrooms. Preparation of canned mushrooms: Sorting to remove foreign material or damaged mushroom; Washing to remove gross debris; Cutting to reduce size of largest mushrooms; Blanching to remove air from mushrooms; Draining and rapid cooling to maintain product texture; Filling into cans; Brine preparation for addition to the cans; Brining- the brine solution was poured into the mushroom filled cans; Seaming to produce a hermetic seal on the cans; Heat processing to produce a commercially sterile product; Cooling to reduce the product temperature and minimize the risk of post process contamination; Drying before handling to reduce the risk of post process contamination. The canned mushrooms were in-container heat processed using a steam retort. The retort was set to a temperature of 121.1 ºC and the cans were processed at this temperature for 31 minutes. The cans were partially cooled in the processing vessel and then transferred to a chlorinated bath to further reduce the intaernal can temperature. The cans were allowed to dry before being transferred to a frozen storage area operating at below –16 ºC on the next working day after processing.
Sampling time points:	Specimens for processing were taken only at the first flush after application. Sampling date was Feb 02 and extraction date was Dec 03.
Method of analysis:	Crop specimens were analysed for residues of diflubenzuron using Agrisearch Method 'Diflubenzuron/Rice/KLS/03/1'. The method involves extraction in dichloromethane followed by purification on a Florisil chromatography column. Any diflubenzuron present is hydrolysed to form 4-chloroaniline, which is subsequently derivatised with heptafluorobutyric anhydride and the derivative quantified by gas chromatography with mass selective detection (MSD). Limit of determination for Diflubenzuron, 4-chlorophenylurea in mushrooms were 0.01 mg/kg. Limit of determination for 4-chloroaniline was 0.005 mg/kg.
Date of experiment:	2002

Findings: Procedural recoveries run concurrently with test specimens at levels of 0.01 mg/kg, and 0.1 mg/kg gave an overall mean recovery of 95 % for whole mushrooms and 78 % for canned mushrooms.

The residue levels of diflubenzuron found in whole mushrooms are summarised below in table B.7.7.2-1.

Table B.7.7.2-1 Magnitude of diflubenzuron residues in whole mushrooms

Trial no.	No. and rate of application (g a.s./m^2)	Timing	Interval after final application	Crop portion	DFB (mg/kg)	PCA (mg/kg)	CPU (mg/kg)
AF/6263/UR/1	1x 0.96 [1,2]	S1	19	Whole mushroom	0.01	< 0.01	0.01
	1x 0.96 [2]	S1	19	Whole mushroom	0.02	< 0.01	< 0.01
	1x 0.96 [3]	S2	31	Whole mushroom	0.01	< 0.01	< 0.01
	1x 0.96 [3]	S2	31	Whole mushroom	0.01	< 0.01	< 0.01
	1x 0.96 [3]	S3	41	Whole mushroom	< 0.01	< 0.01	< 0.01
	1x 0.96 [3]	S3	41	Whole mushroom	0.02	< 0.01	0.01

1. Whole mushroom used for canning
2. Dimilin SC-48
3. Dimilin WG-80

The residue levels of diflubenzuron found in canned mushrooms are summarised in table B.7.7.2-2.

Table B.7.7.2-2 Magnitude of diflubenzuron residues in canned mushrooms

Trial no.	No. and rate ofapplication (g a.s./m^2	Timing	Interval after final application	Crop portion	DFB (mg/kg)	PCA (mg/kg)	CPU (mg/kg)
AF/6263/UR/1	1x 0.96	S3	19	Canned mushroom	< 0.01	< 0.01	< 0.01

Comment: Results from one study of residues in canned mushroom shows no detectable parent diflubenzuron or its metabolites were found after canning.

Reporting table point 3 (28).

Table B.7.7.1.1 (processing of apple). It is recommended to include an extra column in the table for the processing factor of each processing measurement. RMS to consider in a corrigendum.

Table B.7.7.1-1 Magnitude of diflubenzuron residues in processed apple samples

Trial number	Matrix	g a.s./ha	Timing	Interval (days)	Residues mg/kg	Transfer factors
AF/6843/UR/1	Whole apple	4 x 150	S1	14	0.22	
	Washed apple	4 x 150	S1	14	0.22	1
	Washing water	4 x 150	S1	14	0.08	0.36
	Wet pomace	4 x 150	S1	14	0.82	3.7
	Raw juice	4 x 150	S1	14	< 0.05	0.23
	Apple juice	4 x 150	S1	14	< 0.05	0.23
	Blanching water	4 x 150	S1	14	< 0.05	0.23
	Seeds + peels	4 x 150	S1	14	0.65	2.95
	Puree	4 x 150	S1	14	< 0.05	0.23
AF/6843/UR/2	Whole apple	4 x 150	S1	14	0.41	
	Washed apple	4 x 150	S1	14	0.20	0.48
	Washing water	4 x 150	S1	14	0.07	0.17
	Wet pomace	4 x 150	S1	14	0.79	1.9

Trial number	Matrix	g a.s./ha	Timing	Interval (days)	Residues mg/kg	Transfer factors
	Raw juice	4 x 150	S1	14	< 0.05	0.12
	Apple juice	4 x 150	S1	14	< 0.05	0.12
	Blanching water	4 x 150	S1	14	< 0.05	0.12
	Seeds +peels	4 x 150	S1	14	0.62	1.5
	Puree	4 x 150	S1	14	0.05	0.12
AF/6843/UR/3	Whole apple	4 x 150	S1	14	0.26	
	Washed apple	4 x 150	S1	14	0.14	0.54
	Washing water	4 x 150	S1	14	0.05	0.19
	Wet pomace	4 x 150	S1	14	0.99	3.8
	Raw juice	4 x 150	S1	14	< 0.05	0.19
	Apple juice	4 x 150	S1	14	< 0.05	0.19
	Blanching water	4 x 150	S1	14	< 0.05	0.19
	Seeds + peels	4 x 150	S1	14	0.89	3.4
	Puree	4 x 150	S1	14	< 0.05	0.19

Comment: There is a concentration of residues in wet apple pomace. The concentration factors recorded in the different trials are between 1.9-3.8. In JMPRs evaluation of diflubenzuron from 2002 the concentration factor of residues in apple pomace was 5 in wet apple pomace and 13 in dry apple pomace.

B.7.8 Livestock feeding studies (Annex IIA 6.4; Annex IIIA 8.3)

Reporting table point 3 (29).

The argumentation provided by the RMS for not requiring feeding studies should be reconsidered. The calculation of the expected exposure of livestock (expressed as mg/kg diet) is not found in the DAR. A calculation was provided under point 7.2 (animal metabolism) but contains inadequacies (the transfer factor from fresh fruits to pomace was not considered and the STMR should have been used instead of the MRL as highest residue likely to occur. MS to discuss the need for a feeding study in lactating cows in an expert meeting

Residue definition for plants commodities will be discussed in an expert meeting, see Evaluation table

B.7.12 MRL calculations

Reporting table point 3 (33)

For the data set of Northern Europe, XX calculated different values of R max = 0.77 mg/kg and a Rber (2x0.75) = 0.98 mg/kg. However, it is rounded to the same MRL value of 1.0 mg/kg

According to guideline 7039/VI/95 EN 22/7/1997 the maximum residue levels of classes are; 0.01, 0.02, 0.05, 0.1, 0.2, 0.3, 0.5 1.0, 2.0, 3.0 etc. Thus, there is no class in between 0.5 and 1.0. Both Rmax and Rber is closer to 1.0 than to 0.5 and therefore 1.0 mg/kg was chosen as MRL value.

B.7.15 Intake calculations

Reporting table point 3 (31)

As far as the intake calculations for British sub-populations are concerned, the practice is to consider that only 2 commodities (those resulting in the highest intakes) can be together consumed at the 97.5th percentile of the consumption. For the other commodities, the mean consumption value should be taken

The TMDIs were calculated according to the PSD Guidance on the estimation of dietary intakes of pesticides residues, Part Three/A3/Appendix 1c (1999). Results of the calculations are shown in Tables B. 7.15-3 – 7.15-12.

Table B.7.15-3 Theoretical Maximum Daily Intake (TMDI) according to UK consumer exposure model –adults – 76.0 kg bw

Commodity	European intake (kg/person/day)	STMR (mg/kg)	Exposure (mg/person/day)
Apples *high exp.*	0.1064	0.5	0.0532
Pears *high exp.*	0.2038	0.5	0.1019
Strawberry *mean exp.*	0.0454	0.1	0.00454
Raspberry *mean exp.*	0.0544	0.1	0.00544
Blackberry *mean exp.*	L/C	0.1	-
Mushrooms *mean exp.*	0.0289	0.3*	0.00867

*Codex MRL

Total exposure (mg/person/day)	0.17375
Total exposure (mg/kg bw/day) (TMDI)	0.00228
Proposed ADI (mg/kg bw/day)	0.02
Total dietary exposure (% of ADI)	**11.4**

LC = Low % consumers (Less than 60 consumers in survey).

Table B.7.15-4 Theoretical Maximum Daily Intake (TMDI) according to UK consumer exposure model – infant 8.7 kg bw kg bw

Commodity	European intake (high exposure) (kg/child/day)	STMR (mg/kg)	Exposure (mg/child/day)
Apples *high exp.*	0,0733	0.5	0.03665
Pears *high exp.*	0,0222	0.5	0.0111
Strawberry *mean exp.*	0,0019	0.1	0.00019
Raspberry *mean exp.*	L/C	0.1	-
Blackberry *mean exp.*	L/C	0.1	-
Mushrooms *mean exp.*	0,0001	0.3*	0.003

*Codex MRL

Total exposure (mg/child/day)	0.05094
Total exposure (mg/kg bw/day) (TMDI)	0.005855
Proposed ADI (mg/kg bw/day)	0.02
Total dietary exposure (% of ADI)	**29.3**

Table B.7.15-5 Theoretical Maximum Daily Intake (TMDI) according to UK consumer exposure model –1.5-4.5 year toddlers; 14.5 kg bw

Commodity	European intake (high exposure) (kg/toddler/day)	STMR (mg/kg)	Exposure (mg/toddler/day)
Apples *high exp.*	0,2156	0.5	0.1078
Pears *high exp.*	0,0947	0.5	0.04735
Strawberry *mean exp.*	0,0029	0.1	0.00029
Raspberry *mean exp.*	0,0015	0.1	0.00015
Blackberry *mean exp.*	0,0001	0.1	0.0001
Mushrooms *mean exp.*	0,0009	0.3*	0.00027

*Codex MRL

Total exposure (mg/toddler/day)	0.15596
Total exposure (mg/kg bw/day) (TMDI)	0.01076
Proposed ADI (mg/kg bw/day)	0.02
Total dietary exposure (% of ADI)	**53.7**

LC = Low % consumers (Less than 60 consumers in survey).

Table B.7.15-6 Theoretical Maximum Daily Intake (TMDI) according to UK consumer exposure model – 4-6 years old 20.5 kg bw

Commodity	European intake (high exposure) (kg/infant/day)	STMR (mg/kg)	Exposure (mg/child/day)
Apples *high exp.*	0,1934	0.5	0.0967
Pears *high exp.*	0,0745	0.5	0.037
Strawberry *mean exp.*	0,0029	0.1	0.00029
Raspberry *mean exp.*	0,0001	0.1	0.00001
Blackberry *mean exp.*	L/C	0.1	-
Mushrooms *mean exp.*	0,0010	0:3*	0.0003

*Codex MRL

Total exposure (mg/infant/day)	0.1343
Total exposure (mg/kg bw/day) (TMDI)	0.0066
Proposed ADI (mg/kg bw/day)	0.02
Total dietary exposure (% of ADI)	**32,7**

Table B.7.15-7 Theoretical Maximum Daily Intake (TMDI) according to UK consumer exposure model – 7-10 years old; 30.9 kg bw

Commodity	European intake (high exposure) (kg/infant/day)	STMR (mg/kg)	Exposure (mg/child/day)
Apples *high exp.*	0,2324	0.5	0.1162
Pears *high exp.*	0,0682	0.5	0.0341

Strawberry *mean exp.*	0,0038	0.1	0.00038
Raspberry *mean exp.*	0,0002	0.1	0.00002
Blackberry *mean exp.*	0,0001	0.1	0.00001
Mushrooms *mean exp.*	0,0013	0:3*	0.0039

*Codex MRL

Total exposure (mg/infant/day)	0.15461
Total exposure (mg/kg bw/day) (TMDI)	0.0050
Proposed ADI (mg/kg bw/day)	0.02
Total dietary exposure (% of ADI)	**25,0**

Table B.7.15-8 Theoretical Maximum Daily Intake (TMDI) according to UK consumer exposure model – 11-14 years old; 48.0 kg bw

Commodity	**European intake (high exposure) (kg/infant/day)**	**STMR (mg/kg)**	**Exposure (mg/child/day)**
Apples *high exp.*	0,1969	0.5	0.09845
Pears *high exp.*	0,0886	0.5	0.0443
Strawberry *mean exp.*	0,0028	0.1	0.00028
Raspberry *mean exp.*	0,0001	0.1	0.00001
Blackberry *mean exp.*	0,0001	0.1	0.00001
Mushrooms *mean exp.*	0,0020	0:3*	0.0006

*Codex MRL

Total exposure (mg/infant/day)	0.14365
Total exposure (mg/kg bw/day) (TMDI)	0.00299
Proposed ADI (mg/kg bw/day)	0.02
Total dietary exposure (% of ADI)	**14,9**

Table B.7.15-9 Theoretical Maximum Daily Intake (TMDI) according to UK consumer exposure model – 15-18 years old; 63,8 kg bw.

Commodity	**European intake (high exposure) (kg/infant/day)**	**STMR (mg/kg)**	**Exposure (mg/child/day)**
Apples *high exp.*	0,2279	0.5	0.11395
Pears *high exp.*	0,0926	0.5	0.0463

Strawberry *mean exp.*	0,0023	0.1	0.00023
Raspberry *mean exp.*	0,0001	0.1	0.00001
Blackberry *mean exp.*	0,0001	0.1	0.00001
Mushrooms *mean exp.*	0,0036	0:3*	0.00108

*Codex MRL

Total exposure (mg/infant/day)	0.16158
Total exposure (mg/kg bw/day) (TMDI)	0.00253
Proposed ADI (mg/kg bw/day)	0.02
Total dietary exposure (% of ADI)	**12,7**

Table B.7.15-10 Theoretical Maximum Daily Intake (TMDI) according to UK consumer exposure model – Vegeterian; 66.7 kg bw

Commodity	**European intake (high exposure) (kg/infant/day)**	**STMR (mg/kg)**	**Exposure (mg/vegeterian/day)**
Apples *high exp.*	0,2227	0.5	0.11135
Pears *high exp.*	0,1254	0.5	0.0627.
Strawberry *mean exp.*	0,0050	0.1	0.0005
Raspberry *mean exp.*	0,0006	0.1	0.00006
Blackberry *mean exp.*	0,0003	0.1	0.00003
Mushrooms *mean exp.*	0,0084	0:3*	0.00252

*Codex MRL

Total exposure (mg/infant/day)	0.17716
Total exposure (mg/kg bw/day) (TMDI)	0.002656
Proposed ADI (mg/kg bw/day)	0.02
Total dietary exposure (% of ADI)	**13.3**

Table B.7.15-11 Theoretical Maximum Daily Intake (TMDI) according to UK consumer exposure model – Elderly own; 70,8 kg bw

Commodity	**European intake (high exposure) (kg/infant/day)**	**STMR (mg/kg)**	**Exposure (mg/Elderly own/day)**
Apples *high exp.*	0,0659	0.5	0.03295
Pears *high exp.*	0,0736	0.5	0.0368
Strawberry *mean exp.*	0,0044	0.1	0.00044

Raspberry *mean exp.*	0,0001	0.1	0.00001
Blackberry *mean exp.*	0,0002	0.1	0.00002
Mushrooms *mean exp.*	0,0025	0:3*	0.00075

*Codex MRL

Total exposure (mg/infant/day)	0.07097
Total exposure (mg/kg bw/day) (TMDI)	0.00100
Proposed ADI (mg/kg bw/day)	0.02
Total dietary exposure (% of ADI)	**5,0**

Table B.7.15-12 Theoretical Maximum Daily Intake (TMDI) according to UK consumer exposure model – Elderly residential; 61.6 kg bw

Commodity	**European intake (high exposure) (kg/infant/day)**	**STMR (mg/kg)**	**Exposure (mg/Elderly residential/day)**
Apples *high exp.*	0,0659	0.5	0.03295
Pears *high exp.*	0,0736	0.5	0.0368
Strawberry *mean exp.*	0,0044	0.1	0.00044
Raspberry *mean exp.*	0,0001	0.1	0.00001
Blackberry *mean exp.*	L/C	0.1	-
Mushrooms *mean exp.*	0,0009	0:3*	0.00027

*Codex MRL

Total exposure (mg/infant/day)	0.07047
Total exposure (mg/kg bw/day) (TMDI)	0.00114
Proposed ADI (mg/kg bw/day)	0.02
Total dietary exposure (% of ADI)	**5,7**

Table B.7.15-7 Estimation of the potential through the diet

Model	**Consumer Group**	**Total TMDI (mg/kg bw)**	**ADI (mg/kg bw/day)**	**Total TMDI in % of ADI**
WHO (1997)	Adult (60 kg bw)	0.00086	0.02	**4.4**
German BBA (1993)	Girl (13.5 kg bw)	0.00362	0.02	**18.4**
UK PDS (1999)	Adult (76 kg bw)	0.00228	0.02	**11.4**
	11-12 (48.0 kg bw)	0.0031	0.02	**15.5**
	Toddler (14.5 kg bw)	0.01076	0.02	**53.7**
	Infant (8.7 kg bw)	0.005855	0.02	**29.3**
	4-6 year (20.5 kg bw)	0.0066	0.02	**32.7**
	7-10 year (30.9 kg bw)	0.0050	0.02	**25.0**
	15-18 year (63.8 kg bw)	0.00253	0.02	**12.7**
	Vegetarian (66.7 kg bw)	0.002656	0.02	**13.3**
	Elderly own (70.8 kg bw)	0.002656	0.02	**5**

	Eldlery residential (61.6 kg bw)	0.00100	0.02	**5.7**

Comment: Considering the present intended use for Diflubenzuro, TMDI is not expected to exceed ADI for any consumer group.

Reporting table point 3 (32)

The calculations provided under table B.7.15-8 are irrelevant as apple pomace is not a commodity for human consumption. This should be deleted from the DAR.The calculations provided under table B.7.15-8 are irrelevant as apple pomace is not a commodity for human consumption.

Table B.7.15-8 should be deleted from the DAR.

Reporting table point 3 (34)

The header of the table suggests that calculation is made on intake of PCA (chloroaniline). However, this is misleading since the calculation reflects the risk assessment based on diflubenzuron data only.

The calculations provided under table B.7.15-8 are irrelevant as apple pomace is not a commodity for human consumption. Table B.7.15-8 should be deleted from the DAR.

Addendum to
Draft Assessment Report

DIFLUBENZURON

Volume 3

Annex B.8 and B.9
Environmental Fate and Behaviour
Ecotoxicology

Rapporteur Member State: Sweden

December 2008

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Volume 1

Level 1: Statement of subject matter and purpose for which the monograph was prepared

Level 2: Reasoned statement of the overall conclusions drawn by the Rapporteur Member State

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Level 3: Proposed decision with respect to the application for inclusion of the active substance in Annex I

Level 4: Further information to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in Annex 1

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B.8 Environmental fate and behaviour

B.8.2 Adsorption, desorption and mobility in soil

B.8.2.1 Adsorption/desorption studies

Open point 4.2:

The notifier submitted a detailed account on how the K_{OC} for the metabolite DFBA was estimated using PCKOCWIN^{TM} v 1.66, which is summarised below.

Reference:	**Uwe Wanner (Dec 21, 2006). Description of the QSAR model used for the estimation of the adsorption coefficient of DFBA**
Methods	The adsorption coefficient of DFBA was calculated with PCKOCWIN™ v. 1.66 within Estimation Program Interface Suite™ (see Appendix A of the complete EPI Suite™ results printout). A detailed description of EPI Suite™ can be found on EPA's webpage http://www.epa.gov/oppt/exposure/pubs/episuite.htm The EPI (Estimation Programs Interface) SuiteTM is a Windows® based suite of physical/chemical property and environmental fate estimation models developed by the EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC). EPI SuiteTM runs of one single input, a representation of the chemical structure in SMILES notation. SMILES is "Simplified Molecular Input Line Entry System"; a description of this system is available with the EPI SuiteTM. The Soil Adsorption Coefficient Program (PCKOCWIN™) estimates the soil adsorption coeffiecient (Koc) of organic compounds. Traditional estimation methods rely upon the octanol/water partition coefficient or related parameters, but recently the first-order molecular connectivity index (1-MCI) has been used successfully to predict Koc values for hydrophobic organic compounds. PCKOCWIN uses 1-MCI and a series of group contribution factors to predict Koc. The group contribution method outperforms traditional estimation methods based on octanol/water partition coefficients and water solubility. Meylan et al. (1992) summarizes the methodology to predict the sorption coefficient as follows: "The first-order molecular connectivity index (MCI) has been successfully used to predict soil sorption coefficients (Koc) for nonpolar organics, but extension of the model to polar compounds has been problematic. To address this, we developed a new estimation method based on MCI and series of statistically derived fragment contribution factors for polar compounds. After developing an extensive database of measured Koc values, we divided the dataset into a training set of 189 chemicals and an independent validation set of 205 chemicals. Two linear regressions were then performed. First, measured log Koc values for nonpolar compounds in the

training set were correlated with MCI. The second regression was developed by using the deviations between measured log Koc and the log Koc estimated with the nonpolar equation and the number of certain structural fragments in the polar compounds. The final equation for predicting log Koc accounts for 96% and 86% of the variation in the measured values for the training and validation sets, respectively. Results also show that the model outperforms and covers a wider range of chemical structures than do models based on octanol-water partition coefficients (Kow) or water solubility."
In summary Meylan et al (1992) the general equation used to estimate log Koc of any compound is:
log Koc = 0.53 MCI + 0.62 + Summation (Pf)
where MCI is the first order molecular connectivity index and Summation (Pf) is the summation product of all applicable correction factors. A list of the correction factors is presented in Appendix B. See Appendix C, Appendix D and Appendix F for lists of the chemicals used in the regressions and a supplemental validation list.
References:
Meylan, W., P.H. Howard and R.S. Boethling (1992) "Molecular Topology/Fragment Contribution Method for Predicting Soil Sorption Coefficients", Environ. Sci. Technol. 26: 1560-7.
http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Results:
Soil Adsorption Coefficient (PCKOCWIN v1.66): Koc : 39.61; Log Koc: 1.598

Comments:
This account is a more detailed description of the method used and the result is not different from the result presented in the DAR.

