SCIENTIFIC REPORT OF EFSA

on the risk assessment of salts of authorised acids, phenols or alcohols for use in food contact materials[1]

European Food Safety Authority[2, 3]

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ABSTRACT

Following a request from the European Commission for scientific assistance, the EFSA examined whether the current risk assessments of authorised acids, phenols and alcohols as well as these of the cations lithium, copper, barium, cobalt and manganese cover also their salts for use in food contact materials or there is a need for specific evaluation of the salts themselves. To answer the question, EFSA considered the possible concentration of the salts in the stomach which cannot exceed 60 mg/kg, the low pH of the gastric fluids, the dissociation constants of the acids authorised already by August 2009, the solubility of the salts as well as the complexing capacity of some of the cations and acids. Based on these parameters, the EFSA concluded that in all cases the salts will dissociate in the human stomach to the corresponding metal ions and the phenols, alcohols and acids. This is true in most cases even for complexing acids like ethylenediaminetetraacetic acid. However, further considerations may be needed for some complex salts to decide the degree of dissociation. The overall conclusion is that for food contact applications the risk assessments of the acids, phenols and alcohols and of these cations can also be used for their salts..

KEY WORDS

Salts, dissociation, lithium, barium, cobalt, copper, manganese

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SUMMARY

The European Food Safety Authority is asked to provide scientific assistance to the European Commission, in accordance with Article 31 (1) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority for its scientific assistance on the risk assessment of salts used in plastic food contact materials where both anion and cation are already authorised by 31 August 2009. In particular the European Commission asked whether the current risk assessments of the cations copper, barium, cobalt, lithium and manganese allow for an authorisation of the salts of these cations with authorised acids, phenols and alcohols if the salts respect the restrictions and specific migration limits established for both the cation and the acid, phenol or alcohol?
In the current legislation it is foreseen that when an acid, phenol or alcohol is authorised following an evaluation by EFSA or by the SCF, its authorisation covers also the salts derived from these acids, phenols or alcohols with certain cations . The cations covered by this authorisation rule are salts of aluminium, ammonium, calcium, iron, magnesium, potassium, sodium and zinc. For these cations, with the exception of zinc which has a migration limit of 25 mg/kg established in 2005, no specific restriction exists; they are covered by a generic specific migration limit of 60 mg/kg food. The current rules laid down in Directive 2002/72/EC relating to plastic materials and articles intended to come into contact with foodstuffs.

The EFSA Unit on food contact materials, enzymes, flavourings and processing aids (CEF) has considered the possible behaviour of the salts in the human stomach.

Due to the weak or non acidic properties of phenols and alcohols, their salts will always dissociate and give alcohols and phenols and metal ions In the environment of the low pH (pH=2) of the human stomach.

Salts of weak acids will dissociate in the environment of the human stomach into acid and the metal ion. Some minor amounts of ionised acid will also be present.

Salts of weak acids, with a dissociation constant Ka < 10^{-3}, will predominantly dissociate into metal ion and the acid itself.

Worst case acids, regarding the dissociation of their salts, authorised for use in food contact materials can be considered:

- Strong acids (Ka > 10^{-3}) with a low molecular weight. The low molecular weight leads to a higher molar concentration for a given concentration expressed as mass/volume. Among the authorised acids of this category, oxalic acid can be considered the worst case. It can be calculated however that its salts dissociate completely in the low pH environment of the human stomach at concentrations corresponding to the higher migration limit allowed for in the legislation which was conservatively considered to be equal to the overall migration limit of 60 mg/L (EC, 2002).

- Polyfunctional compounds as the chelating agent ethylenediamine tetraacetic acid. Even for this acid, at the low concentrations corresponding to the migration levels set in legislation, the low pH of the stomach leads to a predominant form of the acid which is not complexing. The cations lithium and barium do not form complexes and

the conclusions of the previous indent examining salts of strong acids apply to them, too. The cations cobalt, copper and manganese form complexes with EDTA but they also form complexes with the chloride ions. Considering all parameters influencing the dissociation of the EDTA salts with these cations, it can be calculated that for the cobalt and manganese complexes the dissociation will be complete while for the copper complex more investigation is needed.

