EUROPEAN COMMISSION

Directorate-General for Health & Consumers

Scientific Committee on Consumer Safety

SCCS

OPINION ON

Boron compounds

Scientific Committees
on consumer safety
on emerging and newly identified health risks
on health and environmental risks

The SCCS adopted this opinion at its 7th plenary meeting

of 22 June 2010

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.
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SCCS

The Committee shall provide opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

Scientific Committee members

Contact
European Commission
Health & Consumers
Directorate C: Public Health and Risk Assessment
Unit C7 - Risk Assessment
Office: B232 B-1049 Brussels
Sanco-Sc6-Secretariat@ec.europa.eu

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Prof. J. Angerer
Dr. U. Bernauer
Dr. C. Chambers
Prof. G. Degen
Dr. S.C. Rastogi
Prof. V. Rogiers
Prof. T. Sanner (chairman, rapporteur)
Dr. J. van Engelen
Prof. R. Waring
Dr. I.R. White

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This opinion has been subject to a commenting period of four weeks after its initial publication. In case comments were received during this time, they have been considered by the SCCS and discussed in the subsequent plenary meeting. Where appropriate, the text of the relevant sections of the opinion has been modified or explanations have been added. In the cases where the SCCS after consideration and discussion of the comments, has decided to maintain its initial views, the opinion (or the section concerned) has remained unchanged. Revised opinions carry the date of revision.

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1. BACKGROUND

New classification of some boron compounds as mutagenic and/or toxic to reproduction according to the Commission Regulation 790/2009[1]

Boron Compounds

In its opinion of 23 September 1998 on "boric acid, borates and tetraborates" (SCCNFP/0025/98), the SCCNFP established limits for the safe use of some boron compounds**.** This opinion has been implemented into entries 1a and 1b of Annex III, part 1 of the Cosmetics Directive (76/768/EEC as amended). The detailed entries are included in the annex I to this mandate.

On 21 August 2008 and on 15 of January 2009 the Commission adopted respectively Directives 2008/58/EC[2] and 2009/2/EC[3] amending Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances providing new classifications for some boron compounds[4]. The Annex II attached to this mandate lists the substances concerned by this request. In most instances, the classification of the boron compounds is toxic for reproduction, category 2 (CMR Repr. cat. 2), with varying specific concentration limits. These specific concentration limits set for the boron compounds indicate that thresholds for the reproductive toxicity could be established.

The Cosmetics Directive as modified by the Council and the European Parliament (2003/15/EC[5]), which is based on an opinion of the SCCNFP of September 2001 (SCCNFP/0474/01, final), stipulates that *"the use in cosmetic products of substances classified as carcinogenic, mutagenic or toxic for reproduction, of category 1, 2 and 3, under Annex I to Directive 67/548/EEC shall be prohibited. To that end the Commission shall adopt the necessary measures in accordance with the procedure referred to in Article 10(2). A substance classified in category 3 may be used in cosmetics if the substance has been evaluated by the SCCNFP and found acceptable for use in cosmetic products."*

In light of the new classification of some boron compounds a safety evaluation by the SCCS is necessary, taking into account the scientific data on which the classification has been based.

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1 OJ L 235, 5.9.2009, p. 1. Commission Regulation 790/2009, amending for technical purposes the EC Regulation 1272/2008 which deleted Annex I of Council Directive 67/548/EEC as from 20 January 2009 (Article 55(11)), took over the classification provided by the Directives 2008/58/EC and 2009/2/EC, implementing the 30 and 31 ATP, respectively, to the Directive 67/548/EEC

2 OJ L 246, 15.09.2008, p. 1

3 OJ L 11, 16.01.2009, p. 6

4 As indicated above, the classification provided by these two Directives has been taken over by Commission Regulation 790/2009 amending EC Regulation 1272/2008

5 OJ L 66, 11.03.2003, p. 26. See recital (12)
(12) "The SCCNFP stated in its opinion of 25 September 2001 that substances classified pursuant to Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances(2) as carcinogenic (except substances only carcinogenic by inhalation), mutagenic or toxic for reproduction, of category 1 or 2, and substances with similar potential, must not be intentionally added to cosmetic products, and that substances classified pursuant to Directive 67/548/EEC as carcinogenic, mutagenic or toxic for reproduction, of category 3, and substances with similar potential, must not be intentionally added to cosmetic products unless it can be demonstrated that their levels do not pose a threat to the health of the consumer."
(2) OJ 196, 16.8.1967, p. 1. Directive as last amended by Commission Directive 2001/59/EC (OJ L 225, 21.8.2001, p. 1)