B.8.4.3 Ready biodegradibility

Open point 4.3:
Comments were received that diflubenzuron does not pass the criteria regarding the theoretical CO_2 production as stipulated in the OECD 301B since such studies should be a measure of ultimate biodegradation (i.e. mineralisation) and as 50% of the initial applied diflubenzuron appeared to remain as metabolite CPU after 28 d. The RMS agree with the comments from other MS and considers diflubenzuron as being non biodegradable. This will result in an alteration of the proposed classification. Since DFB is not readily biodegradable and the DT_{50} of diflubenzuron and its classifiable metabolite CPU (96h-LC50 for fish 70 mg CPU/L;whole system water/sediment DT50= 37.6 d) is > 16 days the RMS considers that diflubenzuron should be classified as R53 in addition to R50 (see also addendum to section B.4). The notifier has submitted a document (DIFLUBENZURON - Arguments against R53 classification. Uwe Wanner. December, 2006) arguing against the R 50/53 of

diflubenzuron. This document was however available also for the Meeting on Environmental Effects of Existing Chemicals, Pesticides & New Chemicals in JRC Ispra - January 25, 2007 (Technical Committee on the Classification and Labelling of Dangerous Substances). The TC C&L agreed to classify the substance as N; R50-53 with an M-factor of 100. Hence, the RMS does not consider that this issue needs to be discussed further in this report.

B.8.6 Predicted environmental concentrations in surface water and in groundwater (PEC_{sw}, PEC_{gw}) (Annex IIIA 9.2.1, 9.2.3)

B.8.6.1 Predicted environmental concentrations in ground water (PEC_{GW})

Point of clarification 4.1:

EFSA and one member state noted that the ground water simulation for the metabolite was performed using the QSAR estimated K_{OW} for DFBA. Normally K_{OC}=0 has been used when no K_{OC} experimentally could be derived. The notifier agreed to submit an assessment for DFBA with K_{OC}=0, and this is summarised below.

Reference:	**Uwe Wanner. 2007. Predicted Environmental Concentrations of 2,6-Difluorobenzoic Acid (DFBA), Soil Degradation Product Diflubenzuron in Groundwater following the Application of DIMILIN WG-80® to Orchards in the EU using FOCUS PELMO 3.3.2 and FOCUS PEARL 3.3.3**
Methods	The predicted environmental concentration in groundwater (PEC_{GW}) of the metabolites, DFBA following typical use of Dimilin WG-80 in the EU was investigated using the standardised modelling recommendations of the FOCUS groundwater working group. Simulations were conducted using the PELMO model (FOCUS version 3.3.2, July 2002) and FOCUS PEARL 3.3.3. The annual application rate used for the groundwater calculations is based on the proposed Good Agricultural Practice for the use of Dimilin WG-80® on pome fruit. The application rate of diflubenzuron for this use pattern is 180 g (a.s.) per hectare, applied twice with an interval of 14 days. In order to obtain realistic worse-case groundwater assessment, the calculations are based on an early application Dimilin WG-80®, i.e., 14 days after the default settings for leaf emergence. The peak concentration of DFBA of 13.3% of applied dose was reached after 3 days after the application in the water/sediment studies. Therefore, the initial application of DFBA occurred 17 days after the default day for leaf emergence, followed by a second application 14 days later. The FOCUS interception value of 50% for early applications (i.e., no leaf canopy present) was used for this assessment. In the absence of data on uptake and translocation in plants, a plant uptake factor of 0 was assumed for the degradation products DBFA. Adsorption data for the metabolite DFBA was set to 0. The aerobic soil degradation rate of DFBA was measured in one soil type at 20°C and a further two soil types at 24°C. The observed degradation rate in each soil was then normalised

according to the calculation shown in Table 8.6.1.c.. The overall geometric mean DT_{50} = 5.9 days was used in the simulation.

Table 8.6.1.a. Calculation of equivalent DFBA application rates

Metabolite	Molecular weight	Parent application rate	Metabolite application rate[1]	Maximum observed soil concentration	Sampling Interval	Crop interception	Equivalent metabolite application rate
DFBA	158.1	180 g a.s./ha	91.6 g a.s./ha	13.3%	3 days	50 %	16.1 g a.s./ha

[1] *100 % transformation of parent to metabolite*

Table 8.6.1.b Summary of the relevant physical chemical properties of DFBA.

Property	Data
Molecular weights	DFBA 158.1 g/mol
Water solubility at 25°C pH 4 pH 7 pH 10 unbuffered	3063 (calculated based on chemical structure using EPI Suite version 3.10)
Vapour pressure at 25°C	0.235 (calculated based on chemical structure using EPI Suite version 3.10)
Octanol/water partition coefficient, K_{OW}	DFBA -0.02
Adsorption K_{OC}	DFBA 0 ml/g
Degradation rate (corrected to standard temperature and moisture)	DFBA 5.9 d (geometric mean from 3 soils)

Table 8.6.1.c. Conversion of DFBA DT_{50} values to a common moisture content.

Soil	DT50 [days] reported	Correction factor	DT50 [days] moisture corrected	Geometric mean at 20ºC & pF2
Soil I	9.0	1.06541 (i.e. 1)	9.0	5.9
Soil II	7.9	0.90294	7.1	
Soil III	3.6	0.90816	3.3	

Result:

Results of the FOCUS PELMO 3.3.2 and FOCUS PEARL 3.3.3 PEC groundwater calculations for DFBA after annual application of Dimilin WG-80® in orchards are listed in the table below.

Table 8.6.1.e. Predicted 80th percentile annual average concentrations for DFBA in groundwater (µg/L) at 1 m depth following use in orchards at a an application rate of 180 g/ha.

Location	FOCUS PELMO	FOCUS PEARL
Chateaudun	0.011	0.017
Hamburg	0.003	0.034
Jokioinen	0.020	0.071
Kremsmunster	0.006	0.015
Okehampton	0.005	0.020
Piacenza	0.007	0.016
Porto	0.000	0.000
Sevilla	0.000	0.006
Thiva	0.000	0.000

Comments: The predicted environmental concentrations (PECs) DFBA after the application of the Dimilin in orchards were calculated using FOCUS PELMO 3.3.2 and FOCUS PEARL 3.3.3. These calculations were based

on the assumption that DFBA does not show any adsorption to soil (K_{OC}= 0 mL/g). The PEC_{GW} of all relevant locations were calculated to be less than 0.1 µg/L.

The following difference from the original modelling in the DAR was noted; A crop interception value of 50 % was used when calculating the metabolite application rate, this is considered as acceptable by the RMS. Further, the vapour pressure was estimated to 0.235 Pa and used to model dissipation through volatilisation; in the DAR this dissipation route was excluded in the absence of data. The estimated DFBA vapour pressure implies that DFBA is moderately volatile, and hence volatilisation may have had an impact on the final PECgw estimated in the modelling. The acceptability of the estimated vapour pressure may need to be discussed at an expert meeting. Pending the outcome of the discussion the LoEP needs to be revised.

B.8.6.2 Predicted environmental concentrations in surface water (PEC_{sw})

Table 8.6.2.a. Summary of PECsw

Field of use	Method of application	RMS assessment
Orchards	Tractor-mounted sprayer; spray directed upwards and sideways	PECsw for step 4 with 30 m buffer zones available, however further refinements needed for TER above trigger.
	Hand-held sprayer; spray directed upwards and sideways	Not available. No further information submitted, the notifier considers that this use is covered by the highest load application in orchards.
Forestry and woody ornamentals	Aerial application -ultra low volume (ULV) -low volume (LV)	PECsw calculations submitted by the notifier, however these were not considered as acceptable for risk assessment, see below.
	Ground application -tractor mounted spray	Not available. No further information submitted, the notifier considers that this use is covered by the highest load application in orchards.
	-hand-held sprayer[3]	Available. Acceptable TER with 20 m bufferzone
Mushrooms	Automatic sprayer	No PECsw provided, not required by RMS
	Hand-held sprayer; high volume spray directed downwards	No PECsw provided, not required by RMS

B.8.6.2.1 Predicted environmental concentrations in surface water (PEC_{sw}) and sediment (PECsed) following aerial application to forests

Open Point 4.8:

Forest application is not a standard scenario with in the EU evaluation of pesticides under 91/414/EEC. In the DAR the PEC_{SW} following the use of diflubenzuron in forestry was calculated by RMS assuming spray drift deposition into a 30 cm deep water body, using a drift value of 33.2 % for aerial application as given in the guidance "FOCUS surface water scenarios in the EU evaluation process under 91/414/EEC (SANCO/4802/2001-rev1)". In the Draft Assessment Report submitted in May 2005 no acceptable risk for the aquatic environment could be demonstrated for the proposed use in forests by aerial application. Therefore the notifier submitted a new assessment for the Predicted Environmental Concentrations in surface water following

aerial application in their updated summary dossier (Doc M III, Annex III A, Tier II). The notifier also submitted the back ground report to the new PECsw assessment 'Predicted Environmental Concentrations of Diflubenzuron in surface waters following the use of Dimilin in forests in the EU' by Wanner (2005). For these new PEC calculations the notifier used AGDISP, distributed by the US Department of Agriculture, Forest Service, Forest Health Technology Enterprise Team. Version 8.15, to calculate the spray drift following application in forestry. This model has not been evaluated for the use in the risk assessment of pesticides under 91/414/EEC. The RMS has evaluated the new assessment and report see below.

Reference:	**Wanner, U, (2005). Predicted environmental concentrations of diflubenzuron in surface waters following use of 'Dimilin' WG-80 in forests in the EU**
Material and methods:	PECs were obtained by combining the spray drift results, calculated with the computer model AGDISP, and the standard FOCUS surface water tools for orchards, as a surrogate for forestry. AGDISP is a dedicated aerial spray simulation model to calculate spray drift of pesticides in forestry uses, distributed by the US Department of Agriculture, Forest Service, Forest Health Technology Enterprise Team. Version 8.15 of this model was used to calculate deposition of diflubenzuron on nearby water bodies, resulting from aerial application in forestry at the recommended GAP in the EU (48 g a.s./ha) under realistic worst-case conditions, in which all major parameters that influence the off-target movement of diflubenzuron were taken into consideration. Three different drop sizes (i.e. 80, 100 and 120 µm Volume Median Diameter), derived from typical application equipment and operating conditions, were simulated at two release heights (10- and 15 m) and two canopy heights (i.e. 10- and 24 m). The application is performed either with fixed-wing aircrafts or with helicopters. The application volumes range between 3-5 liters per hectare for 'ultra-low volume' (ULV) applications and 30-50 liters per hectare in case of 'low volume' (LV) applications. The LV applications use only water as carrier whereas in the case of ULV applications up to 0.5 liter of oil per hectare is added to the water carrier in the tank mix. Dimilin® WG 80 is usually applied in late spring/early summer. Therefore, the chosen application window ranged from beginning of May until end of May. The aquatic habitats for this study were aligned parallel to the flight line and perpendicular to the wind direction. Three different surface water geometries (ditch, stream and pond) were created based on the documentation provided with the spray drift calculator of the FOCUS surface water tools. The highest surface water concentration found in AGDISP, was used to obtain the maximum mass load of diflubenzuron per surface area. This parameter was then included into FOCUS surface water calculations in order to estimate the spray drift in forestry applications. Potential surface run-off and drainage of diflubenzuron were evaluated within the FOCUS surface water tools based on orchards as

surrogate for forests.

The surface water PECs were calculated with the help of SWASH (Surface Water Scenarios Help) model (=shell) version 1(=2.1, 9 April 2003), database version 1(=2.2, 9 April 2003). There is no "forest" scenario in the current version of SWASH, as "forests" are not considered as standard crops. In order to evaluate the potential mass load of diflubenzuron via run-off or drainage after the application of Dimilin® WG-80, the crop scenario "orchards" (pome/stone fruits, early applications) was selected as surrogate scenario for forests. As recommended for the use of Dimilin® WG-80 on forests, the simulations were conducted with an application window between May 1st and May 31st (Julian days 121 and 151). The main characteristics of each scenario are presented in the table below.

Scenario	Run-off / drainage	Selected weather data set	Description	Waterbody
D3	Drainage	Vredepeel/ NL	Soil type, topography & climatic conditions typical for Northern EU	FOCUS ditch
D4	Drainage	Skousbo/ DK	Similar to D3, soil not suitable for root vegetables	FOCUS pond & FOCUS stream
D5	Drainage	La Jailliere/ F	Soil type/climate combination not suitable for root crops	FOCUS pond & FOCUS stream
R1	Run-off	Weiherbach/GER	Extensive run-off scenario for wide range of crop	FOCUS pond & FOCUS stream
R2	Run-off	Porto/P	Southern EU, terraced crop production,with high rainfall	FOCUS stream
R3	Run-off	Bologna/I	Southern EU, gently to moderately sloping	FOCUS stream
R4	Run-off	Roujan/F	Southern EU, hot dry summers, irrigation at times of water deficit	FOCUS stream

The SWASH runs were calculated twice. During the initial evaluations, the potential mass load of diflubenzuron via run-off was calculated using PRZM within the SWASH tools. Potential contributions of diflubenzuron to surface waters via drain-flow were simulated with MACRO within SWASH. After these calculations the initial PECs were calculated with TOXSWA within SWASH using the standard drift values given for 'air-blast' in orchards. In a re-run of these TOXSWA evaluations the incorrect application pattern (air-blast in orchards) was corrected by implementing the results obtained from the spray-drift evaluations for forestry uses obtained by AGDISP. This was established by adjusting the spray-drift loads within the TOXSWA files with a value derived from the AGDISP scenarios, which resulted in the highest surface water contamination (in this case

the potential contamination of a ditch after a helicopter application). In the case of stream scenarios this value was multiplied by a factor of 1.2 in order to account for the up gradient drift that is assumed to occur in the stream watershed.

Results:

The results of the AGDISP spray drift evaluation are presented for twelve different "cases" in which the drop size distribution (i.e., volume median diameters VMD), the release height, the air speed, the application volume and the aircraft was varied. Each of these twelve "cases" was run for a canopy height of 10 m (equivalent to a young forestation) and 24 m (old forest). The results of these AGDISP evaluations are presented in the table below:

Table 8.6.1.1.a. AGDISP predicted deposition of diflubenzuron in nearby water bodies (µg/L)

Low Volume application											
Case No.	**Aircraft type**	**Droplet size VMD (µm)**	**Release height (m)**	**Speed (km)**	**Ditch (µg/L)**		**Stream (µg/L)**		**Pond (µg/L)**	
					Canopy height		**Canopyheight**		**Canopy height**	
					10 m	**24 m**	**10 m**	**24 m**	**10 m**	**24 m**
1	Helicopter	100	10	100	0.028	0.006	0.027	0.006	0.005	0.001
2	Helicopter	80	10	100	0.005	<0.001	0.005	<0.001	<0.001	<0.001
3	Helicopter	120	10	100	0.074	0.023	0.073	0.023	0.013	0.005
4	Helicopter	100	15	100	0.015	0.004	0.015	0.004	0.005	0.001
5	Helicopter	100	10	80	0.025	0.006	0.025	0.006	0.005	0.001
6	Airplane	100	10	200	0.020	0.005	0.020	0.005	0.005	0.001
7	Airplane	80	10	200	0.003	<0.001	0.003	<0.001	<0.001	<0.001
8	Airplane	120	10	200	0.059	0.023	0.059	0.023	0.014	0.005
9	Airplane	100	15	200	0.013	0.003	0.013	0.003	0.004	0.001
10	Airplane	100	10	180	0.021	0.005	0.021	0.005	0.005	0.001
Ultra Low Volume application oil carrier										
Case no.	**Aircraft type**	**Droplet size VMD (µm)**	**Release height (m)**	**Speed (km)**	**Ditch (µg/L)**		**Stream (µg/L)**		**Pond (µg/L)**	
					Canopy height		**Canopyheight**		**Canopy height**	
					10 m	**24 m**	**10 m**	**24 m**	**10 m**	**24 m**
11	Helicopter	100	10	100	0.095	0.041	0.094	0.041	0.020	0.011
12	Airplane	100	10	200	0.091	0.042	0.091	0.042	0.023	0.012

Based on these 24 individual evaluations, the highest concentrations in a surface water directly next to a treated forest, i.e. the highest potential spray-drift, occurred in "case" no. 11 (10m forest), which represents ultra-low volume applications of an oil-containing formulation on a forest with an adjacent FOCUS ditch and which is based on an application with a helicopter flying at a speed of 100 km/h at a height of 10 meters above the canopy of a young forestation with a drop size distribution, which can be qualified as "very fine" to "fine" (volume median diameter VMD = 100µm). AGDISP calculated an aquatic concentration of 0.095 µg/L for this FOCUS ditch scenario with a length of 100m, a width of 1 m and a depth of 0.3 m.

Hence, the total mass of diflubenzuron in this FOCUS ditch is therefore:
0.095 µg/L × 100 m × 1 m × 0.3 m × 1000 L/m^3 = 2850 µg.
The mass load per surface area is equal to:
2850 µg/100 m^2 = 28.5 µg/m^2 = 0.029 mg/m^2.

Results of the FOCUS TOXWA calculations - The calculated mass load of diflubenzuron per surface area of 0.029 mg/m^2 based on the results obtained from the FOCUS ditch scenario in AGDISP was used to evaluate all SWASH scenarios. For the FOCUS stream scenarios the mass load was multiplied by a factor of 1.2 (= 0.034 mg/m^2) to account for the up gradient drift that is assumed to occur in the stream watershed.

The global maximum concentrations in surface water and sediment of the different FOCUS ditch, pond and stream scenarios are listed in the table below.

Table 8.6.1.1.b. Global maximum PECs for surface water and sediment (FOCUS - all scenarios)

FOCUS scenario	PECsw (µg/L)	PECsed (µg/kg dry sediment)
	Actual	Actual
FOCUS ditch, drainage scenario D3	0.095	0.045
FOCUS pond, drainage scenario D4	0.029	0.032
FOCUS stream, drainage scenario D4	0.104	0.008
FOCUS pond, drainage scenario D5	0.029	0.031
FOCUS stream, drainage scenario D5	0.106	0.004
FOCUS pond, run-off scenario R1	0.029	0.034
FOCUS stream, run-off scenario R1	0.081	0.007
FOCUS stream, run-off scenario R2	0.111	0.008
FOCUS stream, run-off scenario R3	0.116	0.021
FOCUS stream, run-off scenario R4	0.105	0.052

Comments:
In the worst case simulation a surface water concentration of 0.095 µg/L was predicted by the AGDISP in a surface water body with a length of 100 m, a width of 1 m and a depth of 0.3 m, with a distance of 1 m between the down-wind edge of the spray swath to the up-wind edge of the aquatic environment. A surface water concentration of 0.095 µg/L in surface water body with a length of 100 m, a width of 1 m and a depth of 0.3 m is equivalent to a surface deposition of 28.5 µg/m^2 which corresponds to a drift of 0.6%. (i.e. (0.0285/4.8)×100). This is very much lower than the drift suggested for the EU process in the FOCUSsw document.
As can be seen from the tables 8.6.1.1.c & d (originally from the report by Esterly, D. (2005) " The potential for off target movement of diflubenzuron (Dimilin® WG 80) during aerial applications" which was submitted by the notifier upon request by the RMS and is the basis for the notifier's assessment in the report by U. Wanner "Predicted Environmental Concentrations of Diflubenzuron in Surface Waters following use of 'Dimilin® WG-80' in Forests in the EU" which is summarized above) the canopy removal factor is substantial, e.g. for the ULV application the canopy removes > 95 % of the drift.