The EFSA concludes that salts of cations lithium, copper, barium, cobalt and manganese with authorised acids, phenols and alcohols for use in food contact materials will dissociate in the human stomach in all cases except for the copper salt of EDTA for which further investigation is needed to decide the degree of its dissociation. Consequently, for food contact applications the risk assessments of the acids, phenols and alcohols and these cations can also be used for their salts except for the salt of the EDTA with copper.

Any degradation and/or reaction products should remain in the responsibility of the manufacturer.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The Scientific Committee on Food and the European Food Safety Authority have already evaluated several hundred substances that can be used in plastic food contact materials. When, following their evaluation, substances that are acids, phenols or alcohols are authorised, their authorisation covers also the salts derived from these acids, phenols or alcohols with certain cations . The cations covered by this authorisation rule are salts of aluminium, ammonium, calcium, iron, magnesium, potassium, sodium and zinc. For these cations, with the exception of zinc, no specific restriction exists; they are covered by a generic specific migration limit of 60 mg/kg food. Zinc was also covered by the generic specific migration limit until 2005. In 2005 a specific migration limit of 25 mg/kg was established based on the SCF opinion on tolerable upper intake level of zinc expressed on 5 March 2003[4]. Salts derived from authorised acids, phenols or alcohols with other cations are covered by individual authorisations based on individual risk assessments of the specific salt. The current rules laid down in Directive 2002/72/EC relating to plastic materials and articles intended to come into contact with foodstuffs[5] are attached.

During the current review of the legislation on plastic food contact materials and articles we consider revising the way acids, phenols or alcohols and their salts are authorised and simplifying the current system in the following way. We suggest that in addition to the salts derived from authorised acids, phenols or alcohols with the cations aluminium, ammonium, calcium, iron, magnesium, potassium, sodium and zinc also those with the cations copper, barium, cobalt, lithium, manganese are authorised if they respect the individual restrictions and specific migration limits established for these cations. Currently the restrictions and specific migration limits for these cations were based either on upper intake levels established by the SCF or EFSA or the risk assessment of individual substances in the context of authorisation of that individual substance. The suggested rules are attached as well as the scientific opinions that cover the restriction for the cation.

This revised system would lead to a simplification as it would not be necessary to file an application for a substance for which separately both the anion and the cation are already authorised. In the future any new cation which is evaluated in the context of plastic food contact materials could be added to the list of cations for which these rules apply if its risk assessment would allow for such an inclusion.

We would like to know if the current risk assessment of all the above mentioned cations would qualify for such a system with the current specific migration limits established in Directive 2002/72/EC taking into account also the potential migration behaviour of the salts that would be covered.

We would like to know if such a general system would give rise to risks which should preferably be dealt with by individual assessments.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 31 (1) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority for its scientific assistance on the risk assessment of salts used in plastic food contact materials where both anion and cation are already authorised by 31 August 2009.

[4] http://ec.europa.eu/food/fs/sc/scf/out177_en.pdf
[5] OJ L 220, 15.08.2002, p.18

We would like scientific assistance in particular on the following questions:
Do the current risk assessments of the cations copper, barium, cobalt, lithium and manganese allow for an authorisation of the salts of these cations with authorised acids, phenols and alcohols if the salts respect the restrictions and specific migration limits established for both the cation and the acid, phenol or alcohol?
Does the suggested system give rise to risks which should preferably be dealt with by individual assessments of the salts? If this is the case, for which salts would an individual assessment be preferable to cover adequately the risks from its use?

ASSESSMENT

1. Introduction – General Considerations

The Commission has already authorised hundreds of acids, phenols and alcohols for use in the manufacture of plastic food contact materials (EC, 2002) based on risk assessments of these substances by the SCF or EFSA. The Commission has also authorised salts of some of these substances with the cations lithium, barium, cobalt, copper and manganese setting migration limits for the cations which are similarly based on risk assessments of the SCF or EFSA. The EFSA will examine whether risk assessments already performed for the acids, phenols and alcohols (anions) and for the abovementioned cations can cover also their salts or there is a need for new specific risk assessments of the salts themselves.

It is important to note that for all substances authorised for use in plastic food contact materials the maximum migration in food must not exceed 60 mg/kg according to the legislation (EC, 2002). So, in case that a specific migration restriction is not set for a substance in the Directive the general migration restriction of 60 mg/kg food is still valid.

To answer the question whether the acid, alcohol or phenol salts (A_pM_x) can be covered by the risk assessment of the acid, alcohol or phenol (A^{x-}) and the cation (M^{p+}) the EFSA determined whether the salts are dissociated in the acidic conditions of the human stomach.