Octaborates

Disodium octaborate tetrahydrate was mentioned as one of the test substances for the 1998 SCCNFP opinion on borates. However, the octaborates are not specifically named in the rather generic entry 1a and 1b of Annex III of the Cosmetics Directive, neither are they listed in the inventory or CosIng. So for reasons of clarity, there is a need to know whether they are covered by entry 1a and/or 1b of Annex III of the Cosmetics Directive 76/768/EEC.

Perborates

For perborates, see also the separate mandate for these substances issued in parallel.

2. TERMS OF REFERENCE

Boron compounds

(1) Based on the current knowledge on the chemistry, biology and toxicology of boron can the SCCS inform the Commission which of the substances listed in the annex II, newly classified substances to this mandate, are covered by the entries 1a and 1b of Annex III, of the Cosmetics Directive 76/768/EEC?

(2) Based on the answer to question 1, and taking into account the scientific data used in the classification of these substances, the SCCS is asked if:

(a) the substances that are covered by the entries 1a and 1b of Annex III and which are currently restricted by Directive 76/768/EEC at a maximum use concentration above the specific concentration limits for classification set out in the Commission Regulation 790/2009 are safe when used in cosmetic products below the specific concentration limits set out in the Commission Regulation 790/2009?

(b) the substances that are not covered by the entries 1a and 1b of Annex III can safely be used in cosmetic products at concentrations levels below to the specific concentrations limits laid down the Commission Regulation 790/2009?

Octaborates

(3) (a) Based on the current scientific knowledge on the chemistry, biology and toxicology of boron and its compound does the SCCS consider that octaborates are covered by Annex III of the Cosmetics Directive, entry 1a and 1b? and if covered, considering that octaborates are not classified, should the current restrictions limits of Annex III entry 1a and 1b be applied for the octaborates

(b) if not covered, does the SCCS have any scientific concern about the safe use of octaborates in cosmetic products?

Annex I: Entries 1a and 1b of Annex III (Part 1) of the Cosmetics Directive - List of substances which cosmetic products must not contain except subject to the restriction and conditions laid down

Reference number	Substance	Restrictions			Conditions of use and warnings which must be printed on the label
		Field of application and/or use	Maximum authorized concentration in the finished cosmetic product	Other limitations and requirements	
A	B	C	d	e	F
1a	Boric acid, borates and tetraborates with the exception of substance no 1184 in Annex II	(a) Talc (b) Products for oral hygiene (c) Other products (excluding bath products and hair waving products)	(a) 5% (by mass/mass as boric acid) (b) 0.1% (by mass/mass as boric acid) (c) 3% (by mass/mass as boric acid)	(a) 1. Not to be used in products for children under 3 years of age 2. Not to be used on peeling or irritated skin if the concentration of free soluble borates exceeds 1.5% (by mass/mass as boric acid) (b) 1. Not to be used in products for children under 3 years of age (c) 1. Not to be used in products for children under 3 years of age 2. Not to be used on peeling or irritated skin if the concentration of free soluble borates exceeds 1.5% (by mass/mass as boric acid)	(a) 1. Not to be used in products for children under 3 years of age 2. Not to be used on peeling or irritated skin (b) 1. Not to be swallowed 2. Not to be used in products for children under 3 years of age (c) 1. Not to be used in products for children under 3 years of age 2. Not to be used on peeling or irritated skin
1b	Tetraborates	(a) Bath products (b) Hair waving products	(a) 18% (by mass/mass as boric acid) (b) 8% (by mass/mass as boric acid)	(a) Not to be used in products for children under 3 years of age	(a) Not to be used of bathing children under 3 years of age (b) Rinse well

Annex II: List of boron compounds newly classified as CMR 2 (Commission Regulation 790/2009) and not yet covered by the Annex II of the Cosmetics Directive (76/768/EEC)