Table 8.6.1.1.c. Model Results for a 10 meter Evergreen Canopy Aquatic Concentration

Case Name	Low Volume Application Water Carrier				
	Case No.	Ditch (µg/l)	Stream (µg/l)	Pond (µg/l)	Canopy Removal (%)
Base Case Helicopter = BaseH	1	0.028	0.027	0.005	66
Base H 80 VMD	2	0.005	0.005	<0.001	51
Base H 120 VMD	3	0.074	0.073	0.013	77
Base H 15 RH	4	0.015	0.015	0.005	27
Base H 80 KM	5	0.025	0.025	0.005	76
Base Case Fixed Wing = BaseF	6	0.020	0.020	0.005	34
Base F 80 VMD)	7	0.003	0.003	<0.001	17
Base F 120 VMD	8	0.059	0.059	0.014	49
Base F 15 RH	9	0.013	0.013	0.004	17
Base F 180 KM	10	0.021	0.021	0.005	35
Case Name	**Ultra Low Volume Application Oil Carrier**				
	Case No.	**Ditch (µg/l)**	**Stream (µg/l)**	**Pond (µg/l)**	**Canopy Removal (%)**
Base H Oil	11	0.095	0.094	0.020	>95
Base F Oil	12	0.091	0.091	0.023	>95

Table 8.6.1.1.d. Model Results for a 24 meter Evergreen Canopy Aquatic Concentration

Case Name	Low Volume Application Water Carrier				
	Case No.	Ditch (µg/l)	Stream (µg/l)	Pond (µg/l)	Canopy Removal (%)
Base Case Helicopter = BaseH	1	0.006	0.006	0.001	79
Base H 80 VMD	2	<0.001	<0.001	<0.001	71
Base H 120 VMD	3	0.023	0.023	0.005	85
Base H 15 RH	4	0.004	0.004	0.001	29
Base H 80 KM	5	0.006	0.006	0.001	86
Base Case Fixed Wing = BaseF	6	0.005	0.005	0.001	60
Base F 80 VMD	7	<0.001	<0.001	<0.001	49
Base F 120 VMD	8	0.023	0.023	0.005	85
Base F 15 RH	9	0.003	0.003	0.001	16
Base F 180 KM	10	0.005	0.005	0.001	68
Case Name	**Ultra Low Volume Application Oil Carrier**				
	Case No.	**Ditch (µg/l)**	**Stream (µg/l)**	**Pond (µg/l)**	**Canopy Removal (%)**
Base H Oil	11	0.041	0.041	0.011	>95
Base F Oil	12	0.042	0.042	0.012	>95

The RMS asked the US-EPA for advice when evaluating the AGDISP simulation (AGDISP Technical response No. 07-035). The US-EPA pointed out that in this model the most important factor for reducing the off-target drift deposition appears to be the canopy. When the model includes a canopy, the canopy is assumed to be everywhere including over the water body. This may be a valid assumption for a small water body within the treatment area but outside the forested area a higher deposition can be expected. Furthermore in the simulations where the pesticide is applied in a water solution it is evaporating down to very small droplets that are being blown far downwind, distributing the application over a very large area.

The contact person at US-EPA made a rerun of one of the scenarios (Base F, one of the aircraft cases), but removed the canopy and included an oil carrier in the model. This simulation resulted in that close to 10% of the application rate depositing 200m downwind of the application. This indicates that a considerable higher deposition than 0.6 %, as suggested by the notifier as worst case, is possible. Furthermore, the simulation shows that the highest amount of the deposition may occur at a considerable distance from the forest edge (Fig. 8.6.1.1.a).

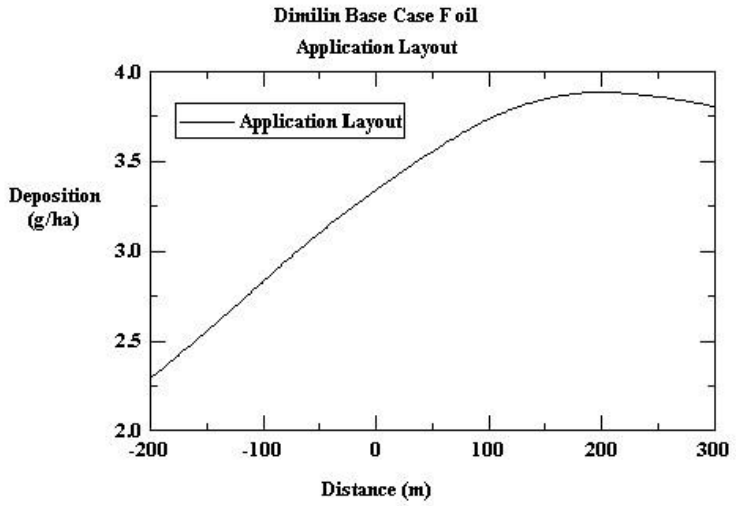


Figure 8.6.1.1.a. Diflubenzuron deposition at various distances from sprayed area.

In conclusion, the RMS considers that the notifier's assessment of the PECsw resulting from application of diflubenzuron in forest using AGDISP and FOCUS SW cannot be considered to represent a realistic worst case and can hence not be acceptable for the risk assessment.

B.8.6.1.2 Predicted environmental concentrations in surface water (PEC_{sw}) following forestry hand held application

The notifier submitted a new calculation of the PECsw for the proposed hand application in forests in the updated summary dossier. The same methodology for calculation as in the DAR was applied, i.e. using spray drift values by Rautmann et al. 2001 and a 30 cm deep water body as a model system. However the notifier proposed a new DT_{50} for the calculations, see table below.

Table 8.6.1.2.a. Aqueous phase degradation rates of diflubenzuron, CPU and DFBA proposed by the notifier

Compound	Average DT_{50} at 20ºC in the aqueous phase (days)
Diflubenzuron	2.25
2,6-difluorobenzoic acid (DFBA)	2.85
4-chlorophenylurea (CPU)	24.95

However, the average DT_{50} for diflubenzuron, as suggested by the notifier, includes results from a study not considered as reliable by the RMS, i.e. the study by Thus et al. 1994. Furthermore, since FOCUS SW simulation is not used for the calculation the worst case water dissipation DT_{50} should be used (in the DAR it is in the text

stated that the average degradation DT_{50} was used, however the RMS used the average dissipation DT_{50}=3 when performing the calculations). In the table 8.6.1.2.b. the worst case dissipation DT_{50} are listed which the RMS consider appropriate for PEC calculations. In Table 8.6.1.2.b. the resulting PECsw are shown, which are slightly different from those presented in the DAR. However, since only the PECinitial was used for the risk assessment the slight change in PEC-values does not alter the aquatic risk assessment and the RMS considers that no further action is required and the assessment in the DAR is still valid.

Table 8.6.1.2.b. Aqueous phase dissipation rates of diflubenzuron, CPU and DFBA considered as appropriate for PEC calculations by the RMS.

Compound	Worst case DT_{50} at 20ºC in the aqueous phase (days)
Diflubenzuron	3.2
2,6-difluorobenzoic acid (DFBA)	4.2
4-chlorophenylurea (CPU)	31.8

Table 8.6.1.2.c. PECsw and time-weighted PECsw values (µg/L) for diflubenzuron and its metabolites CPU and DFBA following forest application using drift values for late vines obtained from Rautmann (1999) into a 30 cm deep water body. For the calculation of TWA_PEC the worst case Dis-DT_{50} was used.

Scenario	Time after maximum	PEC_{sw} Diflubenzuron		PEC_{sw} CPU		PEC_{sw} DFBA	
		Actual (µg/L)	TWA (µg/L)	Actual (µg/L)	TWA (µg/L)	Actual (µg/L)	TWA (µg/L)
Forestry 48 g a.s./ha, hand application, crop height >50 cm	Initial	1.280		0.311		0.110	
	24 hours	1.031	1.151	0.304	0.308	0.094	0.102
	2 days	0.830	1.039	0.298	0.305	0.079	0.094
	4 days	0.538	0.856	0.285	0.298	0.057	0.081
	7 days	0.281	0.659	0.267	0.289	0.035	0.065
	14 days	0.062	0.402	0.229	0.268	0.011	0.043
	21 days	0.014	0.278	0.197	0.250	0.003	0.031
	28 days	0.003	0.211	0.169	0.233	0.001	0.024
	42 days	0.000	0.141	0.125	0.204	0.000	0.016

8.6.1.3 PECsw following tractor mounted application in forestry

Point of clarification No. 4.2:

No calculation has been provided. The notifier states that several safe uses for the highest load applications, i.e. orchard uses based on the NOEC (or EAC) of 0.7 µg/L has been provided which thus cover the risk resulting from the forest scenario. However the EAC will be discussed by the ecotoxicology expert meeting. RMS considers that the EAC should be 0.07 µg/L and using this EAC no safe use is demonstrated for the orchard scenario and the notifiers reasoning fail.

If the ecotox meeting agrees with the notifier that the EAC should be 0.7 µg/L then safe use has been demonstrated for some FOCUS scenarios if a bufferzone of 20 m is implemented for the orchard use. Nevertheless it will still be unclear which buffer zones that will be needed for the tractor mounted application in forest since the application rates differ from the orchard use (48 g/ha compared to 180 g/ha). The corrected values are included in the revised LoEP.

B.8.6.2 PECsw following application in orchards

B. 8.6.2.1 FOCUS step 4 for tractor mounted application in orchards (buffer zones >30 m)

Risk for surface waters was identified for the tractor mounted application also when buffer zones of 30 m was implemented in the FOCUS Step 4 calculations. Hence the RMS and other commenting MS (reporting table no. 4(27)) suggested that modelling using wider buffer zones should be performed.
However, the notifer has not submitted any further calculation instead they submitted a position paper (see APPENDIX I) in which it was stated that drift reducing technologies would be sufficient to reduce drift to an acceptable level for aquatic ecosystems. For this position the notifier referred to the FOCUS report "Landscape and mitigation factors in Aquatic Ecological risk assessment (version 1 draft June 2004)". In this report it is stated spray-drift can be mitigated by up to 99% by drift reducing technologies and bufferzones, and that this should be considered at MS level. The PPR Panel does not agree with the maximum spray drift reduction of 99%, which is considered to be not realistic in praxis. Instead the PPR panel (Opinion of the Scientific Panel on Plant protection products and their residues on a request from EFSA on the Final Report of the FOCUS Working Group on Landscape and Mitigation Factors in Ecological Risk Assessment, December 2006) suggest that the maximum cap for spray drift reduction should be set to 85%.
However, FOCUS Landscape is still under discussion and at present only spray drift reduction trough buffer zones may be assessed at EU level, other potential mitigation measures will be only considered on case to case basis for EU risk assessment taking into account that these risk mitigations options are not general available for all MS, however the information provided may be useful for MS.

B. 8.6.2.2 PECsw following hand held application in orchards (FOCUS simulation)

Point of clarification No. 4.2:
No calculation has been submitted, see above 8.6.1.3.

B.9 Ecotoxicology

B.9.1 Effects on birds

Open point 5 (2):

Further details on the reproductive parameters for the Subchronic toxicity and reproduction was requested.

Reference: **Beavers, J.B., Corbitt, A., Hawrot, R. et al (1990 a). A one-generation reproduction study with the mallard (*Anas platyrhynchos*).**

TABLE 5

BODY WEIGHT DATA (g) - HATCHLINGS

MALLARD

DIFLUBENZURON - PROJECT NUMBER 225-103

		DIFLUBENZURON		
	0 PPM	250 PPM	500 PPM	1000 PPM
No. of Ducklings Weighed	281	212	253	338
Mean Body Weight (g)	33 ± 2	34 ± 3	34 ± 3	34 ± 2

The above differences from the control are not statistically significant.

TABLE 5A

BODY WEIGHT DATA (g) - 14-DAY SURVIVORS

MALLARD

DIFLUBENZURON - PROJECT NUMBER 225-103

		DIFLUBENZURON		
	0 PPM	250 PPM	500 PPM	1000 PPM
No. of Ducklings Weighed	273	202	243	325
Mean Body Weight (g)	229 ± 37	240 ± 19	246 ± 23	240 ± 16

The above differences from the control are not statistically significant.

TABLE 3

REPRODUCTIVE DATA - MALLARD

DIFLUBENZURON - PROJECT NUMBER 225-103

	DIFLUBENZURON			
	0 PPM	250 PPM	500 PPM	1000 PPM
Eggs Laid	622	618	680	634
Eggs Cracked	10	4	15	9
Eggs Set@	556	560	600	562
Viable Embryos	450	518	475	528
Live 3-Week Embryos	443	502	471	510
Hatchlings	282	212	253	338
14-Day Old Survivors	273	202	243	325
Eggs Laid/Hen	39	41	43	40
Eggs Laid/Hen/Day @@	0.59	0.62	0.64	0.60
14-Day Old Survivors/Hen	17	13	15	20

@ - Eggs laid minus eggs cracked, eggs taken for shell thickness, abnormal eggs and eggs inadvertently damaged.
@@ - Based on 66 days.

TABLE 3A

REPRODUCTIVE DATA - (MEAN %^) - MALLARD

DIFLUBENZURON - PROJECT NUMBER 225-103

	DIFLUBENZURON			
	0 PPM	250 PPM	500 PPM	1000 PPM
Eggs Laid	622	618	680	634
Eggs Laid/Max. Laid (%)	66	70	72	67
Eggs Cracked/Eggs Laid (%)	1	1	2	1
Viable Embryos/Set (%)	82	92	77	94
Live 3-Week Embryos/Viable (%)	98	97	98	96
Hatchlings/3-Week (%)	61	42	45	64
14-Day Old Survivors/Hatch (%)	98	94	96	95
Hatchlings/Set (%)	51	38	38	58
14-Day Old Survivors/Set (%)	49	36	37	56
Hatchlings/Max. Set (%)	33	26	29	39
14-Day Old Survivors/Max. Set (%)	32	25	28	38

Reference: **Beavers, J.B., Corbitt, A., Hawrot, R. Et Al (1990 b). A one-generation reproduction study with the bobwhite (*Colinus virginianus*).**

TABLE 3

REPRODUCTIVE DATA - BOBWHITE

DIFLUBENZURON - PROJECT NUMBER 225-102

	DIFLUBENZURON			
	0 PPM	250 PPM	500 PPM	1000 PPM
Eggs Laid	595	459	674	489
Eggs Cracked	23	35	31	31
Eggs Set@	507	363	571	398
Viable Embryos	433	330	539	340
Live 3-Week Embryos	427	325	536	338
Hatchlings	391	312	505	314
14-Day Old Survivors	342	270	468	271
Eggs Laid/Hen	40	35	42	33
Eggs Laid/Hen/Day @@	0.55	0.49	0.59	0.45
14-Day Old Survivors/Hen	23	21	29	18

@ - Eggs laid minus eggs cracked, eggs taken for shell thickness, abnormal eggs and eggs inadvertently damaged.
@@ - Based on 72 days.

TABLE 3A

REPRODUCTIVE DATA - (MEAN %^) - BOBWHITE

DIFLUBENZURON - PROJECT NUMBER 225-102

	DIFLUBENZURON			
	0 PPM	250 PPM	500 PPM	1000 PPM
Eggs Laid	595	459	674	489
Eggs Laid/Max. Laid (%)	65	58	69	53
Eggs Cracked/Eggs Laid (%)	4	8	5	5
Viable Embryos/Set (%)	86	88	95	89
Live 3-Week Embryos/Viable (%)	98	99	99	98
Hatchlings/3-Week (%)	92	89	94	92
14-Day Old Survivors/Hatch (%)	88	86	93	86
Hatchlings/Set (%)	79	77	89	80
14-Day Old Survivors/Set (%)	68	66	83	69
Hatchlings/Max. Set (%)	47	43	56	37
14-Day Old Survivors/Max. Set (%)	41	37	52	32

^ = Mean % values from Appendix VII.
The above differences from the control are not statistically significant.

TABLE 4

EGG SHELL THICKNESS DATA - (mm)

BOBWHITE

DIFLUBENZURON - PROJECT NUMBER 225-102

	DIFLUBENZURON			
	0 PPM	250 PPM	500 PPM	1000 PPM
No. of Eggs Measured	59	51	67	54
Mean Egg Shell Thickness (mm)	0.207	0.212	0.210	0.213
± standard deviation	± 0.011	± 0.011	± 0.008	± 0.013

The above differences from the control are not statistically significant.

TABLE 5

BODY WEIGHT DATA (g) - HATCHLINGS

BOBWHITE

DIFLUBENZURON - PROJECT NUMBER 225-102

		DIFLUBENZURON		
	0 PPM	250 PPM	500 PPM	1000 PPM
No. of Chicks Weighed	391	308	505	314
Mean Body Weight (g)	5.7 ± 0.5	5.9 ± 0.5	5.9 ± 0.4	5.9 ± 0.6

The above differences from the control are not statistically significant.

TABLE 5A

BODY WEIGHT DATA (g) - 14-DAY SURVIVORS

BOBWHITE

DIFLUBENZURON - PROJECT NUMBER 225-102

		DIFLUBENZURON		
	0 PPM	250 PPM	500 PPM	1000 PPM
No. of Chicks Weighed	342	270	468	271
Mean Body Weight (g)	23 ± 2	23 ± 2	22 ± 2	22 ± 2

The at

B.9.1.5 Risk assessment birds

Point of clarification 5.1:

EFSA requested an assessment for the risk for birds resulting from consumption of contaminated drinking water and this is given below. The risk assessment for exposure via drinking water was carried out in accordance with the SANCO/4145/2000 guidance.

Exposure via drinking water; Orchards:

The concentration in drinking water that birds may be exposed to was considered to be equal to the PEC_{SW}. Hence the $PEC_{DRINKING\ WATER}$ was assumed to be 15.7 µg a.s./L (Step 2, FOCUS calculation) and the total water ingestion rate for a small bird was calculated as $0.059*bw^{0.67}$ (=0.0027 L/day). The daily dose of diflubenzuron was calculated as $PEC_{DRINKING\ WATER}$*total water ingestion rate/bw (= 4.23 µg/kg d) which was compared to the acute LD_{50} > 5000 mg/kg bw and the long term NOEC of 42.7 mg as/kg bw day, resulting in a TER_{ACUTE} of 1182033 and a $TER_{LONG\ TERM}$ of 10000, which both are above the Annex VI triggers.

Assuming that birds would drink from puddles formed following hand- or tractor mounted spraying in the field during summer months the PEC $_{\text{Drinking Water}}$ was calculated to be 0.024 g a.s./L, assuming a dilution factor of 5. The daily dose of diflubenzuron was calculated as PEC $_{\text{DRINKING WATER}}$*total water ingestion rate/bw (0.024*0.0027/0.01=) which was compared to the acute LD_{50} of > 5000 mg as/kg bw, resulting in a TER of 772 which is considered acceptable given that the annex VI trigger is 10

Exposure via drinking water Forest:
For the aerial application the RMS used the PEC_{SW} as calculated by the RMS in the DAR, i.e. 5.31 µg/L as an estimate of the PEC $_{\text{DRINKING WATER}}$. The PEC_{SW} of 1.28 µg/l was used for the hand held application. For the tractor mounted application no estimate was available, but it is considered that the drift rate used for calculating aerial application, i.e. 33.2 % is protective for this application.

The total water ingestion rate for a small bird was calculated as $0.059*bw^{0.67}$ =0.0027 L/day. The daily dose of diflubenzuron was calculated as PEC $_{\text{DRINKING WATER}}$*total water ingestion rate/bw (1.28*0.0027/0.01 and 5.31*0.0027/0.01 µg/kg bw d, for the hand held and aerial application, respectively). This was compared to the acute LD_{50} > 5000 mg/kg bw and the long term NOEC of 42.7 mg as/kg bw day, resulting in a TER_{ACUTE} of 16666667 and a TER $_{\text{LONG TERM}}$ of 142333 for the hand held application, and for TER_{ACUTE} 3571428 of and a TER $_{\text{LONG TERM}}$ of 30500 for the aerial application. Hence the risk for birds resulting from drinking surface water is low as all TER are above the Annex VI triggers.

Assuming that birds would drink from puddles formed following hand- or tractor mounted the $PEC_{DRINKING\ WATER}$ was calculated to be 0.016 g a.s./L, assuming a dilution factor of 5. The daily dose of diflubenzuron was calculated as PEC $_{\text{DRINKING WATER}}$*total water ingestion rate/bw (0.016*0.0027/0.01) which was compared to the acute LD_{50} of >5000 mg as/kg bw, resulting in a TER of 312 which is considered acceptable given that the annex VI trigger is 10. Exposure via drinking contaminated water from leaf axils or puddles has not been considered for aerial applications for forests. The mix volumes of spray applied per hectare for the ultra-low volume or high volume aerial applications are 3 and 40 L, respectively. Given that these application volumes result in rates of 0.3 or 4 mL/m^2 it is unlikely that sufficient spray liquid will be available to form puddles either on the ground or in leaf axils.

B.9.2 Effects on aquatic organisms

B.9.2.3. Aquatic Risk assessment for metabolites CPU and DFBA.

Open point 5.8:

Risk of bio-concentration of metabolites CPU and DFBA

The log Pow of CPU is 1.14 and of DFBA -0.02 (this information will be included in an addendum to B.2.), hence the risk of bio-concentration of these metabolites is low.

B.9.2.5 Risk assessment for aquatic organisms

Open point 5.7 and 5.15:

In the DAR it was suggested that the EAC for aquatic risk assessment should be 0.07 µg/L. This was based on a microcosm study (Moffett et al. 1995. Effects, persistence and distribution of diflubenzuron in littoral enclosures, see the DAR), in which a NOAEC for zooplankton could be determined to 0.7 µg/L, and it is further supported by information in a literature review in a weight of evidence approach. The RMS applied a safety factor of 10 on this NOAEC to obtain an EAC since sufficient information on the sensitivity of other aquatic invertebrates than zooplankton not could be derived from the studies. The abundance of amphipods was affected at the lowest concentration (0.7 µg/L) and aquatic insect were not abundant enough for a conclusion to be made on their sensitivity in the littoral enclosure study. The notifier did not agree to this conclusion and submitted a literature review (Risk assessment of diflubenzuron on aquatic organisms with particular emphasis on aquatic invertebrates. Pijst and Wyness, January 2005) in which it was suggested that the EAC should be 13.6 µg/L. The RMS did not consider that the information in the literature review was sufficient for such a conclusion and maintained the EAC of 0.07 µg/L, for argumentation see the DAR.

In the updated summary dossier the notifier argues for an EAC of 0.7µg/L and to support this conclusion they have submitted another literature review, i.e. 'Crompton Europe B.V. proposal for an ecologically acceptable concentration (EAC) in the Draft Assessment Report for diflubenzuron.' by Wyness and Pijst (June 2005). In this literature review the same studies, except for one study, as in the previous literature review (Risk assessment of diflubenzuron on aquatic organisms with particular emphasis on aquatic invertebrates. Pijst and Wyness, January 2005) is cited and the evaluation of these studies is not repeated in the addendum but can be obtained from the DAR. However, in order to provide a transparent assessment the notifiers arguments for an EAC of 0.7 µg/L as well as the notifiers summary of the newly submitted paper is reproduced below.

Furthermore during the commenting round (rep. tab 5(25)) the RMS was asked to clarify the weight of evidence approach used to conclude an EAC of 0.07 µg/L this is done in the RMS discussion section below.