For simplicity the example of a monoacid or phenol or alcohol (AH) and a bivalent cation (M^{2+}) is considered. In this case it has to be assessed whether the equilibrium (1) is shifted to the right.

$$A_2M \rightleftharpoons 2A^- + M^{2+} \qquad (1)$$

In the acidic conditions of the human stomach, pH=2, the following equilibrium which takes into account the influence of the low pH and leads to the protonation of the A^-, has to be assessed:

$$2\,H^+ + A_2M \rightleftharpoons 2\,AH + M^{2+} \qquad (2)$$

The equilibrium (2) in the low pH of the human stomach mainly depends on:

- The solubility of the salt A_2M expressed by the solubility product Ks. The higher the solubility, the higher the dissociation, i.e. equilibrium shifted to the right.
- The strength of the acid AH expressed by the acidity constant Ka or by pKa = -logKa. The higher the pKa, the higher the dissociation, i.e. equilibrium shifted to the right.
- The concentration of the salt. The lower the concentration, the higher the dissociation, i.e. equilibrium shifted to the right.

Other parameters can also play a role.

- The possible formation of complexes
- The redox properties of the anion A^-

However, given the low pH and the low concentration of the migrants they are expected to play a minor role and they can be neglected.
At the stomach temperature, kinetics is rapid. Therefore only the thermodynamic effects above are considered here.

2. Examination of various types of salts

The following cases of salts can be distinguished:

2.1. Salts of alcohols and phenols

In aqueous media, alcohols have no (e.g. ethanol, methanol) or weak (e.g. phenol) acid properties, high pKa. Therefore the corresponding salts will be always dissociated (equilibrium (2) completely shifted to the right). This is in agreement with general chemical knowledge.

2.2. Salts of acids

For the salts of acids the following categories can be distinguished:

2.2.1. Salts of weak acids

The carboxylic acids listed in Table 1 have a pKa lower than 3 and therefore can be considered as worst case acids regarding the dissociation of their salts. It has to be examined carefully if they completely dissociate.

2.2.2. Salts of strong acids

The carboxylic acids listed in Table 1 have a pKa lower than 3 and therefore can be considered as worst case acids regarding the dissociation of their salts. It has to be examined carefully if they completely dissociate.

Table (1): worst case acids, identified from Directive 2002/72/EC on basis of pKa values (pKa<3)

Acid	pKa_1	pKa_2	pKa_3	pKa_4
perfluorooctanoic acid, ammonium salt *	1.3 and/or 3.8			
oxalic acid	1.19	4.21		
malonic acid	1.80	5.67		
maleic acid	2.00	6.26		
o-phthalic acid	2.98	5.30		
salicylic acid	2.98			
ethylenediamine tetraacetic acid	2.0	2.7	6.2	10.3

* This value is under discussion. See Environment Science & Technology 2008, 42, 9283–9288 and the related discussion: DOI: 10.1021/es802047v. comment DOI: 10.1021/es900451s and response DOI: 10.1021/es900815a

Oxalic acid salts can be considered as the worst case for the following main reasons:

- **pKa value**: the lower is the pKa, the lower is the dissociation. Oxalic acid has a very low pKa, compared to other carboxylic acids

- **concentration**: for a given pKa, the higher is the molar concentration (in mol/L), the lower is the dissociation. Taking 60 mg salt/kg food as the highest possible migration of the salt (which is a worst case value), oxalate ions will have the highest molar concentrations among the acids of the table 1 due to the low molecular mass of oxalic acid compared to the other acids. Salts with higher molecular weight have lower molar concentrations
- **solubility product of the salt**: the lower is the solubility product, the lower is the dissociation

A salt may be completely dissociated in an aqueous solution at a given concentration if it is soluble at this concentration. Hence, it has also to be calculated if the product of the concentration of the anion by the concentration of the cation of a salt (ion product) is lower than the solubility product of the salt.