Chemical name	EC No	CAS No	Classification	Concentration Limits of Regulation 790/2009
boric acid; [1] boric acid, crude natural, containing not more than 85 per cent of H_3BO_3 calculated on the dry weight [2]	233-139-2 [1] 234-343-4 [2]	10043-35-3 [1] 11113-50-1 [2]	Repr. Cat. 2; R60-61	C ≥ 5,5 %: T; R60-61
diboron trioxide; boric oxide	215-125-8	1303-86-2	Repr. Cat. 2; R60-61	C ≥ 3,1 %: T; R60-61

Chemical name	EC No	CAS No	Classification	Concentration Limits of Regulation 790/2009
disodium tetraborate, anhydrous; boric acid, disodium salt; [1] tetraboron disodium heptaoxide, hydrate; [2] orthoboric acid, sodium salt [3]	215-540-4 [1] 235-541-3 [2] 237-560-2 [3]	1330-43-4 [1] 12267-73-1 [2] 13840-56-7 [3]	Repr. Cat. 2; R60-61	C ≥ 4,5 %: T; R60-61
disodium tetraborate decahydrate; borax decahydrate	215-540-4	1303-96-4	Repr. Cat. 2; R60-61	C ≥ 8,5 %: T; R60-61
disodium tetraborate pentahydrate; borax pentahydrate	215-540-4	12179-04-3	Repr. Cat. 2; R60-61	C ≥ 6,5 %: T; R60-61
dibutyltin hydrogen borate	401-040-5	75113-37-0	Muta. Cat. 3; R68 Repr. Cat. 2; R60-61 T; R48/25 Xn; R21/22 Xi; R41 R43 N; R50-53	
sodium perborate; [1] perboric acid, sodium salt; [2] perboric acid, sodium salt, monohydrate; [3] sodium peroxometaborate; [4] perboric acid (HBO(O2)), sodium salt, monohydrate; [5] sodium peroxoborate; [containing < 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	239-172-9 [1] 234-390-0 [2] - [3] 231-556-4 [4] - [5]	15120-21-5 [1] 11138-47-9 [2] 12040-72-1 [3] 7632-04-4 [4] 10332-33-9 [5]	O; R8 Repr. Cat. 2; R61 Repr. Cat. 3; R62 Xn; R22 Xi; R37-41	C ≥ 25 %: T; R61-22-37-41-62 22 % ≤ C < 25 %: T; R61-37-41-62 20 % ≤ C < 22 %: T; R61-36/37-62 14 % ≤ C < 20 %: T; R61-36-62 9 % ≤ C < 14 %: T; R61-62 6,5 % ≤ C < 9 %: T; R61
sodium perborate; [1] perboric acid, sodium salt; [2] perboric acid, sodium salt, monohydrate; [3] sodium peroxometaborate; [4] perboric acid (HBO(O2)), sodium salt, monohydrate; [5] sodium peroxoborate; [containing ≥ 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	239-172-9 [1] 234-390-0 [2] - [3] 231-556-4 [4] - [5]	15120-21-5 [1] 11138-47-9 [2] 12040-72-1 [3] 7632-04-4 [4] 10332-33-9 [5]	O; R8 Repr. Cat. 2; R61 Repr. Cat. 3; R62 T; R23 Xn; R22 Xi; R37-41	C ≥ 25 %: T; R61-22-23-37-41-62 22 % ≤ C < 25 %: T; R61-20-37-41-62 20 % ≤ C < 22 %: T ; R61-20-36/37-62 14 % ≤ C < 20 %: T; R61-20-36-62 9 % ≤ C < 14 %: T; R61-20-62 6,5 % ≤ C < 9 %: T; R61-20 3 % ≤ C < 6,5 %: Xn; R20