Reference:	**L. Wyness and H.L.A. Pijst (2005). Crompton Europe B.V. proposal for an ecologically acceptable concentration (EAC) in the Draft Assessment Report for diflubenzuron. Performing Laboratories: Crompton Europe B.V. and TSGE**
	The fate and behaviour of diflubenzuron in the aquatic environment indicates that recovery of impacted invertebrate populations will recover The rapid dissipation of diflubenzuron from the water column (1.1 to 3.2 days) and the rapid microbial decay of residues in the sediment (half-life in entire water/sediment systems of 3.4 to 25 days) must lead to a conclusion that following entry to surface waters, diflubenzuron will fall to below toxic threshold levels within a period of about one month. Thus, any resting stages of aquatic invertebrates present in the contaminated waterbody area when hatched will not be affected. Adults or juveniles, which migrate from outside of the waterbody or from refugia within the waterbody, will not be exposed to toxic threshold levels of diflubenzuron and so population recovery can occur. The field data support this hypothesis (in particular see Ali et al., 1988). Thus, from a theoretical standpoint, aquatic invertebrates, which are capable of movement within and out exposed waterbodies, or capable of movement from uncontaminated waterbodies or have adult or resting stages lasting longer than a

few days, will be able to re-populate in a previously exposed waterbody.

Reassurance can be achieved for recovery of impacted populations between seasons given that diflubenzuron does not accumulate in the water column or sediment.

The biology (life cycle) and mode of action of diflubenzuron would suggest that amphipods and other aquatic invertebrates are less likely to be as sensitive as the Cladocera

Comprehensive field data on the sensitivity and recovery of amphipods are absent. This indicates that amphipods were not present as dominant fauna in the waterbodies under investigation in the various field studies. In accordance with the guidance in support of 91/414/EEC, the CLASSIC workshop recommendation was that 'Structural and functional endpoints are generally equal in importance.' Key ecological process such as the decomposition of organic matter, which is a process that some key amphipod species undertake, are often maintained even when effects occur on structure (e.g. rotifers are relatively insensitive to diflubenzuron and so will continue to contribute to decomposition processes). In all of the eight field studies used in support of Annex I listing of diflubenzuron, amphipods were never dominant (nor were any significant effects observed in one study in which they were present).

Despite a lack of comprehensive field data an informed judgement can be made on the likelihood of impact and recovery of amphipods following exposure of waterbodies to diflubenzuron.

The mode of action of diflubenzuron is such that any exposed invertebrate with a cuticle and with moulting stage is very likely to be affected. In the study by Colwell and Schaefer (1980), the reduction in copepod densities in treated ponds were of lesser magnitude and of shorter duration than cladoceran reductions. Cladocerans moult (synthesising chitin) in all life stages, whereas copepods do not moult after reaching the adult instar. Some adult (non-moulting) copepods can live for more than three weeks and so these individuals will provide a reservoir group until the levels of diflubenzuron decline to below toxic threshold concentrations. This argument can be extended to amphipods. Different amphipod species have different life-cycle processes. Some freshwater amphipods may lay eggs only once per season. Others may lay eggs during each of the last five or six instars (e.g. gammarids). Moulting may begin shortly after hatching and continue through to maturity, although as amphipods increase in size, moulting usually slows to once every 20 to 30 days. The average instar lasts 15 days (U.S. Fish and Wildlife Service, January 1989). The high potential reproductive capacity of gammarids, with rapid production of numerous successive broods when sexual maturity is finally achieved, indicates adaptation to high mortality during relatively long periods of growth to sexual maturity. This provides scope for an opportunistic strategy of emigration from centres of population abundance to colonise new territory when conditions are favourable. So, not only would adult, non-moulting adults be unaffected there would also be sufficient numbers of unaffected individuals or unhatched eggs in and outwith contaminated areas to ensure recovery of affected populations following the rapid dissipation of diflubenzuron from the water column. The Cladocera with more continuous moulting but rapid reproduction would be expected to be affected, but would also be expected to recover, and this is substantiated from numerous field studies.

In summary, there is no scientific basis for assuming that amphipods will be more sensitive to cladocerans and there is no basis for assuming that recovery would not occur. In two studies, the littoral enclosure study and that of Kingsbury et al. (1987) amphipods were present but were caged, thus preventing any opportunity for recovery. Therefore, coming to an overall conclusion on amphipod recovery has shortcomings if based solely on these two studies.

Alternative EAC proposal

An EAC of 0.07 µg/L would have to be reconciled with recovery of sampled invertebrate taxa from three outdoor studies following exposure at concentrations of diflubenzuron approximately x 180 higher and in other studies at concentrations at least x10 higher.

A ten-fold safety factor in the context of higher-tier data and assessments is very large and would indicate fundamental or substantial unresolved concerns. For diflubenzuron, the DAR points to concerns of amphipods and their recovery. The contribution of amphipods in aquatic community is arguable, based on the sampled invertebrates from field studies and indirect evidence points to recovery potential. Direct field evidence exists and is not ideal, but is supportive of the indirect evidence.

The EAC, at the very least, may be set at 0.7 µg/L, accepting that recovery has been demonstrated in different aquatic environments at concentrations x18 this initial maximum concentration.

A final judgement on an EAC value which protects aquatic environments can be decided by expert groups (e.g. EPCO) in the context of the EU evaluation procedure for leading to the Annex I inclusion of diflubenzuron.

Colwell and Schaefer (1980) - not previously submitted to RMS

Of nine experimental ponds of 0.01 ha and depth 1.2m, five were treated once with diflubenzuron, resulting in a mean measured initial concentration of 13.2 µg/L (1 hour post-treatment). Fish were present in the ponds (study objective was to assess changes in fish diets).

The cladoceran (5 genera) densities were reduced in the treated ponds by > 99% compared to pre-treatment levels. Recovery of cladocerans was observed after 4 weeks and returned to pre-treatment levels after 5 weeks. Copepod reductions in treated ponds were observed but were less so than cladocerans and recovery was more rapid. Rotifers were unaffected by treatment. The odonate and chironomid benthic invertebrates declined in treated ponds by about 35% to 47% then increased by day 14 to 16. However, these changes were also observed in the controls and the changes may not have been due to treatment. Gastropod densities decreased by 86% in the first 8 days but natural variation precluded statistical interpretation of impact. Oligochaetes were unaffected. The authors also comment on the failure of an organism to reappear in a specific pond, after impact by diflubenzuron. They quote an example for *Daphnia sp*., where recovery was not observed in one pond but was observed in another similarly treated pond. This was speculated to be due to a lack of chance re-introduction, lack of pre-treatment ephippia, variable predator abundance or other non-treatment related factors.

With respect to the question of sensitivity and recovery:

- Under experimental conditions of enclosed ponds the most sensitive invertebrates, the Cladocera recovered within a 5 week period after exposure to levels of diflubenzuron which reduced their population densities by more than 90%;
- The Cladocera were the most sensitive invertebrates sampled.

Collwell, A.E., Schaefer, C.H., 1980. Diets of *Ictalurus nebulosus* and *Pomoix nigromaculatus* altered by diflubenzuron Can.J.Fish.Aquat.Sci., 37, 632-639

RMS comments:

The RMS agrees that the fate property of diflubenzuron indicates that the concentration following contamination likely will fall below toxic threshold levels within a period of about one month. The notifier therefore claims that aquatic invertebrates which are capable of movement within andout of exposed water bodies or have resting stages lasting longer than a few days will be able to re-populate a previously exposed water body. The RMS agrees that this is possible (but this is true for all pesticides which are not persistent), however the important question is if recovery occur within an acceptable period of time. Since many species of aquatic insects are univolatine and often have synchronised life cycles the RMS considers that there is a risk of long lasting effects on such species if exposure occurs during a sensitive stage. The RMS considers that not enough information was provided by the notifier to resolve this concern. The RMS agrees that insects that are not in a moulting stage will likely be less severely affected by exposure to diflubenzuron as argued by the notifier for e.g. gammarids. However, since aquatic insects species may have synchronised lifecycles it is possible that a large proportion of a population in an aquatic ecosystem will be in a sensitive stage and thus affected by exposure.

The notifier claims that the function of amphipods and aquatic insects in aquatic ecosystems can be maintained by other organisms not sensitive to diflubenzuron, e.g. rotifers. However, rotifers do not occupy the same ecological niche as amphipods or as aquatic insects, which shred much larger particles than rotifers.

The notifier also claims that there is no basis to assume that amphipods will be more sensitive than cladocerans to diflubenzuron exposure. However, the RMS does not consider that the information provided in the literature reviews clearly shows that they are not. Furthermore, the concern is not only for amphipods but also for aquatic insects. The RMS agrees that the study by Colwell and Schaefer (1980) indicates that recovery of zooplankton is possible 6-8 weeks after exposure to a relatively high concentration of diflubenzuron (average in water column after 24 h 5.5-8.7 µg/L). This study also indicated that the chironomids and odonate larvae in the treated ponds were less sensitive compared to the cladocerans. However, effects on aquatic arthropod invertebrates may have been obscured due to the presence of fish in the ponds.

RMS discussion of EAC

In the reporting table the RMS was asked by other memberstates to clarify the weight of evidence approach used to conclude an EAC of 0.07 µg/L. A rational for the EAC of 0.07 µg/l is given below, references and further details can be found in the DAR:

The study by Berends and Laan (1994) indicates that the toxicity of diflubenzuron to zooplankton (i.e. *D. magna*) likely will disappear after a period of days-weeks in the water column of natural systems. Hence, under field conditions there is a potential for recovery of zooplankton from unexposed refugia after a period of days-weeks.

The results presented in the tables from the study by Ali and colleagues (1988) shows that no large decrease in the abundance of zooplankton occurred due to treatment (measured 0.197 µg diflubenzuron /L) in a pond. However, the study has several drawbacks, e.g. there were large

differences in the shape of the control and treatment pond and the treatment was not replicated. Nevertheless, the RMS considers that the study can be part of a weight of evidence approach.
Even though no full recovery of zooplankton occurred in the study by Mulla and colleagues (1975) it indicates that there is a potential for recovery following exposure since the numbers of cladocerans and copepods increased the two last sampling occasions (11 and 15 days after exposure) at both exposure concentrations (i.e 6.8 and 13.6 µg/L). Also the newly cited study by Colwell and Schaefer (1980), see above, shows that recovery of zooplankton is possible within a month following exposure.

The RMS considers that these studies taken together with the results from the littoral enclosure study can be used in a weight of evidence approach to indicate that there is a potential for recovery of zooplankton following exposure to 0.7 µg/l (and possibly also following higher exposure concentrations) depending on availability of unaffected populations/life-stages as source of recolonistation and that this line of evidence can be used to support a NOAEC for the zooplankton community of 0.7 µg/L. However, uncertainty regarding the risk for the aquatic arthropod community remains and hence a safety factor is needed on the zooplankton NOAEC in order to obtain an EAC which also covers the insect community. The magnitude of this factor should be discussed at an expert meeting. However, the RMS considers that a similar factor as would be applied on a single species Daphnia test is warranted in order to account for the variation in species sensitivity since the notifier has not provided information which resolve the uncertainty regarding the sensitivity of the aquatic arthropd community. Hence, the RMS considers that a factor of 10 is appropriate even if higher tier data from microcosms and field studies are available.

Furthermore, the RMS performed a none comprehensive literature search of the open literature and found articles on the effects of diflubenzuron on aquatic organisms which were not cited in the literature review by the notifier. For example in one study (Harray et al. 1994) on the toxicity of diflubenzuron to mayflies (mainly *Cynygmula subaequalis)* it was found that the mortality following exposure to 0.6 µg/l was 45%. The mortality was measured after 96 hours of exposure and 32 days in clean water conditions which is necessary for a species with a long lifecycle given the mode of action of diflubenzuron. The acute toxicity (48-h EC_{50}) to *Daphnia* was 2.6 µg/L (Groeneveld et al 1995, see the DAR), indicating that mayflies may be more sensitive to diflubenzuron compared to cladocerans.
Following exposure of indoor complex laboratory streams to nominal 1 µg diflubenzuron/L (continuous exposure, two replicates per treatment level) Hansen and Garton (1982) found that the insect fauna suffered from

direct toxic effects. Several species of Ephemeroptera and Plecoptera were eliminated following exposure to 1 µg/L at the first sampling occasion which occurred 1 month after treatment. The treatment in this study can be considered as worst case since the exposure was continuous. However, since effects were observed already the first sampling occasion the onset of effects may have been rapid. Following treatment of the streams with 0.1 µg diflubenzuron/L no or only slight effects could be observed. Recovery could not be observed in this study since it was conducted under indoor conditions. In a study by Griffith et al. (1996) the emergence of the stonefly *Peltoperla arcuata* decreased during the first 4 months after treatment of the catchments of two streams with 35.1 g diflubenzuron/ha compared to two reference streams. No effects on other aquatic insects were observed in this study the authors however state that this likely was due to that the other shredder species present in their sampling not are obligate leaf feeder but fed on other material during the study period which was conducted before leaf abscission, while *P. arcuata* is an obligate leaf feeder and likely ingested the few leaves that fell into the streams during the study period and therefore was affected. In a study by Satake and Yasuno (1987) effects on the invertebrate community was found following treatment of a stream for one hour with 1.25 mg/L (a relatively high but short exposure) compared to a control, in the study most invertebrates were eliminated within 2 weeks, but effect on *Hydropsyche* were more gradual. The RMS considers that the results from these studies support an EAC of 0.07 µg diflubenzuron/L.

In conclusion, the RMS does not consider that the argumentation provided by the notifier in the updated summary dossier or in the literature review can resolve the uncertainty regarding possible effect on aquatic insects and maintain that a safety factor should be applied to the NOAEC for zooplankton (0.7 µg diflubenzuron/L). The RMS propose that a factor of 10 should be but this need to be discussed at the expert meeting.

References

Harray et al. 1994. The effects of diflubenzuron (Dimilin) on selected mayflies (Heptageniidae) and stoneflies (Peltoperlidae and Pteronarcyidae). Env. Toxicol. Chem. 13:517-522

Hansen and Garton 1982. The effects of diflubenzuron on a complex laboratory stream community. Arch. Environ. Contam. Toxicol. 11:1-10.

Griffith et al. 1996. Effects of aerial application of diflubenzuron on emergence and flight of adult insects. J. Econ. Entomol. 89:442-446

Satake and Yasuno 1987. The effects of diflubenzuron on invertebrates and fishes in a river. Jpn. J. Sanit. Zool. 38: 303-316

B.9.3 Risk assessment mammals

Point of clarification 5.2:

EFSA requested an assessment for the risk for mammals resulting from consumption of contaminated drinking water, as well as for secondary poisoning, and this is given below . The risk assessment for exposure via drinking water was carried out in accordance with the SANCO/4145/2000 guidance.

<u>Exposure via drinking water</u>

Orchards

The concentration in drinking water that mammals may be exposed to was considered to be equal to the PEC_{SW}, i.e. 15.7 µg a.s./L (i.e. PEC_{SW} from Step 2, FOCUS calculation) and the total water ingestion rate for a small mammal (10 g) was calculated as $0.099*bw^{0.90}$ (=0.0016 L/day). The daily dose of diflubenzuron was calculated as PEC drinking water*total water ingestion rate/bw (2.46 µg as/kg bw d) which was compared to the acute LD50 of > 4640 mg/kg bw and to the long term NOEL of 3678 mg as/kg bw day, resulting in a TER_A of 1886178 TER_{LT} 1495000 which are above the Annex VI triggers.

Assuming that mammals would drink from puddles formed field the $PEC_{drinking\ water}$ was calculated to be 0.024 g a.s./L, assuming a dilution factor of 5. The daily dose of diflubenzuron was calculated as PECdrinking water*total water ingestion rate/bw (0.024*0.0016/0.01) which was compared to the acute LD50 of > 4640 mg/kg bw, resulting in a TER of 1208 which is above the annex VI trigger.

Forest

For the aerial application the RMS used the PEC_{SW} as calculated by the RMS in the DAR, i.e. 5.31 µg/L. The PEC_{SW} of 1.28 µg/l was used for the hand held application For the tractor mounted application no estimate was available, but it is considered that the drift rate used for calculating aerial application, i.e. 33.2 % is protective for this application.

The total water ingestion rate for a small mammal was calculated as $0.099*bw^{0.90}$ =0.0016 L/day. The daily dose of diflubenzuron was calculated as PEC $_{DRINKING\ WATER}$*total water ingestion rate/bw (5.31*0.0016/0.01) which was compared to the acute LD50 of > 4640 mg/kg bw and to the long term NOEL of 3678 mg as/kg bw day, resulting in a TER_A of 5461393 and a TER_{LT} 4329096 for the aerial application, TER_A of 22656250 and a TER_{LT} 17958984 for the hand held application, which all are above the Annex VI triggers.

Assuming that mammals would drink from puddles formed following hand- or tractor mounted spraying in the field during summer months the PEC $_{DRINKING\ WATER}$ was calculated to be 0.016 g a.s./L, assuming a dilution factor of 5. The daily dose of diflubenzuron was calculated as PEC $_{DRINKING\ WATER}$*total water ingestion rate/bw (0.016*0.0016/0.01) which was compared to the acute LD_{50} of > 4640 mg/kg bw, resulting in a TER of 1812 which is above the annex VI trigger. Exposure via drinking contaminated water from leaf axils or puddles has not been considered for aerial applications for forests. The mix volumes of spray applied per hectare for the ultra-low volume or high volume aerial applications are 3 and 40 L, respectively. Given that these application volumes result in rates of 0.3 or 4 mL/m^2 it is unlikely that sufficient spray liquid will be available to form puddles either on the ground or in leaf axils.

Secondary poisoning risk assessment

The Log octanol:water partition coefficient of the active substance diflubenzuron is 3.89. Therefore, the potential risks from bioaccumulation in the food chain (i.e. secondary poisoning effects) require an assessment as pointed out by EFSA in their comments to the DAR. The secondary poisoning risk to birds following the use of diflubenzuron is based on an assessment of exposure from the ingestion of earthworms, fish, birds and mammals.

Earthworm-eating mammals

The risk assessment for secondary poisoning was carried out in accordance with the SANCO/4145/2000 guidance. The BCF (earthworm fresh weight to soil dry weight) was calculated to according to the following formula:

$BCF=(0.84 + 0.01\ K_{OW})/f_{OC}\times K_{OC}$,

where K_{OW} = 7762.5 (see B.2.1.8), K_{OC}= 4609 (see B.8.2.1) and a default value of 0.02 for the organic carbon content of soil (f_{oc}) was used. This calculation resulted in a BCF of 0.85.

The estimation of residues in earthworms are based on the following equation:

$PEC_{WORM} = PEC_{SOIL}$ x BCF,

where the PEC_{SOIL} (21-day time-weighted average) is 0.057 mg/kg (see section B.8.3) for use in orchards. The resulting PEC_{WORM} is 0.048 mg/kg following the proposed representative use in orchards. The earthworm residue estimates are converted to a daily dose (mg/kg/bw/day) by multiplication with a factor 1.4, assuming a 10-g mammal eating 14 g per day. This is compared with the long-term NOEL, based on a daily dose. In the case of use in orchards, the TER for earthworm-eating mammals is 54732 (3678/(1.4×0.048). This assessment is protective for uses in forests where the exposure to mammals via earthworms will be less than in orchards since the application rate is lower. Given that the TER value is significantly greater than 5, the risk for secondary poisoning of mammals from the ingestion of earthworms after the representative use of diflubenzuron in orchards and forests is considered to be low.

Fish-eating mammals

The risk to mammals resulting from consumption of fish was assessed in accordance with the SANCO/4145/2000 guidance document. The 21-day time-weighted average PEC in water and the experimentally-determined (whole-fish) bioconcentration factor (BCF) for fish were used to estimate fish residues following the application of diflubenzuron as follows:

$PEC_{fish} = PEC_{sw} \times BCF$,

where the 21-day time-weighted average PECsw values are 1.77 µg/L (see section B.8.6.2) following the application of diflubenzuron to orchards (FOCUS step2), and the whole-body BCF is 320 (see section B.9.2.3.).This calculation resulted in PEC_{fish} values of 0.57 mg/kg. The fish residue estimates are converted to a daily dose (mg/kg/bw/day) by multiplication with a factor of 0.13, assuming a 3000-g mammal eating 390 g fish/day. This value is compared with the long-term NOEL, based on a daily dose. In the case of use in orchards, the TER for fish-eating birds is 49635 (3678/0.13×0.57).

Since no FOCUS simulations was available for any of the PEC for forestry the initial PECsw for aerial application (5.31 µg/L, see section B.8.6.2) was used in the calculations as a worst case. These calculations resulted in a TER= 16650 (3678/(0.00531×320×0.13). Given that the TER values are greater than 5, the secondary poisoning risk to mammals from the ingestion of fish after the use of diflubenzuron in forests is considered to be low.

B.9.4. Effects on bees

B.9.4.2 Cage and field tests

Open point 5.20:

Reference:	**Beuschel, S. (2006). Dimilin WG 80: Assessment of side effects to the honey bee (*Apis Mellifera L.*) In the field following application during bee-flight in germany 2005. Report Gab Biotechnologie GMBH, Germany no. 20051124/g1-bfeu.**
Guideline:	OEPP/EPPO Guideline No. 170 (3); 2001 Bulletin of Insectology 56 (1); 2003
GLP:	Yes

Material and methods:

Test substance:	Dimilin WG-80
Species:	Honey bee (*Apis Mellifera L.*)
Treatments:	Dimilin WG-80 at an application rate of 180 g a.i./ha in 200 L water/ha was applied twice with an interval of 9 days (3 and 9 July) during daily flight activity of the bees and during flowering. An untreated field served as control.
Number of animals:	Four bee colonies for treatment and four for control with 25000-30000 bees per colony.
Duration:	3 July- 19 September
Test conditions:	The size of each test field with flowering of *Phacelia tanacetifolia* was at least 3400 m^2. The colonies were placed at the border of each field before the first application of the test item.
Observations:	Mortality in front of the bee hives and in the field. Flight intensity (number of forager bees/m^2). Conditions of the colonies (strength) and brood development Behaviour of the bees at the entrance of the hives and in the field. The termination rate was calculated as each cell with successful development was titled with a 1 and everyone with an termination with 0. Subsequently, the sum of development was formed and the termination rate was determined as follows: Termination rate [%] = 100 -100 x $\frac{\text{sum of development}}{\text{sum of observed cells}}$
Data analysis	None

Results:

Neither after the first application of the test item nor after the second application an increase of mortality was observed compared to the values observed before application as well as compared to the control up to the end of observation period, see table below. Comparing the values before application to the after application in the test item no decrease of flight intensity was observed neither after the first nor after the second application.