As an example the dissociation of a salt (AM) of oxalic acid (AH_2) with a bivalent metal ion (M) is described by the equilibrium (3):

$$3\ H^+ + 3\ AM \rightleftharpoons A^{2-} + AH^- + AH_2 + 3\ M^{2+} \quad (3)$$

The following equations apply too:

$$Ka_1 = \frac{(AH^-)*(H^+)}{(AH_2)} \quad (4)$$

$$Ka_2 = \frac{(A^{2-})*(H^+)}{(AH^-)} \quad (5)$$

If c is the concentration of the salt (AM) the concentration of the oxalate ion (A^{2-}) is:

$$(A^{2-}) = c - (AH^-) - (AH_2) \quad (6)$$

Solving the equations (4) , (5) and (6) at pH = 2 and taking the values from the table 2 for the Ka_1 and the Ka_2, we have:

$$(A^{2-}) = \frac{C}{1 + \frac{(H^+)}{Ka_2} + \frac{(H^+)^2}{Ka_1 * Ka_2}} \quad (7)$$

And finally: $(A^{2-}) = c/185$ (8)

The ion product of a salt of oxalic acid with a bivalent metal ion can then be calculated as $c^2/185$.

As an example we can consider the dissociation of copper oxalate. The overall molar concentration of oxalate species (dissociated and non dissociated) may be as high as 3.96 x 10^{-4} mol/L (value corresponding to 60 mg CuC_2O_4/L), the salt will not be completely dissociated if its solubility product is lower than its ion product, 8.47 x 10^{-10} mol/L. As for CuC_2O_4 the solubility product is 2. 9 x10^{-8} mol/L, the dissociation is complete. Similar considerations for other salts and for the maximum allowed concentrations are in the table (2) below. The maximum concentration of the salt in the stomach is taken equal to the maximum value of the overall migration (60 mg/kg) as set in the

Directive 2002/72/EC and assuming that there is no dilution in the stomach which is a conservative approach.

Table (2): Dissociation of oxalate salts

Salt (molecular weight, g/mol)	Maximum concentration of salt (g/L) **	Maximum concentration of salt (mol/L)	Ion product (mol/L)	Solubility product of salt (mol/L)	Dissociation at pH of stomach (pH 2)
Sodium oxalate $Na_2C_2O_4$	at 60 mg salt/kg food	4.48×10^{-4}	1.94×10^{-12}	8.4 $x10^{-2}$ (a)	Complete
Iron oxalate FeC_2O_4	at 60 mg salt/kg food	4.17×10^{-4}	9.4×10^{-10}	2.1 $x10^{-7}$ (b)	Complete
Zinc oxalate ZnC_2O_4	at 60 mg salt/kg food	3.91×10^{-4}	8.27×10^{-10}	1.4 $x10^{-9}$ (b)	Complete
Copper oxalate CuC_2O_4	at 60 mg salt/kg food	3.96×10^{-4}	8.47×10^{-10}	2. 9 $x10^{-8}$ (b)	Complete
Manganese oxalate MnC_2O_4, $2H_2O$	at 60 mg salt/kg food	3.35×10^{-4}	6.08×10^{-10}	3.1 $x10^{-6}$ (a)	Complete
Cobalt oxalate CoC_2O_4	at 60 mg salt/kg food	4.08×10^{-4}	9.1×10^{-10}	6.3 $x10^{-8}$ (c)	Complete

(**) corresponding to the overall migration limit set in the Directive 2002/72/EC. For some salts the concentration of the salt will be even lower restricted by the migration limit set in the Directive for the metal ions (e.g. 0.05 mg/kg for cobalt, 0.6 mg/kg for manganese)

(a) Handbook of Chemistry and Physics 69th edition, CRC Press
(b) Electrochemical data, D. DOBOS, ed. Elsevier 1975
(c) Handbook of Chemistry and Physics, Cleveland, 1955 37th ed, in "separation of impurities from cobalt with complexing agents by V. N. Zaichenko, G. Ya. Kolbasov, and Yu. S. Krasnov in *Russian Journal of Applied Chemistry, 2008, Vol. 81, No. 1, pp. 158-159*

2.2.3. Salts of complexing acids

Polyfunctional acids (e.g. citric acid, ethylenediaminetetraacetic acid, tartaric acid) have a complexing capacity. Among them ethylenediamine tetraacetic acid (EDTA) forms the most stable complexes. However, the complexing agent is the anionic form of the acid (e.g. for ethylenediaminetetraacetic acid, the complexing species is A^{4-}) and taken into account the pKa values of the acid and the low molar concentration of the acid corresponding to the overall migration limit of 60 mg/kg, in most cases the acid will predominantly be not in this form in the human stomach.