Chemical name	EC No	CAS No	Classification	Concentration Limits of Regulation 790/2009
perboric acid (H3BO2(O2)), monosodium salt trihydrate; [1] perboric acid, sodium salt, tetrahydrate; [2] perboric acid (HBO(O2)), sodium salt, tetrahydrate; [3] sodium peroxoborate hexahydrate; [containing < 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	- [1] - [2] - [3]	13517-20-9 [1] 37244-98-7 [2] 10486-00-7 [3]	Repr. Cat. 2; R61 Repr. Cat. 3; R62 Xi; R37-41	C ≥ 36 %: T; R61-37-41-62 22 % ≤ C < 36 %: T; R61-36/37-62 20 % ≤ C < 22 %: T; R61-37-62 14 % ≤ C < 20 %: T; R61-62 10 % ≤ C < 14 %: T; R61
perboric acid (H3BO2(O2)), monosodium salt, trihydrate; [1] perboric acid, sodium salt, tetrahydrate; [2] perboric acid (HBO(O2)), sodium salt, tetrahydrate; [3] sodium peroxoborate hexahydrate; [containing ≥ 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	- [1] - [2] - [3]	13517-20-9 [1] 37244-98-7 [2] 10486-00-7 [3]	Repr. Cat. 2; R61 Repr. Cat. 3; R62 Xn; R20 Xi; R37-41	C ≥ 36 %: T; R61-20-37-41-62 25 % ≤ C < 36 %: T; R61-20-36/37-62 22 % ≤ C < 25 %: T; R61-36/37-62 20 % ≤ C < 22 %: T; R61-37-62 14 % ≤ C < 20 %: T; R61-62 10 % ≤ C < 14 %: T; R61

3. OPINION

The information used in this opinion is primarily taken from IRIS (US EPA, 2004), publications from Meeting of the Commission Working Group on the Classification and Labelling of Dangerous Substances, and the European Union Draft Risk Assessment Report on Disodium Tetraborate, Anhydrous Boric Acid, Boric Acid, Boric Acid, Crude Natural (EU, 2009a). Unless explicitly stated otherwise, the SCCS endorses the conclusions drawn in the cited parts of the assessments.

Term of reference: 1 and 3a

Boric acid is a weak acid with a pK_a of 9.2 and exists primarily as the undissociated acid (H_3BO_3) in aqueous solution at physiological pH, as do the borate salts. Therefore, the toxicity associated with the boron compounds listed in Annex II to this mandate is expected to be similar based on boron equivalents. Boron oxide will produce similar effects because it is an anhydride that reacts exothermically with water in the body to form boric acid. In aqueous solutions of sodium perborate at room temperature an equilibrium between sodium perborate and hydrogen peroxide/sodium metaborate is instantly established. Sodium metaborate is the salt of a strong base (sodium hydroxide) and a weak acid (boric acid). Therefore, it is expected to be present in aqueous solutions at environmental temperature and pH mainly as the weakly dissociated boric acid. Disodium octaborate tetrahydrate is a solid solution of boric acid and disodium tetraborate decahydrate. Disodium octaborate tetrahydrate is converted into boric acid//borate upon dissolution in water (EU, 2009b).

Annex III entry 1a of the Cosmetic directive 76/768/EEC concerns boric acid, borates, and tetraborates (with the exception of N,N-Dimethylanilinium tetrakis(pentafluorophenyl)borate [EINECS No. 422-050-6, CAS No. 118612-00-3] listed as entry no 1184 in Annex II of 76/768/EEC; as used in a) Talc, b) Products for oral hygiene, c) Other products (excluding bath products and hair waving products). Annex III entry 1b concerns tetraborates as used in a) Bath products, b) Hair waving products.

SCCS consider that substances listed in Annex II of this mandate that have chemical, biological and toxicological properties similar to "boric acid, borates and tetraborates", and are not covered by other specific regulations in the Cosmetic directive, are covered by Annex III entry 1a. (and 1b for tetraborates).

Consequently, the SCCS is of the opinion that the following substances listed in annex II to this mandate are covered by the Annex III entry 1a of the Cosmetics Directive (Table 1). Tetraborates are also covered by Annex III 1b.