Table 9.4.2.a. Mortality rates and effects on flight intensity of honey bees following exposure to Dimilin WG-80

	Treatment	Control
Average Mortality Rate[dead bees / hive / day]		

Average values for day -3 to 0	3.9	8.1
Day after first application	0.8	1.0
Day after second application	1.5	2.3
Mean value for days 0 – 36 after application	3.1	5.4
Average Flight Intensity [foraging bees/ m²/day]		
Average values for day -3 to 0	3.4	4.4
Day after first application	8.4	10.0
Day after second application	8.3	10.2
Mean value for days 0 – 36 after application	6.1	7.6

By comparing the individual brood assessments of single cells, the indices (the values of the different brood stages of all cells in each hive, assessed at the same date, summed up and divided by the number of observed cells) showed the course to be expected in natural bee development cycle in all four hives of the test item treatment and in three hives of the control treatment at the first observed development period (BFD before first application) and in three hives of the test item and control treatment each at the second observed development period (BFD before second application) and most of the eggs which were marked at the start of the test developed until hatch.

Table 9.4.2.b. Brood indices of the first development period

Treatment	Assessment date				
	BFD	BFD+5	BFD+9	BFD+15	BFD+21
	01.07.05	06.07.05	10.07.05	16.07.05	22.07.05
1T1	1.00	1.86	3.63	3.51	4.36
1T2	1.00	1.98	3.90	3.97	4.90
1T3	1.00	1.97	3.87	4.00	4.87
1T4	1.00	1.90	3.73	3.75	4.65
Mean	**1.00**	**1.93**	**3.78**	**3.81**	**4.70**
STD	0.00	0.06	0.13	0.23	0.25
Treatment	**Assessment date**				
	BFD	**BFD+5**	**BFD+9**	**BFD+15**	**BFD+21**
1C1	1.00	2.41	3.77	3.80	4.77
1C2	1.00	1.59	3.39	3.55	4.18
1C3	1.00	1.98	3.77	3.93	4.63
1C4	1.00	2.02	3.87	3.90	4.76
Mean	**1.00**	**2.00**	**3.70**	**3.80**	**4.58**
STD	0.00	0.34	0.21	0.17	0.28

Table 9.4.2.c. Brood indices of the second development period

Treatment	Assessment date				
	BFD	BFD+6	BFD+12	BFD+16	BFD+22
	10.07.05	16.07.05	22.07.05	26.07.05	01.08.05
2T1	1.00	3.23	3.82	3.82	4.82
2T2	1.00	2.98	3.94	3.94	4.92
2T3	1.00	2.03	2.97	2.97	3.97
2T4	1.00	3.18	3.73	3.73	4.71
Mean	**1.00**	**2.86**	**3.61**	**3.61**	**4.61**
STD	0.00	0.56	0.44	0.44	0.43
2C1	1.00	3.46	3.87	3.88	4.87
2C2	1.00	2.67	2.98	3.01	4.03
2C3	1.00	3.30	3.54	3.56	4.52
2C4	1.00	3.08	3.73	3.79	4.82
Mean	**1.00**	**3.13**	**3.53**	**3.56**	**4.56**
STD	0.00	0.34	0.39	0.39	0.39

The termination rate was in the same range except hive 3 of test item treatment in the second development period (26.52 %) and hive 2 of the control at both development periods. Most of the cells remained empty up to the end of the development period, which resulted in lower brood indices on each assessment date compared to the values of the other hives of the same treatment and development period. The mean termination rate of the test item treatment was in both observed development periods below the level of the control, see below.

Table 9.4.2.d. Termination rate of the first development period

Treatment	1T1	1T2	1T3	1T4
Termination %	13.45	2.40	3.25	8.87
Mean %	6.99			
Treatment	**1C1**	**1C2**	**1C3**	**1C4**
Termination %	5.65	33.06	7.32	7.32
Mean	13.34			

Table 9.4.2.e. Termination rate of the second development period

Treatment	2T1	2T2	2T3	2T4
Termination %	4.62	1.53	26.52	0.0
Mean	8.16			
Treatment	**2C1**	**2C2**	**2C3**	**2C4**
Termination %	4.55	27.69	12.24	7.41
Mean	12.97			

No behavioural differences of the bees in the test item (Dimilin WG 80) treatment group were observed during the entire post-application period neither after the first nor after the second application compared to the bees in the control group.

Comments: The study was well performed and is considered as valid for risk assessment. In this study no adverse effects on honey bees were observed following treatment with diflubenzuron.
However, the RMS notes that diflubenzuron is mentioned as a reference substance in the OECD Draft guidance document on honey bee (*Apis mellifera L.*) brood test under semi-field conditions (February 2006) and consider

that this fact need to be discussed at an expert meeting before the restriction that diflubenzuron should not be applied to flowering crop is removed.

Furthermore , the RMS searched the open literature and found an article by H. Thompson et al. (The Effects of Four Insect Growth-Regulating (IGR) Insecticides on Honeybee (Apis mellifera L.) Colony Development, Queen Rearing and Drone Sperm Production, Ecotoxicology) in which significant effects on honey bees in field were observed following exposure to diflubenzuron. In this study significant effects on brood replacement was observed week 5 and 6 after treatment. There was no significant effect on the development of the brood the following spring but there did appear to be a slower increase in levels of brood compared to controls.

APPENDIX I

Diflubenzuron Step 4 surface water assessment and latest opinion of the Scientific Panel in the EU
Uwe Wanner, MDBY January 18, 2007

History:

After completing Step 1-3 surface water assessment using FOCUS surface water models the obtained highest PECs after the use of Dimilin WG 80 in orchards ranged between 0.915-13.622 µg/L , i.e., all above our own NOEC trigger value of 0.7 µg/L stated in Chemtura's Annex I Dossier. KEMI, the RMS for diflubenzuron, disagreed with the NOEC and added a safety factor of 10 leading to a NOEC of 0.07 µg/L.

Further, KEMI was concerned about the potential effect of surface water runoff which might have a potential effect on the PECs in surface waters (pond, ditch & stream) in the EU.

Therefore, higher-tiered modeling was required. KEMI suggested using the 2004 draft version of the FOCUS report "Lansdscape and Mitigation Factors in Aquatic and Ecological Risk Assessment" (version 1, draft, June 18, 2004). This report includes possible strategies to mitigate factors such as spray-drift and run-off.

I conducted these higher-tiered, initial Step 4 PECs implementing buffer zones of 10m, 20m & 30m and wrote & submitted a supplemental report to the initial PEC surface water report (2004-011) on April 01, 2005.

The inclusion of a 10m-buffer led to the reduction of PECs in pond scenarios below our internal trigger of 0.7 µg/L (0.583-0.631 µg/L). Larger buffer even further decreased the PECs. At this time point the decision was made to submit the additional report, as we felt strongly that we have proven safe scenarios for the inclusion of diflubenzuron into Annex I. Further, the assessment revealed that runoff, which occurs 14 days after the application, only increased the actual concentration in a pond in 1 run-off scenario; however, the amount was even below KEMI's trigger value (0.058 µg/L). Therefore, no mitigation for run-off was necessary.

KEMI insisted in the DAR, that a safety factor of 10 is still necessary. Therefore, KEMI concluded that Chemtura hasn't provided evidence of safe uses as our lowest predicted concentration was still above KEMI's NOEC of 0.07 µg/L.

Further Step 4 assessments

At the same time when I wrote the supplemental report I conducted additional higher-tiered assessments following the draft version of the FOCUS mitigation document. This document was finalized in May 2005. There are certain differences between the draft version I used and the final document; yet, the sections 3.2 "General principles for implementing risk mitigation measures under 91/414" and 3.4 "Risk mitigation for spray drift", I referred to, did not change significantly: "…[Recommendation 2] There is already sufficient evidence to implement certain measures into ecological risk assessment and it is recommended that this is done immediately. Authorisations of products that present unacceptable ecological risk under standard use conditions can be made subject to the application of suitable restrictions ensuring mitigation of the risk. These mitigation measures should be grouped by the extent to which they reduce exposure in the following categories: 50, 75, 90, 95 and 99%..."

"…Three types of mitigation measure are recommended for immediate implementation into the risk assessment. These are the use of no-spray buffer zones, the application of drift-reducing technology and the reduction of exposure using windbreaks… No-spray buffer zones are widely implemented at present and have been successfully incorporated into the risk assessment over several years. Implementation into the risk assessment should continue as at present with the FOCUS drift calculator used to demonstrate the mitigating effect for assessments supporting Annex I listing… Technical solutions to reduce spray drift have advanced significantly over the last 10 years. Drift-reducing nozzles are widely adopted by farmers in some Member States and have been incorporated into the risk assessment. It is recommended that the use of this technology is incorporated into risk assessment at the European as well as Member State level. Specific technologies that are recommended for use include drift-reducing nozzles, air assistance,
tunnel sprayer, shielded spraying, and band spraying. The application of a particular technique can be considered to cause a relative reduction in deposition of pesticide that is selected as a conservative value from the possible distribution of effects. It should be noted that drift-reducing techniques only need to be implemented for applications made in the area of crop bordering the edge-of-field/water body, since drift interception beyond this point reduces drift to insignificant levels. At the European level, it will only be necessary to stipulate the reduction in exposure via spray drift necessary to reduce risk to acceptable levels. The relevant technology can then be applied at Member State level based on classification systems for drift-reducing techniques which already exist in several Member States… [Recommendation 6] It is recommended that the maximum values identified in Table 5 act as an absolute cap for the incorporation of mitigation into risk assessments for Annex 1 listing (more differentiated maxima can be derived on a case-by-case basis according to the use conditions and options for mitigation)…"

Based on these recommendations I calculated the PECs starting with the Step 3 results. The buffer between the orchard trees and the surface water is standardized in Step 3 and basically directly adjacent. Different inflows of the pesticide into the surface water are calculated using the Spray Drift Calculator, PRZM (for potential run-off) and MACRO (for potential drainage). All of these inputs are fed into TOXSWA which calculates the PECs in different surface water scenarios including effects of degradation, water flow etc.

In order to see the effect of buffer zones, the "mass load by spray drift" (mlsd) value in each Step 3 TOXSWA file for each of the 10 orchard scenarios is manually changed. The "mlsd" value is calculated with the Spray Drift Calculator at different buffer zones (10m, 20m, & 30m).

Similarly, the effect of spray drift mitigating equipment (50%, 75%, 90%, 95% and 99% reduction) can be calculated by changing the "mlsd" value accordingly. It turned out, not surprisingly, that, e.g. a reduction of the "mlsd" value by 50% results in a reduction of highest PECs between 50.0-50.1% or a reduction of the "mlsd" value by 99% results in a reduction of highest PECs between 97.6-99.1%. This evaluation of spray-drift reducing equipment involved 5 days of non-stop computing. The end results seemed to be pretty obvious: If the spray drift is reduced by X% the resulting highest PECs are reduced by a similar percentage.

This effect allowed me to quickly evaluate the impact of combinations of buffer zones and spray drift mitigating equipment on the PECs. For example: I combined the reduction of the "mlsd" value based on buffer zones with the range of PEC reductions achieved with equipment mitigation (e.g., effective PEC reduction of 97.6-99.1% in case of a 99% equipment reduction). The results of these assessments are in the Excel file "Landscape & equipment mitigation for buffer zones for different NOEC.xls" and were communicated within Chemtura.

Effect of the opinion by the Scientific Panel on plant protection products

The Panel does not fully agree with the exposure reduction groups of 50%, 75% 90%, 95% and 99%. They suggest that the grouping needs to be done according to real field situations. They consider the 5 given groups as exaggerated and not relevant because it can be different for different kinds of mitigation measure. However, they agree with "Recommendation 3" which basically states that the actual measure to mitigate the risk does not need to be specified on Annex I level. Individual Member States need to decide on national authorizations the exact measure to assure X% of mitigation. So, basically my approach is okay; yet, they don't agree with the %-age groups.

The Panel agrees with the FOCUS statement that spray drift mitigation is generally well established. Further, they agree that mitigating effects such as re-population of surface waters due to interconnected water systems should not be used on a field scale. These effects are true, yet, they are on a more "landscape scale" which is above & beyond the "field scale" used as the basis of risk assessments for Annex I.

The Panel does not agree with the maximum spray drift reduction of 99%, which is considered to be not realistic in the praxis. Instead they suggest that the maximum cap for spray drift reduction should be set to 85%.

Further, the opinion paper states their disagreement on the proposed probabilistic risk assessments, on new scenario development and the catchment scale modeling. All of these are irrelevant in our diflubenzuron Step 4 assessment. I found it interesting that monitoring data can be used as supportive evidence; yet, only when uncertainties are taken into consideration. The Panel is of the opinion that the current state-of-the-art monitoring programs are not supportive as none of them would be able to detect short-term effects caused by short-term peak concentrations of pesticides.

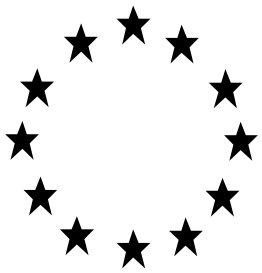
The remaining discussion on GIS based mitigation etc. is once again not relevant for this Step 4 assessment.

Conclusion:

The Panel considers the FOCUS report as a "promising vision for higher tier approaches"; yet, in order to have it implemented as a real guidance document it needs to be revised.

So, de facto, there is currently no guideline on higher-tiered risk assessments for surface water. I still think, that the approach I used is sound and robust; yet, I am pretty sure that KEMI is aware of this position paper and is, therefore, likely to be extremely critical on any higher-tiered assessment derived from the FOCUS document (although they suggested to use it…).

Addendum 2 to
Draft Assessment Report



DIFLUBENZURON

Volume 3
Annex B.6
Toxicology

Rapporteur Member State: Sweden

February 2009

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Volume 1

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New open point 2.7 identified at PRAPeR 64 meeting: Information submitted by the applicant on PCA to be evaluated by the RMS.

RMS has received the following document about 4-chloroaneline (PCA) from the notifier.

Toxicological Evaluation of 4-Chloroaniline[1] (PCA): A Minor Impurity in Technical Diflubenzuron

[redacted]

September 5, 2006

Summary

Diflubenzuron contains 4-chloroaniline (PCA) as a minor impurity. The maximum certified level of PCA in technical diflubenzuron from Chemtura is 30 ppm. PCA does not constitute a toxicological or more specifically a carcinogenic risk as an impurity in Chemtura's technical diflubenzuron.

4-Chloroaniline (PCA) toxicity review

Results of toxicity testing with PCA are publicly available (CICAD, NTP, HSDB). Repeated exposure to PCA leads to cyanosis and methemoglobinemia, followed by effects in blood, liver, spleen, and kidneys, manifested as changes in hematological parameters, splenomegaly, and moderate to heavy hemosiderosis in spleen, liver, and kidney, partially accompanied by extramedullary hematopoiesis. These effects occur secondary to excessive compound-induced hemolysis and are consistent with a regenerative anemia (HSDB, 2006). A variety of *in vitro* genotoxicity tests (Salmonella mutagenicity test, mouse lymphoma assay, chromosomal aberration test, induction of sister chromatid exchange) indicate that PCA is possibly genotoxic, although results are sometimes conflicting. Due to lack of data, it is impossible to make any conclusion about PCA's *in vivo* genotoxicity. No studies are available on reproductive toxicity.

PCA has been tested for its carcinogenic potential in rats and mice. The proposed carcinogenic mechanism of action is that the methemoglobin bound with PCA and similar aniline compounds or their reactive metabolites is broken down in the red pulp of the spleen and the reactive metabolites are released, binding to splenic mesenchymal tissues and resulting in fibrosis, which progresses to the formation of splenic tumors. Another proposed mechanism suggests that the splenic tumors are a result of erythrocyte toxicity. The damaged erythrocytes are scavenged by the spleen, where they cause vascular congestion, hyperplasia, fibrosis, and tumors. Whether the mechanism of carcinogenesis is mediated through genotoxic or non-genotoxic events is not resolved. PCA is genotoxic *in vitro* but appears to be dependent on metabolism for its full expression. There is one positive study *in vivo* (micronucleus test), but this was positive only at a dose level in the range of the LD_{50} (HSDB, 2006). PCA is a threshold carcinogen with clear carcinogenic results in only one animal species, at a dose level exhibiting overt systemic toxicity.

[1] Synonym: parachloroaniline

Critical Review of the U.S. National Toxicology Program (NTP) Carcinogenicity Studies with PCA

Critical assessment of the PCA studies reveal that PCA is weakly carcinogenic upon dietary exposure and these carcinogenic effects in both the dietary and oral gavage studies occur in the presence of excessive toxicity.

NTP concluded that PCA may have carcinogenic potential based on gavage studies in rodents (clear evidence in male rats, equivocal in female rats, some in male mice and no evidence in female mice; NTP, 1989). The levels used in these gavage studies were 0, 2, 6, 18 mg/kg/day in rats and 0, 3, 10, 30 mg/kg/day in mice. There was clear evidence of overt toxicity including methemoglobinemia, including overt cyanosis and extensive non-neoplastic pathology in the spleen at the 6 and 18 mg/kg/day doses in which a clear carcinogenic response was observed in the rat study. Other non-neoplastic findings in the rat chronic study include bone marrow hyperplasia, hepatic hemosiderosis and splenic fibrosis which correlate with the toxic effect of PCA on the hematopoietic system. In B6C3F1 mice administered PCA by gavage, there was an increased incidence of hepatocellular tumors in male mice, and an increased incidence of hemangiosarcomas in the liver and spleen of high dose male mice only. NTP considered that there was "some" or limited evidence of carcinogenicity of PCA for male mice and no evidence for female mice. Basically, the evidence for PCA carcinogenicity is not very strong, with only one sex in one species showing a response considered by the NTP to be "clear" evidence of a neoplastic effect in gavage studies with high and toxic dose levels.

Dietary chronic studies of PCA concluded that sufficient evidence was not found to establish the carcinogenicity of 4-chloroaniline in rats and mice (equivocal in male rats, negative in female rats, equivocal in male mice and equivocal in female mice). These studies support the conclusion that PCA is a relatively weak carcinogen, with equivocal neoplastic effects only in a single target tissue in the presence of extensive non-neoplastic pathology resulting from the primary action of PCA inducing methemoglobinemia. The levels used in the dietary studies were 250 and 500 ppm for rats and 2500 and 5000 ppm for mice (NTP 1979). Dietary studies in rats with PCA at 250 or 500 ppm showed marked non-neoplastic proliferative and chronic inflammatory lesions in the spleens of treated rats, with only a slight non-statistically significant increase in fibromas or fibrosarcomas of the spleen of male rats. Similar equivocal findings were made in mice at dietary dose levels of 2500 and 5000 ppm with non-statistically significant increases in hemangiomatous tumors in the spleen, kidney and other sites. In treated mice there were also significant non-neoplastic proliferative and inflammatory pathologic findings in the spleen. The conclusion from the dietary studies was that there was insufficient evidence to establish the carcinogenicity of PCA.

There are important toxicological and biotranformational (absorption, distribution, metabolism and excretion) differences between gavage and dietary administration of test substances. Although both study designs involve "oral" administration and

digestive absorption, the implications of bolus gavage dosing must be considered in evaluating toxicological studies. The introduction of a bolus dose involves immediate delivery of the full administered dose directly to the stomach. Doses are usually given in the morning, and as rodents are nocturnal and eat in accordance, their stomachs are usually empty. This allows for increased absorption and decreased food interaction (slowing of digestion). In contrast, a dietary study allows the animal a more true to life and applicable administration through the diet with interaction with food and at levels which are not excessive or bolus. Furthermore, bolus administration may overwhelm normal metabolic capacities that are involved in the detoxification reactions. In conclusion, the dietary exposure studies are a more true evaluation of the toxic potential of a test material and are definitely more predictable for the evaluation of PCA in diflubenzuron.

Adequate Testing of PCA Levels in Diflubenzuron

A full toxicological testing package is available for diflubenzuron. Technical diflubenzuron used in our toxicological testing was a typical representative sample, containing 18-19 ppm of the impurity PCA.

Diflubenzuron is not metabolized *in vivo* to PCA, as experimentally demonstrated in the diflubenzuron rat metabolism study (Cameron, 1990). The major urinary metabolite identified in the Cameron study was 4-chloroaniline-2-sulfate. This metabolite is most likely responsible for the formation of methemoglobinemia formation in the diflubenzuron study, since components of this type (ring halogenated/hydroxylated anilines) are known methemoglobin producers (Kiese, 1974).

The testing results of technical diflubenzuron further demonstrated that the test substance is not overtly toxic, is not mutagenic, is not a reproductive or developmental toxicant and is not carcinogenic when tested up to 10,000 ppm in dietary studies with rats and mice. Diflubenzuron is considered a category E substance by the US EPA for carcinogenic classification. The European Agency for the Evaluation of Medicinal Products - Veterinary Medicines (EMEA, 1999) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) reached similar conclusions in their most recent re-evaluation of diflubenzuron's toxicological data package (WHO, 2002).