Due to their electronic configuration, lithium and barium ions do not give many complexes and the solubility of their salts is mainly depending on Ks and Ka. The problem is different for manganese, cobalt and copper which give many complexes. On the other hand, these ions can be involved in reactions with chloride ions to form complex ions. This shifts the equilibrium (2) towards the right side.

EDTA salts:

The dissociation of complex salts of EDTA with the cations cobalt, copper and manganese will depend on the same considerations as above for oxalic acid, i.e. the dissociation constants of the acid, the pH, the concentration of the salt, the solubility of the salt and in addition the stability constant of the salt.

$$\mathrm{K}stab = \frac{(\mathrm{MA})}{(\mathrm{M}) * (\mathrm{A})}$$

The higher the stability constant of the salt is, the lower the dissociation.

For the specific question of complex salts of EDTA for use in food contact materials, it can be calculated that if the stability constant of the salt is lower than 10^{17} the dissociation of the acid will be almost complete in the human stomach. For the complete set of equations ruling the dissociation of EDTA salts, please APPENDIX A. For the cations in question only the copper complex which has a stability constant of $10^{18,8}$ needs further considerations to answer the question. (APPENDIX B - Stability Constants (log K1) of Various Metal Chelates from Chapter 6 - Sequestrants in Foods, by Thomas E. Furia, in CRC Handbook of Food Additives, 2nd ed. 1972 as revised by cited authors - latest revision October 26, 2006)

In conclusion, at the low concentrations corresponding to the migration levels set in legislation, even complex salts of ethylenediamine tetraacetic acid will dissociate in human stomach in the presence of hydrochloric acid. However, for some very stable complexes like the copper ethylenediamine tetraacetate, more investigation is needed.

It must be noted that these calculations do not take into account the other reactions in which the metal ions can be involved, in particular the complexation with hydroxy and chloride ions, and it can be assumed that the dissociation would be more effective.

CONCLUSIONS

The EFSA examined whether the current risk assessments of authorised acids, phenols and alcohols as well as these of the cations lithium, copper, barium, cobalt and manganese cover also their salts for use in food contact materials or there is a need for specific evaluation of the salts themselves.

Due to the weak or non acidic properties of phenols and alcohols, their salts will always dissociate and give alcohols and phenols and metal ions In the environment of the low pH (pH=2) of the human stomach.

Salts of weak acids will dissociate in the environment of the human stomach into acid and the metal ion. Some minor amounts of ionised acid will also be present.

Salts of weak acids, with a dissociation constant Ka < 10^{-3}, will predominantly dissociate into metal ion and the acid itself.

Worst case acids, regarding the dissociation of their salts, authorised for use in food contact materials can be considered:

- Strong acids (Ka > 10^{-3}) with a low molecular weight. The low molecular weight leads to a higher molar concentration for a given concentration expressed as mass/volume. Among the authorised acids of this category, oxalic acid can be considered the worst case. It can be calculated however that its salts dissociate completely in the low pH environment of the human stomach at concentrations corresponding to the higher migration limit allowed for in the legislation which was conservatively considered to be equal to the overall migration limit of 60 mg/L (EC, 2002).

- Polyfunctional compounds as the chelating agent ethylenediamine tetraacetic acid. Even for this acid, at the low concentrations corresponding to the migration levels set in legislation, the low pH of the stomach leads to a predominant form of the acid which is not complexing. The cations lithium and barium do not form complexes and the conclusions of the previous indent examining salts of strong acids apply to them, too. The cations cobalt, copper and manganese form complexes with EDTA but they also form complexes with the chloride ions. Considering all parameters influencing the dissociation of the EDTA salts with these cations, it can be calculated that for the cobalt and manganese complexes the dissociation will be complete while for the copper complex more investigation is needed.

The EFSA concluded that salts of cations lithium, copper, barium, cobalt and manganese with authorised acids, phenols and alcohols for use in food contact materials will dissociate in the human stomach in all cases except for the copper salt of EDTA for which further investigation is needed to decide the degree of its dissociation. Consequently, for food contact applications the risk assessments of the acids, phenols and alcohols and these cations can also be used for their salts except for the complex salt of the EDTA with copper.

Any degradation and/or reaction products should remain in the responsibility of the manufacturer.