Table 1: *Substances listed in annex II to this mandate that are considered to be covered by 76/768/EEC Annex III/1a, b*

Chemical name	Annex III	EC No	CAS No	Classification	"Concentration Limits"
Boric acid; H_3BO_3 [1]	1a	233-139-2 [1]	10043-35-3 [1]	Repr. Cat. 2; R60-61	C ≥ 5.5 %: T; R60-61
Boric acid, crude natural, containing not more than 85 per cent of H_3BO_3 calculated on the dry weight [2]	1a	234-343-4 [2]	11113-50-1 [2]		
Diboron trioxide, boric oxide; B_2O_3	1a	215-125-8	1303-86-2	Repr. Cat. 2; R60-61	C ≥ 3.1 %: T; R60-61
Disodium tetraborate, anhydrous; boric acid, disodium salt;	1a,b	215-540-4 [1]	1330-43-4 [1]	Repr. Cat. 2; R60-61	C ≥ 4.5 %: T; R60-61

Chemical name	Annex III	EC No	CAS No	Classification	"Concentration Limits"
$Na_2B_4O_7$[1] Tetraboron disodium heptaoxide, hydrate; $Na_2B_4O_7xH_2O$ [2] Orthoboric acid, sodium salt, boric acid, sodium salt; H_2NaBO_3 [3]	1a,b 1a	235-541-3 [2] 237-560-2 [3]	12267-73-1 [2] 13840-56-7 [3]		
Borax, disodium tetraborate decahydrate, borax decahydrate; $Na_2B_4O_7x10H_2O$	1a,b	215-540-4	1303-96-4	Repr. Cat. 2; R60-61	C ≥ 8.5 %: T; R60-61
Disodium tetraborate pentahydrate, borax pentahydrate; $Na_2B_4O_7x5H_2O$	1a,b	215-540-4	12179-04-3	Repr. Cat. 2; R60-61	C ≥ 6.5 %: T; R60-61
Sodium perborate; NaH_2BO_4 [1] Perboric acid sodium salt; NaH_2BO_3 [2] Perboric acid sodium salt monohydrate; $NaH_2BO_3xH_2O$ [3] Peroxymetaborate, sodium perborate, perboric acid sodium salt; $NaBO_3$ [4]	1a 1a 1a 1a	239-172-9 [1] 234-390-0 [2] - [3] 231-556-4 [4]	15120-21-5 [1] 11138-47-9 [2] 12040-72-1 [3] (10332-33-9 tox) 7632-04-4 [4]	Repr. Cat. 2; R61 Repr. Cat 3; R62	C ≥ 6.5 %: T; R61
Perboric acid ($H3BO2(O2)$) monosodium salt trihydrate, sodium peroxyborate; $NaH_2BO_3x3H_2O$ [1] Perboric acid sodium salt tetrahydrate; $NaH_2BO_3x4H_2O$ [2]	1a 1a	- [1] - [2]	13517-20-9 [1] 37244-98-7 [2] (10486-00-9 tox)	Repr. Cat. 2; R61 Repr. Cat 3; R62	C ≥ 10 %: T; R61

Disodium octaborate tetrahydrate is a solid solution of boric acid and disodium tetraborate decahydrate. Octaborates have not been classified as toxic to reproduction and no specific concentration limits are assigned to them. However, based on its composition, Disodium octaborate tetrahydrate is expected to have similar toxicological properties on a boron equivalents basis as the compounds listed in table 1. Therefore it is considered to be covered by entries III 1 a and 1b.
The toxicological properties of perborates/perboric acid are discussed in a separate opinion (SCCS/1345/10). According to the considerations laid out in this opinion, these substances are also covered by entry III/12 of the Cosmetics Directive.

The SCCS considers that the following substance listed in annex II to this mandate is not covered by the entries Annex III 1a and 1b of the Cosmetics Directive (Table 2), since it is an organic metal compound. No specific concentration limit has been established for its classification as reprotoxic, cat. 2. It is also classified as a mutagen (Cat. 3).

Table 2: Substances listed in annex II to this mandate that are not considered to be covered by 76/768/EEC Annex III/1a, b.

Chemical name	EC No	CAS No	Classification	Concentration Limits

Chemical name	EC No	CAS No	Classification	Concentration Limits
Dibutyltin hydrogen borate	401-040-5	75113-37-0	Repr. Cat 2; R60-61 Muta Cat 3; R68	

Term of reference: 2 and 3b

3.1. Chemical and Physical Specifications

The chemical and physical properties of boron and selected boron compounds are shown in Table 4.