As mentioned above, this toxicological data set for diflubenzuron was generated with test material containing PCA at 18-19 ppm. Therefore, PCA was tested experimentally through the whole diflubenzuron toxicology package. The risk of exposure to trace levels of PCA in DIMILIN® has therefore been adequately assessed through testing and is experimentally demonstrated not to be toxic, mutagenic or carcinogenic!

In addition, the previous review of PCA demonstrates that PCA is only a toxicological concern at overtly toxic levels, which is clearly not the case at the levels present in diflubenzuron. The results of our testing have demonstrated the low toxicity of diflubenzuron.

Conclusion

PCA has not been shown to be a strong carcinogen, and the carcinogenicity of PCA is clearly established to occur only in the presence of extensive non-neoplastic damage to the hematopoietic system. There is a critical threshold of PCA exposure below which toxic responses do not occur. It is clear that at low doses of PCA, for example at the level present as an impurity in technical diflubenzuron (max. 30 ppm), there is no evidence of adverse toxicological effects, as demonstrated by the favorable diflubenzuron toxicity profile.

Therefore, at the levels present in diflubenzuron, PCA is not considered to be a carcinogenic or toxicological concern.

References

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6. Kiese, M. 1974 Methemoglobinemia: A Comprehensive Treatise pp. 80-83.

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http://www.emea.europa.eu/pdfs/vet/mrls/062199en.pdf

Evaluation of the document by RMS and some additional information of diflubenzuron metabolites:

The metabolic fate of diflubenzuron has been studied in various species. The major route of metabolism in mammals is via hydroxylation. The major metabolites in sheep, swine, and chickens are 2,6-difluorobenzoic acid and 4-chlorophenylurea (CPU); minor metabolites are 2,6-difluorobenzamide and 4-chloroaniline (PCA). In rats and cattle, 80% of the metabolites are 2,6-difluoro-3-hydroxydiflubenzuron, 4-chloro-2-hydroxy-diflubenzuron and 4-chloro-3-hydroxydiflubenzuron. The metabolic studies indicate that little or no 4-chloroaniline is formed in rats or cattle.
No human studies on the kinetics and metabolism of diflubenzuron, including the extent of biotransformation to 4-chloroaniline, are available. However, 4-chloroaniline has been reported to cause methaemoglobinaemia in exposed workers and in neonates inadvertently exposed. Some individuals who are deficient in NADH-methaemoglobin reductase may be particularly sensitive to 4-chloroaniline and, hence, to diflubenzuron exposure (ref 1). The tolerable intake of PCA has been set to 2µg/kg bw and day (ref 2)

In the toxicological studies in the diflubenzuron dossier similar effects are seen as in studies with PCA (e.g. methemoglobinemia, effects of blood parameters, increased spleen and liver weight, haemosiderosis in spleen, liver and kidney and extramedullary hematopoiesis.
With the existing information it is impossible to know if the effects seen in the diflubenzuron studies are due to the PCA contamination in the used diflubenzuron (maximum 30ppm but in the five batch analysis 18-19 ppm) or due to metabolism of diflubenzuron to PCA, although under the detection limit (0.4ppb) in the Wang et al rat study, or due to the major urinary metabolite 4-chloroaniline-2-sulfate (suggested by the notifier). It is possible that PCA is formed but quickly metabolised to metabolites that react with the erythrocytes. N-hydroxylation seems to be the critical enzymatic step that forms the metabolite that causes methemoglobinemia (which is the case for PCA and the similar compound aniline). If also 4-chloroaniline-2-sulfate can be metabolised by N-hydroxylation is unknown.

In the PCA studies discussed in the notifier's statement paper the carcinogenic potential seems to be slightly higher in the gavage than the feeding studies. The notifier has compared the carcinogenic potential between gavage and feeding studies and concludes that "the dietary studies are a more true evaluation of the toxic potential a test material and are definitely more predictable for the evaluation of PCA". RMS does not agree with this statement as PCA has been found to be unstable in feed (ref 3) and the animals in the feeding study thereby might have received a lower concentration then expected.
Anyhow, PCA has to be regarded as a carcinogen as it has been classified according to Directive 67/548/EEC as Carcinogen Cat 2; R 45 (May cause cancer) T; R 23/24/25 (Toxic by inhalation, in contact with skin and if swallowed) R43 (May cause sensitization by skin contact).

In the five batch analysis the content of PCA in the batches of diflubenzuron used was 18-19 ppm. The Notifier therefore concludes that PCA was tested experimentally through the whole diflubenzuron toxicology package. This would have been true if we had known that the content of PCA was 18-19 ppm in all the batches used but

this information is not available. The concentration of PCA could have been lower in some of the batches for example.

Conclusion

PCA has to be regarded as a carcinogen and it can not be excluded that PCA is formed in humans exposed to diflubenzuron. Diflubenzuron is metabolised differently in different mammalian species; rats and cows being similar (less toxic route) and swine, hen and sheep being similar (more toxic rote). PCA has to be considered as a metabolite of toxicological concern.

4-chlorophenylurea, CPU

EPA has previously concluded that "CPU by association with PCA has carcinogenic potential and the same carcinogenic potency as PCA. In the NTP report of the PCA bioassay, it is proposed that PCA undergoes N-hydroxylation to form the corresponding N-hydroxylamine metabolites. This metabolite is then conjugated to form the ultimate carcinogen capable of ionizing and reacting with DNA to form adducts which results in splenic tumor formation. An alternate mechanism involving toxicity resulting in erythrocyte damage, splenic scavenging, hemorrhage, hyperplasia and fibrosis and ultimately splenic tumor formation is also proposed, but both mechanisms are based on the formation of N-hydroxy PCA." However, in more recent rat studies (both dietary and gavage), it has been demonstrated that CPU does not induce methemoglobin formation and is neither metabolised to PCA nor forms an N-hydroxylamine derivate. Since N-hydroxylation is the required first step in mechanism of action of PCA's carcinogenicity, it can be concluded that CPU's mechanism of action and toxicity is different from that of PCA's (ref 4). Moreover, Significant levels of CPU was observed in the urine from rats (DAR B.6.1.2). Therefore the toxicity CPU is covered by the diflubenzuron toxicity packet.

DFBAM, 2,6-difluorobenzamide and DFBA, 2,6-difluorobenzoic acid

Significant levels of 2,6-difluorobenzoic acid and 2,6-difluorobenzamide and were observed in the urine from rats (DAR B.6.1.2). Therefore the toxicity of these two metabolites is covered by the diflubenzuron toxicity packet.

References

1) IPCS, Health and Safety Guide No. 99, World Health Organization, Geneva 1995
2) IPCS, CICADS 48, 2003, 4-Chloroaniline
3) IPCS, CICADS 48, 4-Chloroaniline, 2003
4) EPA, Federal register, Dec 14, vol. 66, Number 241, 2001: Notice of filing pesticide petitions to establish a tolerance for a certain pesticide chemical I or on food.

B.6.14 Exposure data (Annex IIIA 7.2)

Dimilin WG-80 is a water-dispersible granular (WG) formulation containing 800 g diflubenzuron/kg recommended for use in pome fruit, mushrooms and forestry. Dimilin WG-80 is applied to pome fruit by tractor-mounted or hand-held spray equipment, to mushrooms by hand-held spray equipment or automatic sprayer, and to forestry by aerial application. A summary of the application methods and the recommended "worst case" application rates are provided in the following table:

Table B.6.14-1: Summary of application methods and rates of Dimilin WG-80 relevant for the operator exposure assessment

Field of use	Method of application	Max. application rate	Spray volume	Max. application concentration
Pome fruit	Tractor-mounted sprayer; spray directed upwards and sideways	180 g a.s./ha	1 500 L/ha	0.12 g a.s./L
	Hand-held sprayer; spray directed upwards and sideways			
Forestry	Aerial application - ultra low volume (ULV)	48 g a.s./ha	3 - 5 L/ha in oil	16 g a.s./L
	Aerial application - low volume (LV)		30 - 50 L/ha in water	1.6 g a.s./L
Mushrooms	Automatic sprayer	1 g a.s./m^2 (=10 000 g a.s./ha)	1 - 1.5 L/m^2	1 g a.s./L
	Hand-held sprayer; high volume spray directed downwards			

B.6.14.1 Operator exposure

B.6.14.1.1 Estimation of operator exposure in orchards

Estimation of operator exposure in orchards using UK POEM and the German model

The estimates of total diflubenzuron exposure predicted by UK POEM[7](Predictive operator exposure model) and the German model[8] were calculated as a proportion of the proposed AOEL for the active ingredient. Two different application techniques are used: Tractor-mounted sprayer (spray directed upwards and sideways) and hand-held sprayer (spray directed upwards and sideways).

Additional assumptions/data utilised in the models are as follows:

Area Treated in One Day:	15 ha/day (UK model) or 8 ha/day (German model) for tractor-mounted sprayer 1 ha for hand-held treatment
Application Rate:	180 g as./ha

[7] *Scientific Subcommittee on Pesticides and British Agrochemicals Joint Medical Panel., Estimation of Exposure and Absorption of Pesticides by Spray Operators (UK MAFF) 1986 and the Predictive Operator Exposure Model (POEM – UK MAFF) 1992*

[8] *Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem, no. 277, 1992*

Inhalation Exposure for Mixer/Loader:	0.01 ml/hr
Application Volume – Groundboom Application:	1 500 l/ha
Inhalation absorption	100%
Dermal absorption	6 %

Tractor-mounted and hand-held sprayer in orchards

The estimated operator exposure values for tractor-mounted sprayer and hand-held sprayer in orchards, determined on the basis of the model scenarios without or with minimum acceptable protective clothing, were set out in Table B.6.14.1.1-1. Systemic exposure was taken into consideration in relation to the AOELsystemic. Total systemic exposure was calculated from the addition of dermal and inhalation exposure (see also calculation in Appendix 1, A-H).

Table B.6.14.1.1-1: Estimations of operator exposure to Dimilin WG-80 and comparison in relation to the systemic AOEL in orchards

DIMILIN WG-80		
Tractor-mounted sprayer		
PPE	**Operator total exposure (**mg kg^{-1} bw day^{-1}**)**	**% of AOEL[1)]**
	UK POEM	
Without	0.0415	**125 %**
With gloves during mixing and loading and during spraying	0.0219	**66 %**
	German model	
Without	0.0172	**52 %**
With gloves during mixing and loading and during spraying	0.0139	**42 %**
Hand-held sprayer		
PPE	**Operator total exposure (**mg kg^{-1} bw day^{-1}**)** **UK POEM**	**% of AOEL[1)]**
Without	0.0401	**121 %**
With gloves during mixing and loading and during spraying	0.0063	**19 %**
	German model	
Without	0.0103	**31 %**
With gloves during mixing and loading and during spraying	0.0055	**17 %**

$AOEL_{sys}$=0.033 mg kg^{-1} bw day^{-1}; Dermal exposure 6%

Conclusion:

The modelling data based on UK POEM and the German model for tractor-mounted spraying in orchards showed that the exposure to diflubenzuron is acceptable if gloves are used during mixing and loading and during spraying, 66 % (UK-model) and 42 % (German model) of the AOEL. The exposure during hand-held spraying is also acceptable if gloves are used during mixing and loading and during spraying, 19 % (UK-model) and 17 % (German model) of the AOEL.

B.6.14.1.2 Estimation of operator exposure in forestry

The scenario for application Dimilin WG-80 in forestry is either by aerial application using fixed-wing aircraft or helicopters with enclosed cockpits or by ground application by tractor-mounted or hand –held spray. All the applications are done by specialist companies who are licensed by local government bodies. The intended use of Dimilin WG-80 in forestry is dependent on the biological cycle of the pest but no more than one application per crop and year. The applications are made in spring or autumn. Treatments are not sprayed routinely but if an infestation of the pest is present. For aerial application separate operators do the mixing/loading and the applications.

Aerial application by aircraft or helicopter

Mixing and loading is done in the same way as for applications by tractor-mounted equipment. The appropriate weight of product is mixed with the required volume of water for low volume (LV) applications or with water plus mineral oil or crop oil for ultra-low volume (ULV) applications. Sufficient product is mixed to apply up to 200 ha per flight.

Applications by air are generally made in early morning (four to five hours spraying time) and/or late afternoon (two to three hours spraying time) to reduce drift and evaporation of the droplets during windy or hot weather conditions. For ULV applications, the nozzles are designed to apply droplets of between 80 and 120 µm to give good crop coverage and to reduce drift. Each flight takes approximately one hour for application to 200 ha. Based on a working day of 8 hours, assuming 0.5 hours for mixing/loading and 4 times taking off and landing the airplane (5 x 0.5 hour = 2.5 hours), the maximum flying time would be 5 hours per day. Therefore, the maximum area that could be treated in a day is 1 000 ha. This can be considered to represent the worst-case use for the assessment of operator exposure.

'Ground markers' or 'flaggers', i.e. persons on the ground who direct the pilots to the correct location for spraying, are not used in forestry. The crop canopy is high and such persons would not be visible from the air. Modern forest plantations are set out in separate blocks allowing the pilot to locate the correct target area. The potential exposure of operators during aerial application is therefore limited to persons involved in mixing/loading and to the pilots of the aircraft or helicopters.

Ground application by tractor-mounted or hand-held spray

The application of Dimilin WG-80 could be done by tractor-mounted spray or hand –held spry equipment, "high" crop application.

Estimation of mixing/loading and application based on the German model during aerial and ground application

Exposure during mixing prior to application by air can be estimated using the German model as the product is prepared in the same way as for application by tractor-mounted equipment. The exposure was 0.878 mg kg^{-1} bw day^{-1} without PPE and 0.00891 mg kg^{-1} bw day^{-1} using gloves, corresponding to 2660 % respective 68 % of the AOEL. (For calculations se Appendix 1 I-J)

Total systemic exposure was calculated for Dimilin WG-80: application to forest with tractor-mounted or hand – held spray equipment, from the addition of dermal and inhalation exposure (see also calculation in Appendix 1). Without the use of PPE the exposure was 0.00459 and 0.00275 mg kg^{-1} bw day^{-1} respectively which corresponds to 14and 8 % of the AOEL. (For calculations se Appendix 1 K-L)

Additional assumptions/data utilised in the models are as follows:

	Application from air	Ground application Tractor-mounted spray	Ground application Hand-held spray
Area Treated in One Day:	1 000 ha	8 ha	1 ha
Application Rate:	48 g as./ha	48 g as./ha	48 g as./ha
Inhalation absorption	100%	100%	100%
Dermal absorption	6 %	6 %	6 %

Table B.6.14.1.2-1: Estimations of operator exposure during mixing/loading and application to Dimilin WG-80 with and without PPE and comparison in relation to the systemic AOEL in aerial and ground application

DIMILIN WG-80 Application-Forest		
PPE		**% of AOEL[1)]**
	Aerial application	
	Calculation only for exposure during mixing and loading (mg kg^{-1} bw day^{-1}**)**	
	German model mixing and loading	
Without	0.878	**2660 %**
With gloves	0.00891	**68 %**
	Ground application	
	Operator total exposure (mg kg^{-1} bw day^{-1}**)**	
	Tractor-mounted sprayer (German model)	
Without	0.00459	**14 %**
	Hand-held sprayer(German model)	
Without	0.00275	**8 %**

[1] *$AOEL_{sys}$=0.033 mg kg^{-1} bw day^{-1}; Dermal exposure 6%*

Conclusion

The exposure of the operators to diflubenzuron during mixing/loading in the scenario of aircraft application has been calculated from the German model; the exposure during mixing and loading, using gloves was 68% of the AOEL. However, there are no EU-models for estimating the exposure for aerial application and therefore the decision of use have to be left to the national product authorisation step. Ground application using either tractor-mounted or hand-held sprayer resulted in exposure 14 % and 8 % of the AOEL respectively, without the use of PPE. The application using either tractor-mounted or hand-held spray is acceptable.

B.6.14.1.3 Estimation of operator exposure in greenhouse using mushrooms grower

Mushrooms are grown in insulated houses and planted in compost in wooden trays or aluminium shelves stacked in tiers on either side of a central aisle. The compost consists of peat and is pasteurised prior to use. Mushroom spawn (mycelium culture) is incorporated into the compost and this is subsequently covered with casing medi, which is typically a mixture of peat and sugar beet lime. Mushroom farms vary in size and an average area of

production would be approximately 300 to 400 m^2 with the largest farms growing a total of up to 1 500 m^2, i.e. 0.15 ha, in three to four mushroom houses. Applications are made routinely to the casing media as a high volume low pressure sprays drench. There is one application of Dimilin WG-80 per cropping cycle (which takes 6 to 8 weeks) and up to five cycles per year. Cycles start at different times within a mushroom house to provide continuous cropping and so an application of Dimilin WG-80 could be made once a week with each application taking approximately one hour. The same operators do the mixing/loading and the applications. Product is prepared and used by each mushroom grower and applications are not made at several mushroom farms by spray contractors.

Applications are made automatically through the irrigation system in many modern houses. Alternatively, applications are made using hand-held equipment. The product is mixed and loaded prior to application by both methods but application by hand-held equipment involves the higher potential for exposure of operators. Sprays are applied at high volume (up to 1.5 L/m^2, equivalent to 15 000 L/ha) and the spray is directed downwards to the casing media. The water volume incorporates the active substance into the casing media.

Additional assumptions/data utilised in the models are as follows:

Area Treated in One Day:	1 ha
Application Rate:	10 kg a.s./ha
Application volume:	15 000 L/ha
Inhalation absorption	100 %
Dermal absorption	6 %

Estimation of operator exposure in greenhouse for growing mushrooms during mixing and loading

The operator exposure during mixing and loading is estimated using the German model. It is assumed that a maximum of 0.15 ha/day can be treated as the farmers are not bigger (see above). Based on a maximum use rate of 1 g a.s./m^2 (10 kg a.s./ha), this will result in the following estimated exposure of spray operators to diflubenzuron without or with personal protective equipments (see also Appendix 1, M-O):

Table B.6.14.1.3-1: Estimations of operator exposure during mixing/loading to Dimilin WG-80 with and without PPE and comparison in relation to the systemic AOEL in greenhouse using mushrooms grower

DIMILIN WG-80 **Aerial application-mushroom**		
PPE	**Operator total exposure (**mg kg^{-1} bw day^{-1}**)**	**% of AOEL[1)]**
	German model automatic spraying (only mixing and loading)	
Without	0.0274	**83 %**
	German model hand-held spraying	
Without	0.0858	**260 %**
With gloves during mixing and loading and gloves, coverall and sturdy footwear during spraying	0.0150	**46 %**

[1] *$AOEL_{sys}$=0.033 mg kg^{-1} bw day^{-1}; Dermal exposure 6%*

No calculations have been presented by the notifier on the operator exposure during spraying in greenhouse. The arguments are that the application in greenhouse is comparable to "high" crops in orchards. RMS doesn't agree with this argument since the greenhouses are closed rooms and the operator exposure could be higher than

outside. However, the operator exposure during spraying automatically is consider as acceptable, the exposure during mixing/loading is 83 % of AOEL and since the operator doesn't need to be in the greenhouse during spraying the exposure during spraying should be negligible. The operator exposure with hand-held sprayer is acceptable if gloves are used during mixing and loading and gloves together with coverall and sturdy footwear during spraying (46 % of AOEL). **In conclusion, the operator exposure to diflubenzuron in greenhouse using mushrooms grower is considered as acceptable using automatic sprayer and it is also acceptable using hand-held spraying if PPE is used.**

B.6.14.1.4 Summary of operator exposure

The proposed AOEL for diflubenzuron is 0.033 mg kg^{-1} day^{-1} using 100 as safety factor and correlated with an oral absorption of 33%. Skin absorption value of 6 % for the concentrated product and the spray solution is used.

The operator exposure of diflubenzuron for pome fruit using tractor-mounted sprayer and hand-held sprayer was calculated using the German model and the UK POEM. The outcome exposure was below the systemic AOEL when gloves were used. In forestry and greenhouse, the operator exposure during mixing/loading was also calculated using the German model. If gloves was used during the mixing and loading for areal application the exposure level was lower then the AOEL. However, no appropriate calculations were presented by the notifier for the exposure during spraying from the air in forestry. Spraying in the forestry using tractor-mounted or hand-held sprayer is accepted. In greenhouse, the operator exposure during automatic spraying was considered as negligible and accepted as the exposure was less than AOEL during the mixing and loading step. During hand-held sprayer the operator exposure was considered acceptable, not even when all possible PPE was worn.

The overall exposure modelling assessments is presented in Table below:

Table B.6.14.1.4-1: Summary of the predicted operator exposure using Dimilin WG-80 in pome fruit, forestry and mushrooms

Field of use	Method of application	Dose (kg a.s./ha) Work rate (ha/day)	Exposure mg kg^{-1} day^{-1}	% AOEL[1]	PPE
Pome fruit	Tractor-mounted sprayer; spray directed upwards and sideways	0.18 8[2] 15[3]	0.0415[2] 0.0219[2] 0.0172[3]	**>100 %** **66 %** **52 %**	no yes[4] no
	Hand-held sprayer; spray directed upwards and sideways	0.18 1	0.0401[2] 0.0063[2] 0.0103[3]	**>100 %** **19 %** **31%**	no yes[4] no
Forestry	Aerial application - ultra low volume (ULV) Aerial application - low volume (LV)	0.048 1000	Mix/loading only: 0.878[3] 0.00891[3]	**>100 %** **68 %**	no yes[4]
	Ground application Tractor-mounted sprayer Hand-held sprayer	8[3] 1[3]	0.00459[3] 0.00275[3]	**14 %** **8 %**	no no
Mushrooms	Automatic sprayer	10	Mix/loading only: 0.0274[3]	**83 %**	no

	Hand-held sprayer; high volume spray directed downwards	1	0.0858[3] 0.0150	**>100 %** **46 %**	no yes [5]
[1]*AOEL= 0.033 mg kg^{-1}day^{-1};* [2] *UK POEM;* [3] *German model;* [4] *gloves;* [5] *gloves and overall during spraying*					

In conclusion, the operator exposure of diflubenzuron in pome fruit with tractor mounted and hand-held application is acceptable when PPE are used. The exposure of the operators to diflubenzuron during mixing/loading in the scenario of aircraft application has been calculated and found to be acceptable using gloves. However, there are no EU-models for estimating the exposure for aerial application and therefore the decision of use have to be left to the national product authorisation step. The application using either tractor-mounted or hand-held spray is acceptable. The operator exposure to diflubenzuron in greenhouse using mushrooms grower is considered as acceptable using automatic sprayer and it is also acceptable using hand-held spraying if PPE is used.