DOCUMENTATION PROVIDED TO EFSA

(1) Current rules in Directive 2002/72/EC covering the authorisation of salts of acids, phenols and alcohols

(2) Suggested new rules covering the authorisation of salts of acids, phenols and alcohols

- Scientific opinions on which the restriction of the cations is based

(3) Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Copper (expressed on 5 March 2003)

(4) Opinion of the Scientific Committee on Food on the 13th additional list of monomers and additives for food contact materials (Adopted by the SCF on 30 May 2001) covering Barium Tetraborate Ref No: 36840

(5) Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to a 1st list of substances for food contact materials (Opinion adopted on 1 October 2003) covering; Oleic acid, cobalt salt Ref. No 69160

(6) Opinion of the Scientific Committee on Food on the 21st additional list of monomers and additives for food contact materials (Opinion expressed on 5 March 2003) covering, Myristic acid, lithium salt, Ref No. 67896

(7) Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request from the Commission related to a 7th list of substances for food contact materials adopted on 29 March 2005 by written procedure covering 2,2'-Methylenebis(4,6-di-tert-butylphenyl) lithium phosphate Ref. No. 66350

APPENDICES

APPENDIX A

EQUATIONS GOVERNING THE EQUILIBRIA OF EDTA SALTS

$$Kstab = \frac{(MA)}{(M^+)(A^{-4})} \sim > \frac{(M^+)}{(MA)} = \frac{1}{Kstab\ (A^{-4})} \quad (1)$$

$$\begin{aligned} H_4A &\leftrightarrows H_3A + H^+ \qquad Ka_1 = \frac{(H_3A^-)\,(H^+)}{(H_4A)} \\ H_3A^- &\leftrightarrows H_2A^{2-} + H^+ \qquad Ka_2 = \frac{(H_2A^{2-})\,(H^+)}{(H_3A^-)} \\ H_2A^{2-} &\leftrightarrows HA^{-3} + H^+ \qquad Ka_3 = \frac{(HA^{-3})\,(H^+)}{(H_2A^{2-})} \\ HA^{-3} &\leftrightarrows A^{-4} + H^+ \qquad Ka_4 = \frac{(A^{4-})\,(H^+)}{(HA^{-3})} \end{aligned} \quad (2)$$

$$\frac{(A^{-4})}{(H_4A)} = \frac{Ka_1 * Ka_2 * Ka_3 * Ka_4}{(H^+)^4} \quad (3)$$

$$C = (MA)_{init} = (H_4A) + (H_3A^-) + (H_2A^{2-}) + (HA^{3-}) + (A^{4-}) \quad (4)$$

$$(A^{4-}) = \frac{C}{1 + \frac{(H^+)}{Ka_4} + \frac{(H^+)^2}{Ka_4 * Ka_3} + \frac{(H^+)^3}{Ka_4 * Ka_3 * Ka_2} + \frac{(H^+)^4}{Ka_4 * Ka_3 * Ka_2 * Ka_1}} \quad (5)$$

$$\frac{(M^+)}{(MA)} = \frac{1}{Kstab} * \frac{1 + \frac{(H^+)}{Ka_4} + \frac{(H^+)^2}{Ka_4 * Ka_3} + \frac{(H^+)^3}{Ka_4 * Ka_3 * Ka_2} + \frac{(H^+)^4}{Ka_4 * Ka_3 * Ka_2 * Ka_1}}{C} \quad (6)$$

APPENDIX B

Stability Constants (log K_1) of Various Metal Chelates
from
Chapter 6 - Sequestrants in Foods, by Thomas E. Furia, in CRC Handbook of Food Additives,
2nd ed. 1972 as revised by cited authors (where data shows a letter corresponding to citation at bottom of table)

latest revision October 26, 2006
NOTE: THIS FILE IS UPDATED UPON FINDING USEFUL FOOD CHEMISTRY DATA

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What are " Stability Constants"

The A. E. Martell's NIST Critically Selected Stability Constants of Metal Complexes is the Bible for stability data for metal and ligand reactions. However, it is an expensive and vast document. Stability constants for *very strong chelators* is found on the Stanford MAXCHELATOR page. A general search for A.E. Martell's critical stability constants is here. Unfortunately, Dr. Martell died in 2003.

Metal (to right) Ligand (below)	***Al(III)***	***Ba***	***Ca***	***Co(II)***	***Cu***	***Fe(II)***	***Fe(III)***	***Hg***	***Mg***	***Mn***	***Ni***	***Sr***	***Zn***
Acetic acid		0.39	0.53	2.24				3.7d	0.51		0.74	0.43	1.03
Adenine													
Adipic acid		1.92	2.19		3.35								
ADP		2.36	2.82	3.68	5.90				3.11	3.54	4.50	2.50	4.28
Alanine		0.80	1.24	4.82	8.18					3.24	5.96	0.73	5.16
β-Alanine					7.13						4.63		4
Albumin			2.20										
Arginine						3.20				2.0			
Ascorbic acid			0.19									0.35	
Asparagine			0									0.43	
Aspartic acid		1.14	1.16	5.90	8.57				2.43	3.74	7.12	1.48	~~5.84~~ 2.90a
ATP	9.8	3.29	3.60	4.62	6.13				4.0	3.98	5.02	3.03	4.25
Benzoic acid					1.6						0.9		0.9
n-Butyric acid		0.31	0.51		2.14				0.53			0.36	1.00
Casein			2.23										
Citraconic acid			1.3									1.3	
Citric acid	11.7e	2.3	3.5	4.4	6.1	3.2	11.85	10.9 d	2.8	3.2	4.8	2.8	4.5

Cysteine				9.3	19.2	6.2		14.4 d	< 4	4.1	10.4		9.8
Dehydracetic acid					5.6						4.1		
Desferri-ferrichrysin							29.9						
Desferri-ferrichrome							29.0						
Desferri-ferrioxamin E				11.8	13.7		32.5				12.2		12.0
3,4-Dihydroxybenzoic acid			3.71	7.96	12.79				5.67	7.22	8.27		8.91
Dimethylglyoxime					11.94						14.6		7.7
O,O-Dimethylpurpurogallin			4.5	6.6	9.2				4.9		6.7		6.8
DNA	<5.6e												
Metal (to right) Ligand (below)	***Al(III)***	***Ba***	***Ca***	***Co(II)***	***Cu***	***Fe(II)***	***Fe(III)***	***Hg***	***Mg***	***Mn***	***Ni***	***Sr***	***Zn***
EDTA	16.13	7.78	10.70	16.21	18.8	14.3	25.7	21.5 d	8.69	13.56	18.56	8.63	16.5
Formic acid		0.60	0.80		1.98		3.1					0.66	0.60
Fumaric acid		1.59	2.00		2.51					0.99		0.54	
Globulin			2.32										
Gluconic acid		0.95	1.21		18.29				0.70			1.00	1.70
Glutamic acid		1.28	1.43	5.06	7.85	4.6			1.9	3.3	5.9	1.37	5.45
Glutaric acid		2.04	1.06		2.4				1.08			0.6	1.60
Glyceric acid		0.80 b	1.18 b						0.86 b			0.89 b	1.80 b
Glycine		0.77	1.43	5.23	8.22	4.3	10.0	10.3 d	3.45	3.2	6.1	0.91	5.16
Glycolic acid		0.66	1.11	1.60	2.81		4.7		0.92 b			0.80 b	1.92 b
Glycylglycine			1.24	3.00	6.7	2.62	9.1		1.34	2.19	4.18		3.91
Glycylsarcosine				3.91	6.50					2.29	4.44		
Guanosine				3.2	6	4.3			3.0		3.8		4.6
Histamine				5.16	9.55	9.60	3.72				6.88		5.96
Histidine				7.30	10.60	5.89	4.00			3.58	8.69		6.63
β-Hydroxybutyric		0.43 b	0.60 b						0.60 b			0.47 b	1.06 b
3-Hydroxyflavone				9.91	13.20								9.70
Inosine				2.6	5	3					3.3		
Inosine triphosphate			3.76	4.74					4.04	4.57			