B.6.14.2 Bystander exposure

Orchard

Bystanders could be exposed to spray drift if they were walking next to an orchard being treated with Dimilin WG-80. However, the bystander can always be expected to be several metres away from the spray boom. At 10 m from the sprayer, estimates that for pome fruit the maximum drift estimate (90th percentile data, single application; late application for pome fruit) is 3.60%[9].

Based on the maximum application rate for diflubenzuron to pome fruit of 0.18 kg/ha and assuming a bystander is located 10 m from the sprayer, they could receive 3.6% drift, i.e. 0.65 mg diflubenzuron/m^2. Assuming that 50% of a body surface, assumed to be 2 m^2 in total (US EPA[10]), is covered with clothing and that dermal exposure is reduced to 50 % with long shirt and trousers, direct deposition on the skin could be 0.975 mg diflubenzuron. Using 6 % skin absorption, the absorbed dose of diflubenzuron would be 0.0585 mg.

As a worst case scenario the inhalation value can be assumed to be the same as for the operator and can be taken from the German model, tractor-mounted sprayer which is 0.01152 mg/day.

Taken together the dermal and inhalation exposure is 0.07 mg and assuming a 60 kg body weight (as appropriate for adult men and women), the systemic exposure would be 0.001167 mg kg^{-1} day^{-1}.

[9] *Rautmann, D., Streloke, M., Winkler, R. (2001) New basic drift values in the authorisation procedure for plant protection products. In: Workshop on risk assessment and risk mitigation measures in the context of the authorisation of plant protection products (WORMM; Forster, R., Streloke, M. Eds.), 27-29 September, 1999, Heft 383, Biologischen Bundesanstalt für Land - und Fortwirtschaft, Berlin and Braunschweig, Germany.*

[10] *Central estimate for adults. The EPA Exposure Factors Handbook (1997)*

Compared with the AOEL for diflubenzuron of 0.033 mg kg^{-1} day^{-1}, the potential exposure of bystanders is 3.5 % of systemic AOEL. Therefore, the bystander exposure during the use of Dimilin WG-80 is considered as acceptable.

Forestry

Bystanders could be exposed to spray drift if they were walking next to a forestry being treated with Dimilin WG-80. However, as the maximum application rate for diflubenzuron to pome fruit is 180 g/ha and only 48 g/ha in the forest the calculation for bystander exposure made for the orchard can be used as a worst case for the bystanders in forestry. Thus, the bystanders in the forestry would be exposed to less than 3.5 % of AOEL which is an acceptable exposure.

Mushroom houses

Bystanders are not expected to be present in mushroom houses during application.

B.6.14.3 Worker exposure

B.6.14.3.1 Estimation of worker exposure in orchards

Worker exposure to diflubenzuron during re-entering the application area in orchards has been estimated using the coefficients from EUROPOEM[11]. Table below shows the calculation of the potential dermal exposure:

Table B.6.14.3.1-1: Worker exposure of Dimilin 80WG in orchards

Dimilin 80WG in orchards

Worker exposure=	DFR*TC*T * DA/bw	
Dislogeable foliar residue (DFR)	3	µg/cm2
Transfer Coefficient (TC)	4500	cm2/h
Time in contact with the crop (T)	8	h
Dermal abs (DA):	6	%
Body weight (bw)	60	kg

Worker exposure of *Dimilin 80 WG* Pome fruit = 0.108 mg kg-1 day-1

%AOEL (0.033 mg $kg^{-1}day^{-1}$) **327 %**

The systemic exposure for workers harvesting pome fruit or carrying out maintenance operations such as pruning without PPE is 0.108 mg kg^{-1} day^{-1}, equivalent to 327 % of the AOEL of 0.033 mg kg^{-1} day^{-1}. **If the workers wear gloves, the dermal absorption could be reduced to 0.6 % and give an exposure of 0.0108 mg kg^{-1} day-**

[11] *EUROPOEM-the developmenta, maintenance and dissemination of generic european databases and predictive exposure models to plant protection products. Final report December 2002*

[1], equivalent to 33 % of the AOEL. In conclusion, the worker exposure of Dimilin WG-80 is acceptable in orchards for pome fruit under the conditions that PPE is used.

B.6.14.3.2 Estimation of re-entry exposure in forestry

RMS has made a re-entry calculation for 2 h scouting activities in a Dimilin WG-80 in treated forest.

Table B.6.14.3.2-1: Re-entry exposure of Dimilin 80WG in forest

Dimilin 80WG in forest

Re-entry exposure=	DFR*TC*T * DA/bw	
Dislogeable foliar residue (DFR)	3	µg/cm2
Transfer Coefficient (TC)	4500	cm2/h
Time in contact with the crop (T)	2	h
Dermal abs (DA):	6	%
Body weight (bw)	60	kg

Worker exposure of *Dimilin 80 WG* Pome fruit = 0.027 mg kg-1 day-1

%AOEL (0.033 mg $kg^{-1}day^{-1}$) **81 %**

The systemic exposure for re-entering the forest is 0.027 mg kg^{-1} day^{-1}, equivalent to 81 % of the AOEL of 0.033 mg kg^{-1} day^{-1}. This is a conservative value as a person walking in the forest would probably not be in contact with trees and leafs all the time.

B.6.14.3.3 Estimation of worker exposure in greenhouse using mushrooms grower

A study to measure the exposure of workers handling treated compost, which is relevant to harvesting mushrooms treated with Dimilin WG-80 is summarised below.

REFERENCE 01:	BELCHER,T. (1997). **GREENHOUSE WORKER REENTRY EXPOSURE TO ETRIDIAZOLE**
Formulation/a.s.	Terrazole 35%WP/ Etridiazole or Truban 5g Granular fungicide/4.58%etridiazole
Guideline/GLP:	OPPTS Harmonised Test Guideline Series 875 (875.2200, 875.1200 and 875.1400)/yes
Acceptability:	**Yes**
Test system:	The exposure of workers to etridiazole residues when handling soil media treated with 'Terrazole 35% Wettable Powder' (a WP formulation containing 33.39% etridiazole) or 'Truban 5G Granular Fungicide' (a G formulation containing 4.58% etridiazole) was measured under greenhouse conditions in California, USA. The results with 'Terrazole 35% Wettable Powder' are considered to be applicable to Dimilin WG-80 as a WP formulation type is similar to a WG, whereas a G formulation is designed to release active substance more slowly over time. The results with 'Truban 5G Granular Fungicide' are therefore not considered further. Soil media consisting of bark, peat moss and sand was treated evenly with 'Terrazole 35% Wettable Powder' at a nominal rate of 37.2 g a.s./m3. At 4 hours, 12 hours and 24 hours after application (re-entry times), four workers each filled 12 plastic pots (10 cm diameter) by scooping them into the treated soil media with their bare hands. They then brushed off excess soil media so that the media was level with the top of the pot, and placed the full pot in a pot holder. All workers were observed and actions such as brushing their faces with their hands noted. Dermal

	exposure was measured using whole body dosimeters (worn over workers underwear and under cotton trousers and shirt), facial and neck swabs of cotton gauze and hand washings. Inhalation exposure was measured using personal air sampling tubes clipped to the shirt collar and fitted to a personal sampling pump on the workers belt. Monitoring took place over approximately a 4-hour period at each interval. Samples of treated and untreated soil media were also collected and 'dislodged' 0, 4, 8, 12, 24, 48 and 72 hours after treatment for measurement of residue decline. Samples were analysed for etridiazole after extraction from the matrices using gas chromatography with electron capture detection. Field fortifications were made for all matrices.

Findings:

Etridiazole residues in the soil media declined from 14.4 µg/g immediately after application to 11.3 4 µg/g after 72 hours (Table B.6.14.3.3-1). The data were used to construct a decline curve using linear regression. The dislodgeable soil residues at 4, 12 and 24 hours were calculated from the regression line.

Table B.6.14.3.3-1: Dislodgeable residues of etridiazole in soil following application of 'Terrazole 35% WP'

Sampling interval (hours)	Dislodgeable etridiazole residues in soil media (µg/g)
0	14.3
4	14.6
8	9.83
12	9.57
24	9.05
48	10.8
72	11.3

Etridiazole residues were found in sections of the cotton whole body dosimeters and all inhalation tubes at all re-entry times. Residues in facial swabs were absent with the exception of one worker at the 12-hour re-entry time. Residues in hand washings were found in the 4-hour re-entry time but not in other samplings. The residues found were used to calculate total dermal and inhalation exposure. From these values, total exposure for an 8-hour working day and the total exposure rate were calculated. Transfer factors were calculated by dividing the exposure rate by the dislodgeable soil residues at each re-entry time. Transfer factors for the 4, 12 and 24-hour time intervals were 9.15, 5.45 and 8.62 g/hour, respectively (Table B.6.14.3.3-2). The worst case value for the transfer factor was 9.15 g/hour and was found after 4 hours. The mean transfer factor was 7.74 g/hour.

Table B.6.14.3.3-2: Measured exposure of etridiazole residues and calculated transfer factors from soil dislodgeable residues

Parameter	4 hours	12 hours	24 hours
Dermal exposure over 8 hours (µg)	249.6	143.3	177.9
Inhalation exposure over 8 hours (µg)	595.5	352.8	591.2
Dermal plus inhalation exposure over 8 hours (µg)	845.1	496.1	769.1
Total exposure rate (µg/hour)	105.6	62.0	96.1
Dislodgeable soil residues (µg/g)*	11.54	11.38	11.15

Transfer factor (g/hour)	9.15	5.45	8.62
Worst case/Mean transfer factor (g/hour)	9.15/7.74		
* *Calculated from regression line from decline curve.*			

For workers handling soil media treated with etridiazole, a mean soil transfer factor of 7.74 g/hour from dislodgeable soil residues to human exposure was calculated.

Dimilin WG-80 is recommended for application to the casing media at 1 g diflubenzuron/m^2. The active substance is incorporated into the casing media by the high volume of water applied. Assuming the active substance is incorporated evenly to a depth of 15 cm, the concentration of diflubenzuron in the casing media would be 6.67 g a.s./m^3.

In the study with 'Terrazole 35% Wettable Powder', etridiazole was applied to soil media at 37.2 g a.s./m^3. Assuming that the density of the soil media in the study and the casing media used in mushroom growing in the EU are the same, the concentration of etridiazole was approximately 5.6 times the expected concentration of diflubenzuron. Dislodgeable residues of etridiazole in soil media 0 and 4 hours after application were 14.3 and 14.6 µg/g (mean 14.5 µg/g). The mean of the values at 0 and 4 hours can be used as surrogates for diflubenzuron. Residues of etridiazole at later samplings are not applicable as levels declined and this decline is likely to be specific to etridiazole. Thus, the application of 'Terrazole 35% Wettable Powder' at a rate of active substance 5.6 times higher than Dimilin WG-80 led to dislodgeable residues in soil media of 14.5 µg/g. Therefore, at the recommended rate of Dimilin WG-80, dislodgeable residues of diflubenzuron can be expected to be 2.6 µg/g a.s.

In the worker exposure study, workers scooped treated soil media into plastic pots and brushed off the excess with their hands. These tasks are considered to be a suitable surrogate for workers harvesting mushrooms by hand. Harvesting involves leaning over the mushroom beds to pick the ripe crop and this would involve contact with diflubenzuron treated casing media. In the study with etridiazole, a worst case soil transfer factor of 9.15 g/hour was calculated.

Therefore, the daily exposure to diflubenzuron for an 8-hour working day and a worker of body weight 60 kg is calculated as follows:

Exposure without PPE = 0.0026 mg/g x 9.15 g/hour x 8 hours/day ÷ 60 kg = 0.0032 mg kg^{-1} day^{-1}

The systemic exposure for workers harvesting mushrooms without PPE and without taking the dermal absorption into consideration was 10 % of the AOEL. The exposure of workers carrying out other tasks in mushroom houses is likely to be lower than during harvesting as contact with the casing media would be lower. Therefore, the risk to workers is considered to be acceptable and it is not necessary to set a re-entry period before workers can re-enter mushroom houses to harvest the crop or handle the treated casing media after applications of Dimilin WG-80, and it is not necessary for workers to wear personal protective equipment.

B.6.14.3.4 Summary of worker exposure

The worker exposure of Dimilin WG-80 in pome fruits, forestry and mushrooms are considered as acceptable under the conditions studied. PPE are needed for the workers using Dimilin WG-80 in the orchards.

Appendix 1

A. UK POEM: tractor-mounted, orchard without PPE using Dimilin WG-80

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM) WITH GERMAN MODEL MIX/LOAD DATA (75th PERCENTILE)

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha				
Product	**Dimilin WG80**		Active substance	**diflubenzuron**	
Formulation type	WG or SG		a.s. concentration	**800**	mg/g
Dermal absorption from product	**6**	%	Dermal absorption from spray	**6**	%
PPE during mix/loading	None		PPE during application	None	
Dose	**0,225**	kg product/ha	Work rate/day	**15**	ha
Application volume	**1500**	l/ha	Duration of spraying	**6**	h
AOEL	**0,033**	mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	5,72	mg/kg a.s.
Hand contamination/day	15,444	mg/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to a.s.	15,444	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,242	mg/kg a.s.
Inhalation exposure/day	0,6534	mg/day
RPE	None	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,6534	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha			
Application volume	1500	spray/ha		
Volume of surface contamination	400	ml/h		
Distribution	Hands	Trunk	Legs	
	10%	65%	25%	
Clothing	None	Permeable	Permeable	
Penetration	100%	2%	5%	
Dermal exposure	10	5,2	5	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	121,2	ml/day		
Concentration of a.s. in spray soluti	0,12	mg/ml		
Dermal exposure to a.s.	14,544	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure to spray	0,05	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0,12	mg/ml
Inhalation exposure to a.s.	0,036	mg/day
Percent absorbed	100	%
Absorbed dose	0,036	mg/day

ABSORBED DOSE

	Mix/load		Application		
Dermal exposure to a.s.	15,444	mg/day		14,544	mg/day
Percent absorbed	6	%		6	%
Absorbed dose (dermal route)	0,92664	mg/day		0,87264	mg/day
Inhalation exposure to a.s.	0,6534	mg/day		0,036	mg/day
Absorbed dose	1,58004	mg/day		0,90864	mg/day

PREDICTED EXPOSURE

Total absorbed dose	2,48868	mg/day
Operator body weight	60	kg
Operator exposure	**0,041478**	**mg/kg bw/day**
Operator exposure % of AOEL	**125,6909091**	**%**

B. UK POEM: tractor-mounted, orchard with PPE using Dimilin WG-80

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM) WITH GERMAN MODEL MIX/LOAD DATA (75th PERCENTILE)

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha			
Product	**Dimilin WG80**		Active substance	**diflubenzuron**
Formulation type	WG or SG		a.s. concentration	**800** mg/g
Dermal absorption from product	**6** %		Dermal absorption from spray	**6** %
PPE during mix/loading	Gloves		PPE during application	Gloves
Dose	**0,225** kg product/ha		Work rate/day	**15** ha
Application volume	**1500** l/ha		Duration of spraying	**6** h
AOEL	**0,033** mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	5,72	mg/kg a.s.
Hand contamination/day	15,444	mg/day
Protective clothing	Gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,15444	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,242	mg/kg a.s.
Inhalation exposure/day	0,6534	mg/day
RPE	None	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,6534	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha			
Application volume	1500	spray/ha		
Volume of surface contamination	400	ml/h		
Distribution	Hands	Trunk	Legs	
	10%	65%	25%	
Clothing	Gloves	Permeable	Permeable	
Penetration	10%	2%	5%	
Dermal exposure	4	5,2	5	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	85,2	ml/day		
Concentration of a.s. in spray soluti	0,12	mg/ml		
Dermal exposure to a.s.	10,224	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure to spray	0,05	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0,12	mg/ml
Inhalation exposure to a.s.	0,036	mg/day
Percent absorbed	100	%
Absorbed dose	0,036	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	0,15444	mg/day	10,224	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,0092664	mg/day	0,61344	mg/day
Inhalation exposure to a.s.	0,6534	mg/day	0,036	mg/day
Absorbed dose	0,6626664	mg/day	0,64944	mg/day

PREDICTED EXPOSURE

Total absorbed dose	1,3121064	mg/day
Operator body weight	60	kg
Operator exposure	**0,02186844**	**mg/kg bw/day**
Operator exposure % of AOEL	**66,268**	**%**

C. German model: tractor-mounted, orchard without PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**0,225** kg product/ha		Work rate/day		**8** ha
AOEL	**0,033** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2	mg/kg a.s.
Hand contamination/day	2,88	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	2,88	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,008	mg/kg a.s.
Inhalation exposure/day	0,01152	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,01152	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Tractor-mounted/trailed broadcast air-assisted sprayer

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	1,2	0,7	9,6	
Dermal contamination/day	1,728	1,008	13,824	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	16,56	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,018	mg/kg a.s.
Inhalation exposure/day	0,02592	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,02592	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	2,88	mg/day	16,56	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,1728	mg/day	0,9936	mg/day
Inhalation exposure to a.s.	0,01152	mg/day	0,02592	mg/day
Total systemic exposure	0,18432	mg/day	1,01952	mg/day

PREDICTED EXPOSURE

Total systemic exposure	1,20384	mg/day
Operator body weight	70	kg
Operator exposure	**0,017197714**	**mg/kg bw/day**
Operator exposure % of AOEL	**52**	**%**

D. German model: tractor-mounted, orchard with PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	Gloves				
PPE during application: Head	None	Hands	Gloves	Body	None
Dose	**0,225** kg product/ha		Work rate/day		**8** ha
AOEL	**0,033** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2	mg/kg a.s.
Hand contamination/day	2,88	mg/day
Protective clothing	gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,0288	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,008	mg/kg a.s.
Inhalation exposure/day	0,01152	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,01152	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Tractor-mounted/trailed broadcast air-assisted sprayer

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	1,2	0,7	9,6	
Dermal contamination/day	1,728	1,008	13,824	
Protective clothing	none	gloves	none	
Transmission to skin	100	1	100	%
Total dermal exposure to a.s.	15,56208	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,018	mg/kg a.s.
Inhalation exposure/day	0,02592	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,02592	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	0,0288	mg/day	15,56208	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,001728	mg/day	0,9337248	mg/day
Inhalation exposure to a.s.	0,01152	mg/day	0,02592	mg/day
Total systemic exposure	0,013248	mg/day	0,9596448	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0,9728928	mg/day
Operator body weight	70	kg
Operator exposure	**0,013898469**	**mg/kg bw/day**
Operator exposure % of AOEL	**42**	**%**

E. UK POEM: hand-held, orchard without PPE using Dimilin WG-80

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM) WITH GERMAN MODEL MIX/LOAD DATA (75th PERCENTILE)

Application method	Hand-held rotary atomiser equipment (2.5 l tank). Outdoor, high level target				
Product	**Dimilin WG80**		Active substance	**diflubenzuron**	
Formulation type	WG or SG		a.s. concentration	**800**	mg/g
Dermal absorption from product	**6**	%	Dermal absorption from spray	**6**	%
PPE during mix/loading	None		PPE during application	None	
Dose	**0,225**	kg product/ha	Work rate/day	**1**	ha
Application volume	**1500**	l/ha	Duration of spraying	**6**	h
AOEL	**0,033**	mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	171,4	mg/kg a.s.
Hand contamination/day	30,852	mg/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to a.s.	30,852	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,0628	mg/kg a.s.
Inhalation exposure/day	0,011304	mg/day
RPE	None	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,011304	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Hand-held rotary atomiser equipment (2.5 l tank). Outdoor, high level target			
Application volume	1500	spray/ha		
Volume of surface contamination	50	ml/h		
Distribution	Hands	Trunk	Legs	
	10%	65%	25%	
Clothing	None	Permeable	Permeable	
Penetration	100%	15%	20%	
Dermal exposure	5	4,875	2,5	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	74,25	ml/day		
Concentration of a.s. in spray soluti	0,12	mg/ml		
Dermal exposure to a.s.	8,91	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure to spray	0,01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0,12	mg/ml
Inhalation exposure to a.s.	0,0072	mg/day
Percent absorbed	100	%
Absorbed dose	0,0072	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	30,852	mg/day	8,91	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	1,85112	mg/day	0,5346	mg/day
Inhalation exposure to a.s.	0,011304	mg/day	0,0072	mg/day
Absorbed dose	1,862424	mg/day	0,5418	mg/day

PREDICTED EXPOSURE

Total absorbed dose	2,404224	mg/day
Operator body weight	60	kg
Operator exposure	**0,0400704**	**mg/kg bw/day**
Operator exposure % of AOEL	**121,4254545**	**%**

F. UK POEM: hand-held, orchard with PPE using Dimilin WG-80

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM) WITH GERMAN MODEL MIX/LOAD DATA (75th PERCENTILE)