Iron-free ferrichrome							24.6						
Isovaleric acid			0.20		2.08								
Itaconic acid			1.20		2.8						1.8	0.96	1.9
Kojic acid	7.7		2.5	7.11	6.6		9.2		3.0		7.4		4.9
Lactic acid		0.55	1.07	1.89	3.02		6.4		0.93	1.19	2.21	0.70	1.86
Leucine				4.49	7.0	3.42	9.9			2.15	5.58		4.92
Lysine							4.5			2.18			
Maleic acid		2.26	2.43		3.90					1.68	2.0	1.1	2.0
Malic acid		1.30	1.80		3.4				1.55	2.24		1.45	2.80
Methionine						3.24	9.1				5.77		4.38
Methylsalicylate					5.90		9.77						
NTA	>10	4.82	6.41	10.6	12.68	8.84	15.87		5.41	7.44	11.26	4.98	10.45
Metal (to right) Ligand (below)	***Al(III)***	***Ba***	***Ca***	***Co(II)***	***Cu***	***Fe(II)***	***Fe(III)***	***Hg***	***Mg***	***Mn***	***Ni***	***Sr***	***Zn***
Orotic acid				6.39c							6.82c		6.42c
Ornithine				4.02	6.90	3.09	8.7			<2	4.85		4.10
Oxalic acid	7.26	2.31	3.0	4.7	6.3	>4.7	9.4		2.55	3.9	5.16	2.54	4.9
β-Phenylalanine					7.74	3.26	8.9						
Pimelic acid										1.08			
Pivalic acid			0.55		2.19								
Polyphosphate			3.0		3.5	3.0			3.2	5.5	3.0		2.5
Proline						4.07	10.0			3.34			
Propionic acid		0.34	0.50		2.2		3.45		0.54			0.43	1.01
Purine					6.90						4.88		
Pyrophosphate			5.0		6.7		22.2		5.7		5.8		8.7
Pyruvic acid			0.8		2.2								
Riboflavin				3.9	<6					3.4	4.1		<4
Salicylaldehyde				4.67	7.40	4.22	8.70		3.69	3.73	5.22		4.50
Salicylic acid	14.11e			6.72	10.60	6.55	16.35		4.7	2.7	6.95		6.85
Sarcosine				4.34	7.83	3.52	9.7				5.41		
Serine			1.43			3.43	9.2				5.44		
Succinic acid		1.57	1.20	2.08	3.3		7.49		1.2	2.11	2.36	0.9	1.78
(±)-Tartaric acid		1.95	1.80		3.2		7.49		1.36		3.78	1.94	2.68
Tetrametaphosphate		4.9	5.2		3.18				5.17		4.95	2.8	
Threonine						3.30	8.6						

Transferrin	12.3e												
Trimetaphosphate			2.50		1.55				1.11	3.57	3.22	1.95	
Triphosphate		6.3	6.5		9.8				5.8			3.80	9.7
Tryptophan							9.0						
Uridine diphosphate									3.17				
Uridine triphosphate			3.71	4.55					4.02	4.78			
n-Valeric acid		0.20	0.30		2.12								
Valine					7.92	3.39	9.6			2.84	5.37		5.0
Xanthosine				2.8	3.4	<2					3.0		2.4
Metal (to right) Ligand (above)	***Al(III)***	***Ba***	***Ca***	***Co(II)***	***Cu***	***Fe(II)***	***Fe(III)***	***Hg***	***Mg***	***Mn***	***Ni***	***Sr***	***Zn***

a. Berthon G et al., *Agents and Actions*, 1982;12:619-629. (considering protonated ammonium group)

b. Cannan, RK et al., *Journal of American Chemical Society*, 1938;60:2314-2320.

c. Tucci, ER et al., *Journal of Inorganic Neuclear Chemistry*, 1967;29:1657-1667.

d. Martell et al., Critical Stability Constants, 1998.

e. R. Bruce Martin, *Accounts of Chemical Research*, volume 27, number 7, 1994, pages 204-210

In the distribution of the zinc and gluconic acid system, pK values are used as shown after these reactions: $Zn2^{+}$ + L_ <=> ZnL^{+} (1.62) and ZnL^{+} + OH_ <=> $ZnL(OH)^{0}$ (8.14). The pK values are courtesy of Gerritt Bekendam, Akzo Chemicals BV Research Centre, Deventer, The Netherlands, 1989. The Zn^{2+} fraction over pH 6 is strongly affected by the second pK value. Precipitates of hydroxides of zinc result in supersaturated solutions. Page 1185, vol. 2, Handbook of metal-Ligand Interactions in Biologic Fluids - Bioinorganic Medicine, ed. Berthon , Marcel Dekker, NY, 1995.

k_1=2.3 for zinc sulfate

ABBREVIATIONS

CEF	Scientific Panel on "food contact materials, enzymes, flavourings and processing aids"
EDTA	ethylenediaminetetraacetic acid
EFSA	European Food Safety Authority
Ka	acid dissociation constant
pKa	negative logarithm of the acid dissociation constant