Application method	Hand-held rotary atomiser equipment (2.5 l tank). Outdoor, high level target			
Product	**Dimilin WG80**		Active substance	**diflubenzuron**
Formulation type	WG or SG		a.s. concentration	**800** mg/g
Dermal absorption from product	**6** %		Dermal absorption from spray	**6** %
PPE during mix/loading	Gloves		PPE during application	Gloves
Dose	**0,225** kg product/ha		Work rate/day	**1** ha
Application volume	**1500** l/ha		Duration of spraying	**6** h
AOEL	**0,033** mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	171,4	mg/kg a.s.
Hand contamination/day	30,852	mg/day
Protective clothing	Gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,30852	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,0628	mg/kg a.s.
Inhalation exposure/day	0,011304	mg/day
RPE	None	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,011304	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Hand-held rotary atomiser equipment (2.5 l tank). Outdoor, high level target				
Application volume	1500	spray/ha			
Volume of surface contamination	50	ml/h			
Distribution	Hands		Trunk	Legs	
	10%		65%	25%	
Clothing	Gloves		Permeable	Permeable	
Penetration	10%		15%	20%	
Dermal exposure	0,5		4,875	2,5	ml/h
Duration of exposure	6	h			
Total dermal exposure to spray	47,25	ml/day			
Concentration of a.s. in spray solut	0,12	mg/ml			
Dermal exposure to a.s.	5,67	mg/day			

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure to spray	0,01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0,12	mg/ml
Inhalation exposure to a.s.	0,0072	mg/day
Percent absorbed	100	%
Absorbed dose	0,0072	mg/day

ABSORBED DOSE

	Mix/load		Application		
Dermal exposure to a.s.	0,30852	mg/day		5,67	mg/day
Percent absorbed	6	%		6	%
Absorbed dose (dermal route)	0,0185112	mg/day		0,3402	mg/day
Inhalation exposure to a.s.	0,011304	mg/day		0,0072	mg/day
Absorbed dose	0,0298152	mg/day		0,3474	mg/day

PREDICTED EXPOSURE

Total absorbed dose	0,3772152	mg/day
Operator body weight	60	kg
Operator exposure	**0,00628692**	**mg/kg bw/day**
Operator exposure % of AOEL	**19,05127273**	**%**

G. German model: hand-held, orchard without PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**0,225**	kg product/ha	Work rate/day		**1** ha
AOEL	**0,033**	mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	3,78	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	3,78	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,0036	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,0036	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	0,864	1,908	4,5	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	7,272	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,054	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,054	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	3,78	mg/day	7,272	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,2268	mg/day	0,43632	mg/day
Inhalation exposure to a.s.	0,0036	mg/day	0,054	mg/day
Total systemic exposure	0,2304	mg/day	0,49032	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0,72072	mg/day
Operator body weight	70	kg
Operator exposure	**0,010296**	**mg/kg bw/day**
Operator exposure % of AOEL	**31**	**%**

H. German model: hand-held, orchard with PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target				
Product	**Dimilin WG-80**		Active substance	**diflubenzuron**	
Formulation type	WG		a.s. concentration	**800**	g/kg
Dermal absorption from product	**6**	%	Dermal absorption from spray	**6**	%
RPE during mix/loading	None		RPE during application	None	
PPE during mix/loading	Gloves				
PPE during application: Head	None	Hands	Gloves	Body	None
Dose	**0,225**	kg product/ha	Work rate/day	**1**	ha
AOEL	**0,033**	mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	3,78	mg/day
Protective clothing	gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,0378	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,0036	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,0036	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	0,864	1,908	4,5	
Protective clothing	none	gloves	none	
Transmission to skin	100	1	100	%
Total dermal exposure to a.s.	5,38308	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,054	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,054	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	0,0378	mg/day	5,38308	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,002268	mg/day	0,3229848	mg/day
Inhalation exposure to a.s.	0,0036	mg/day	0,054	mg/day
Total systemic exposure	0,005868	mg/day	0,3769848	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0,3828528	mg/day
Operator body weight	70	kg
Operator exposure	**0,005469326**	**mg/kg bw/day**
Operator exposure % of AOEL	**17**	**%**

I. German model: Estimated dermal and inhalation exposure during mixing/loading with aerial application in forestry using Dimilin WG-80 without PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target				
Product	**Dimilin WG-80**		Active substance	**diflubenzuron**	
Formulation type	WG		a.s. concentration	**800**	g/kg
Dermal absorption from product	**6**	%	Dermal absorption from spray	**6**	%
RPE during mix/loading	None		RPE during application	None	
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**0,06**	kg product/ha	Work rate/day	**1000**	ha
AOEL	**0,033**	mg/kg bw/day			

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	1008	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	1008	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,96	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,96	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	230,4	508,8	1200	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	1939,2	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	14,4	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	14,4	mg/day

ABSORBED DOSE

	Mix/load		Application		
Dermal exposure to a.s.	1008	mg/day	1939,2	mg/day	
Percent absorbed	6	%	6	%	
Absorbed dose (dermal route)	60,48	mg/day	116,352	mg/day	
Inhalation exposure to a.s.	0,96	mg/day	14,4	mg/day	
Total systemic exposure	61,44	mg/day	130,752	mg/day	

PREDICTED EXPOSURE

Total systemic exposure	192,192	mg/day
Operator body weight	70	kg
Operator exposure	**2,7456**	**mg/kg bw/day**
Operator exposure % of AOEL	**8320**	**%**

Operator exposure = 0.878mg/kg
2660 % of AOEL

J. German model: Estimated dermal and inhalation exposure during mixing/loading with aerial application in forestry using Dimilin WG-80 with PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target					
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**	
Formulation type	WG		a.s. concentration		**800**	g/kg
Dermal absorption from product	**6**	%	Dermal absorption from spray		**6**	%
RPE during mix/loading	None		RPE during application		None	
PPE during mix/loading	Gloves					
PPE during application: Head	None	Hands	None	Body	None	
Dose	**0,06**	kg product/ha	Work rate/day		**1000**	ha
AOEL	**0,033**	mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	1008	mg/day
Protective clothing	gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	10,08	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,96	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,96	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	230,4	508,8	1200	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	1939,2	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	14,4	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	14,4	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	10,08	mg/day	1939,2	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,6048	mg/day	116,352	mg/day
Inhalation exposure to a.s.	0,96	mg/day	14,4	mg/day
Total systemic exposure	1,5648	mg/day	130,752	mg/day

PREDICTED EXPOSURE

Total systemic exposure	132,3168	mg/day
Operator body weight	70	kg
Operator exposure	**1,89024**	**mg/kg bw/day**
Operator exposure % of AOEL	**5728**	**%**

Operator exposure = 0.00891mg/ kg bw/ dag
68 % of AOEL

K. German model: tractor-mounted, forestry, without PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**0,06** kg product/ha		Work rate/day		**8** ha
AOEL	**0,033** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2	mg/kg a.s.
Hand contamination/day	0,768	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	0,768	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,008	mg/kg a.s.
Inhalation exposure/day	0,003072	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,003072	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Tractor-mounted/trailed broadcast air-assisted sprayer

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	1,2	0,7	9,6	
Dermal contamination/day	0,4608	0,2688	3,6864	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	4,416	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,018	mg/kg a.s.
Inhalation exposure/day	0,006912	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,006912	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	0,768	mg/day	4,416	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,04608	mg/day	0,26496	mg/day
Inhalation exposure to a.s.	0,003072	mg/day	0,006912	mg/day
Total systemic exposure	0,049152	mg/day	0,271872	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0,321024	mg/day
Operator body weight	70	kg
Operator exposure	**0,004586057**	**mg/kg bw/day**
Operator exposure % of AOEL	**14**	**%**

L. German model: hand-held, forestry, without PPE using Dimilin WG-80

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**0,06** kg product/ha		Work rate/day		**1** ha
AOEL	**0,033** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	1,008	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	1,008	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,00096	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,00096	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	0,2304	0,5088	1,2	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	1,9392	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,0144	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,0144	mg/day

ABSORBED DOSE

	Mix/load		Application		
Dermal exposure to a.s.	1,008	mg/day	1,9392	mg/day	
Percent absorbed	6	%	6	%	
Absorbed dose (dermal route)	0,06048	mg/day	0,116352	mg/day	
Inhalation exposure to a.s.	0,00096	mg/day	0,0144	mg/day	
Total systemic exposure	0,06144	mg/day	0,130752	mg/day	

PREDICTED EXPOSURE

Total systemic exposure	0,192192	mg/day
Operator body weight	70	kg
Operator exposure	**0,0027456**	**mg/kg bw/day**
Operator exposure % of AOEL	**8**	**%**

M. German model: Estimated dermal and inhalation exposure during mixing/loading for mushroom grower in greenhouse using automatic spraying of Dimilin WG-80 without PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target				
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**
Formulation type	WG		a.s. concentration		**800** g/kg
Dermal absorption from product	**6** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None		RPE during application		None
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**12,5** kg product/ha		Work rate/day		**0,15** ha
AOEL	**0,033** mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	31,5	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	31,5	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,03	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,03	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	7,2	15,9	37,5	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	60,6	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,45	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,45	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	31,5	mg/day	60,6	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	1,89	mg/day	3,636	mg/day
Inhalation exposure to a.s.	0,03	mg/day	0,45	mg/day
Total systemic exposure	1,92	mg/day	4,086	mg/day

PREDICTED EXPOSURE

Total systemic exposure	6,006	mg/day
Operator body weight	70	kg
Operator exposure	**0,0858**	**mg/kg bw/day**
Operator exposure % of AOEL	**260**	**%**

Operator exposure = 0.0274mg/ kg bw/ day
83 % of AOEL

N. German model: Estimated dermal and inhalation exposure during mixing/loading for mushroom grower in greenhouse using Dimilin WG-80 and hand-held sprayer without PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target					
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**	
Formulation type	WG		a.s. concentration		**800**	g/kg
Dermal absorption from product	**6**	%	Dermal absorption from spray		**6**	%
RPE during mix/loading	None		RPE during application		None	
PPE during mix/loading	None					
PPE during application: Head	None	Hands	None	Body	None	
Dose	**12,5**	kg product/ha	Work rate/day		**0,15**	ha
AOEL	**0,033**	mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	31,5	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	31,5	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,03	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,03	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	7,2	15,9	37,5	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	60,6	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,45	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,45	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	31,5	mg/day	60,6	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	1,89	mg/day	3,636	mg/day
Inhalation exposure to a.s.	0,03	mg/day	0,45	mg/day
Total systemic exposure	1,92	mg/day	4,086	mg/day

PREDICTED EXPOSURE

Total systemic exposure	6,006	mg/day
Operator body weight	70	kg
Operator exposure	**0,0858**	**mg/kg bw/day**
Operator exposure % of AOEL	**260**	**%**

O. German model: Estimated dermal and inhalation exposure during mixing/loading for mushroom grower in greenhouse using Dimilin WG-80 and hand-held sprayer with PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target					
Product	**Dimilin WG-80**		Active substance		**diflubenzuron**	
Formulation type	WG		a.s. concentration		**800**	g/kg
Dermal absorption from product	**6**	%	Dermal absorption from spray		**6**	%
RPE during mix/loading	None		RPE during application		None	
PPE during mix/loading	Gloves					
PPE during application: Head	None	Hands	Gloves	Body	Coverall and sturdy footwear	
Dose	**12,5**	kg product/ha	Work rate/day		**0,15**	ha
AOEL	**0,033**	mg/kg bw/day				

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	21	mg/kg a.s.
Hand contamination/day	31,5	mg/day
Protective clothing	gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0,315	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,02	mg/kg a.s.
Inhalation exposure/day	0,03	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,03	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	7,2	15,9	37,5	
Protective clothing	none	gloves	coverall and sturdy footwear	
Transmission to skin	100	1	5	%
Total dermal exposure to a.s.	9,234	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,45	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,45	mg/day

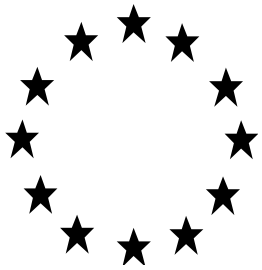
ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	0,315	mg/day	9,234	mg/day
Percent absorbed	6	%	6	%
Absorbed dose (dermal route)	0,0189	mg/day	0,55404	mg/day
Inhalation exposure to a.s.	0,03	mg/day	0,45	mg/day
Total systemic exposure	0,0489	mg/day	1,00404	mg/day

PREDICTED EXPOSURE

Total systemic exposure	1,05294	mg/day
Operator body weight	70	kg
Operator exposure	**0,015042**	**mg/kg bw/day**
Operator exposure % of AOEL	**46**	**%**

Addendum 2 to
Draft Assessment Report



DIFLUBENZURON

Volume 3

Annex B.8 and B.9
Environmental Fate and Behaviour
Ecotoxicology

Rapporteur Member State: Sweden

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

February 2009

Volume 1

Level 1: Statement of subject matter and purpose for which the monograph was prepared

Level 2: Reasoned statement of the overall conclusions drawn by the Rapporteur Member State

Appendix 1: Standard terms and abbreviations

Appendix 2: Specific terms and abbreviations

Appendix 3: List of endpoints

Level 3: Proposed decision with respect to the application for inclusion of the active substance in Annex I

Level 4: Further information to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in Annex 1

Volume 2

Annex A: List of the tests and studies submitted and of information available

Volume 3

Annex B: RMS summary, evaluation and assessment of the data and information

Annex B.1: Identity

Annex B.2: Phys/chem.

Annex B.3: Data application and further information.

Annex B.4: Proposal for classification and labelling

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Annex B.6: Toxicology and metabolism

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Appendix 1: Standard terms and abbreviations

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B.9.2.5.Risk assessment for aquatic organism

At PRAPeR 63 it was concluded that the risk to zooplankton could be addressed by this endpoint (0.7 µg/L) together with an AF of 5. However, for the insect community no NOAEC could be determined in the littoral enclosure study. The experts were of the opinion that the risk to insects (and amphipods) needs to be addressed by further data, to demonstrate that they are less sensitive or that a recovery can take place in an acceptable time after the exposure event. The TER values for the zooplankton community are given below.

Crop and application rate: Forest 0.048 kg a.s./ha. Test substance a.s.

Application rate (kg as/ha)	Crop	Organism	Time scale	Toxicity endpoint (µg/L)	$PEC_{initial,sw}$ * µg a.s./L	Distance (m)	TER	Annex VI Trigger
0.048	Forest, aerial application	*D. magna*	21 d	0.04	5.31	3 m	0.008	10
0.048	Forest, hand application	*D. magna*	21 d	0.04	1.28	3 m	0.03	10
0.048	Forest, aerial application	~~EAC~~ NOEAEC zooplankton **	-	~~0.07~~ 0.14	5.31	3 m	~~0.013~~ 0.026	1
0.048	Forest, hand application	~~EAC~~ NOEAEC zooplankton **	-	~~0.07~~ 0.14	1.28	3 m	~~0.054~~ ~~5~~ 0.109	1
0.048	Forest, hand application	~~EAC~~ NOEAEC zooplankton **	-	~~0.07~~ 0.14	0.2	10	~~0.035~~ 0.7	1
0.048	Forest, hand application	~~EAC~~ NOEAEC zooplankton **	-	~~0.07~~ 0.14	0.07	20	~~1~~ 2	1

* PEC based on spray drift over a static 30-cm deep waterbody. Distance x m from treated area, drift rates according to "Focus surface water scenarios in the EU evaluation process under 91/414/EEC (SANCO/4802/2001-rev-1)".
** the risk to insects (and amphipods) needs to be addressed by further data

Refined aquatic risk assessment using higher tier FOCUS modelling. FOCUS Step 3

Crop and application rate: Pome fruit 2 applications á 180 g /ha, 14 days interval. Test substance: a.s.

Scenario[1]	Water body type[2]	Test organism[3]	Time scale	Toxicity endpoint (µg/L)	$PEC_{initial,sw}$ µg a.s./L	TER	Annex VI trigger
D3	ditch	D. magna	21 d	0.04	11.989	0.003	10
D4	pond	D. magna	21 d	0.04	0.976	0.041	10
D4	stream	D. magna	21 d	0.04	11.400	0.004	10
D5	pond	D. magna	21 d	0.04	0.989	0.040	10
D5	stream	D. magna	21 d	0.04	12.494	0.003	10
R1	pond	D. magna	21 d	0.04	0.915	0.044	10
R1	stream	D. magna	21 d	0.04	9.629	0.004	10
R2	stream	D. magna	21 d	0.04	12.756	0.003	10
R3	stream	D. magna	21 d	0.04	13.622	0.003	10

R4	stream	D. magna	21 d	0.04	9.686	0.004	10
D3	ditch	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	11.989	~~0.006~~ 0.012	1
D4	pond	~~EAC~~ NOEAEC zooplankton **	-	~~0.07~~ 0.14	0.976	~~0.072~~ 0.144	1
D4	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	11.400	~~0.006~~ 0.012	1
D5	pond	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	0.989	~~0.0355~~ 0.071	1
D5	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	12.494	~~0.006~~ 0.012	1
R1	pond	~~EAC~~ NOEAEC zooplankton **	-	~~0.07~~ 0.14	0.915	~~0.077~~ 0.154	1
R1	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	9.629	~~0.007~~ 0.014	1
R2	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	12.756	~~0.005~~ 0.01	1
R3	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	13.622	~~0.005~~ 0.01	1
R4	stream	~~EAC~~ NOEAEC zooplankton **	-	~~0.07~~ 0.14	9.686	~~0.007~~ 0.014	1

** the risk to insects (and amphipods) needs to be addressed by further data

FOCUS Step 4

Crop and application rate: Pome fruit 2 application á 180 g /ha. Test substance: a.s.

Scenario[1]	Water body type[2]	Test organism[3]	Time scale	Toxicity endpoint (mg/L)	Buffer zone distance	$PEC_{initial,sw}$ µg a.s./L	TER	Annex VI trigger
D3	ditch	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	20 m	1.42	~~0.049~~ 0.098	1
D4	pond	~~EAC~~ NOEAEC zooplankton **	-	~~0.07~~ 0.14	20 m	0.19	~~0.372~~ 0.736	1
D4	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	20 m	1.48	~~0.047~~ 0.094	1
D5	pond	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	20 m	0.19	~~0.37~~ 0.74	1
D5	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	20 m	1.62	~~0.043~~ 0.86	1
R1	pond	~~EAC~~ NOEAEC zooplankton **	-	~~0.07~~ 0.14	20 m	0.18	~~0.40~~ 0.8	1
R1	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	20 m	1.25	~~0.056~~ 0.115	1
R2	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	20 m	1.66	~~0.042~~ 0.084	1
R3	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	20 m	1.77	~~0.040~~ 0.080	1
R4	stream	~~EAC~~ NOEAEC	-	~~0.07~~ 0.14	20 m	1.26	~~0.056~~	1

		zooplankton **					0.112	
D3	ditch	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	30 m	0.49	~~0.14~~ 0.07	1
D4	pond	~~EAC~~ NOEAEC zooplankton **	-	~~0.07~~ 0.14	30 m	0.08	~~0.84~~ 1.68	1
D4	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	30 m	0.51	~~0.14~~ 0.28	1
D5	pond	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	30 m	0.08	~~0.83~~ 1.66	1
D5	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	30 m	0.56	~~0.13~~ 0.26	1
R1	pond	~~EAC~~ NOEAEC zooplankton **	-	~~0.07~~ 0.14	30 m	0.08	~~0.90~~ 1.80	1
R1	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	30 m	0.43	~~0.16~~ 0.32	1
R2	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	30 m	0.57	~~0.12~~ 0.24	1
R3	stream	~~EAC~~ NOEAEC zooplankton**	-	~~0.07~~ 0.14	30 m	0.61	~~0.12~~ 0.24	1
R4	stream	~~EAC~~ NOEAEC zooplankton **	-	~~0.07~~ 0.14	30 m	0.43	~~0.16~~ 0.32	1

** the risk to insects (and amphipods) needs to be addressed by further data

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

At the PRAPeR it was concluded that a correction factor of 5 should be used for the calculation of the drift rate according to the recommendations for higher tier risk assessment in ESCORT 2. Resulting in the following alterations of the off-crop risk assessment.

OFF-crop risk assessment for non-target arthropods

Application rate	Crop	Organism	Distance from edge	Drift rate early application * (g a.s./ha)	Drift rate late application * (g a.s./ha)	LR50
180 g/ha	Pome fruit	*C. carnea*	3	~~78~~ 390	~~37~~ 185	1.3
	Pome fruit	*C. carnea*	5	~~52~~ 260	~~21~~ 105	1.3
	Pome fruit	*C. carnea*	10	~~29~~ 145	~~10~~ 50	1.3
	Pome fruit	*C. carnea*	15	~~17~~ 85	~~5~~ 25	1.3
	Pome fruit	*C. carnea*	20	~~8~~ 40	~~3~~ 15	1.3
	Pome fruit	*C. carnea*	30	~~3~~ 24	~~1~~ 5	1.3
	Pome fruit	*C. carnea*	40	~~1~~ 5	~~0.7~~ 3.5	1.3
	Pome fruit	*C. carnea*	50	3.5	2.5	1.3
	Pome fruit	*C. carnea*	75	1	1	1.3
	Pome fruit	*C. carnea*	100	0.5	0.5	1.3

Application rate	Crop	Organism	Distance from edge	Drift rate * (g a.s./ha)	LR50
48 g a.s./ha	Forest, hand application	C. carnea	3	~~3.84~~ 19.2	1.3
	Forest, hand application	C. carnea	5	~~1.7~~ 8.5	1.3
	Forest, hand application	C. carnea	10	~~0.59~~ 2.95	1.3
	Forest, hand application	C. carnea	15	~~0.31~~ 1.55	1.3
	Forest, aerial application	C. carnea	3	~~15.8~~ 79	1.3

* For the calculation of the drift rate a correction factor of 5 has been used according to the recommendations for higher tier risk assessment in ESCORT 2.

Field or semi-field tests:
Additional data was submitted in the form of a literature review, summarized in the DAR. The overall conclusion from all available information is that the risk to non target arthropods in-field is not acceptable; the in-field recovery/recolonisation needs to be further addressed. ~~may be considered acceptable provided off-field habitats are protected which require buffer zones of 10-40 m(depending on the use). This may need to be discussed at an expert meeting.~~. In order to protect off-crop non-target arthropods buffer zones is needed (for the use in orchards 75 m is needed.).