Table 4: Physical and chemical properties of boron and selected boron compounds (modified from U.S. EPA (2004)

	Boron	Boric Acid	Borax	Borax Penta-hydrate	An-hydrous Borax	Boron Oxide	Disodium octaborate tetrahydrate
CAS Registry Number	7440-42-8	10043-35-3	1303-96-4	12179-04-3	1330-43-4	1303-86-2	12280-03-4
EC Number	231-151-2	233-139-2	215-540-4	215-540-4	215-540-4	215-125-8	234-541-0
Molecular Formula	B	H_3BO_3	$Na_2B_4O_7x$ $10H_2O$	$Na_2B_4O_7x$ $5H_2O$	$Na_2B_4O_7$	B_2O_3	$Na_2B_8O_{13}$ $4H_2O$
Molecular Weight	10.81	61.83	381.43	291.35	201.27	69.62	412.52
Boron Content (%)	100	17.48	11.34	14.85	21.49	31.06	20.98
Boron Equivalent of 1 mg/kg bw	1	5.7	8.8	6.7	4.7	3.2	4.8
Physical Form	black crystal or yellow-brown amorphous powder	white or colourless crystalline granules or powder	white or colourless crystalline granules or powder	white or colourless crystalline granules or powder	white or colourless vitreous granules	white or colourless vitreous granules	White or colourless powder
Specific Gravity (20°C)	2.34	1.51	1.73	1.81	2.37	2.46	1.9
Melting Point (°C) closed space	2300	171	>62	<200	No data	No data	813/803
Melting Point (°C) anhydrous form (crystal)	2300	450	742	742	742	450	No data
Water Solubility (% w/w (20°C))	Insoluble	4.72	4.71	3.6	2.48	Rapidly hydrates to boric acid	Is converted into boric acid/borate

3.2. Function and uses

Boric acid and sodium salts of boron (primarily borax, or disodium tetraborate decahydrate) are widely used for a variety of industrial purposes including manufacture of glass, fibreglass insulation, porcelain enamel, ceramic glazes, and metal alloys. These compounds are also used in cellulose insulation (as fire retardants), antifreeze agents, paints, wood preservatives, cosmetics, detergents, laundry additives, fertilizers (boron is an essential

element for plants), herbicides (at high concentrations, boron is toxic to certain plant species) and insecticides. Elemental boron has only limited industrial applications.

Octaborates are used in fungicide and insecticide products. The most common use is as a fungicide on wood products to control decay fungi. Two forms of octaborates are considered in this Opinion:

Disodium octaborate, anhydrous; CAS no. 12008-41-2. Mol weight 340.56; 25.42% B
Disodium octaborate, tetrahydrate; CAS no. 12280-03-4. Mol weight 412.64; 20.98% B

The use of boric acid, borates and tetraborates in cosmetics is regulated in entries 1a and 1b of Annex III of the Cosmetic Directive. The substances may be used in powder (5% [expressed as boric acid]), products for oral hygiene (0.1% [expressed as boric acid]), other products except bath products and products for waving hair (3% [expressed as boric acid]). In addition tetraborates are used in bath products (18% [expressed as boric acid]) and products for waving hair (8% [expressed as boric acid]).

3.3. Toxicological Evaluation

3.3.1. Acute toxicity

3.3.1.1. Acute oral toxicity

Boron
Acute oral toxicity (LD50) for cat, dog, guinea pig, mouse, rabbit and rat have been found to be in the range 250 – 650 mg/kg bw.

Boric acid
Mouse LD50 3450 mg/kg bw.
Rat LD50 2660 mg/kg bw.

Human
Acute adult quantitative dose response data range from 1.4 to 70 mg B/kg bw. In cases where ingestion was less than 3.7 mg B/kg bw, subjects remained asymptomatic.

The human oral lethal dose is regularly quoted as 2 – 3 g boric acid for infants, 5 – 6 g boric acid for children and 15 – 30 g for adults. Symptoms of acute effects may include nausea, vomiting, gastric discomfort, skin flushing, excitation, convulsions, depression and vascular collapse.

3.3.1.2. Acute dermal toxicity

The acute dermal toxicity of borates in animals is low, being >2000 mg/kg bw for all borates tested. Although no test was carried out on disodium tetraborate anhydrous, it can be assumed that this would have a similar low acute dermal toxicity.

Several poisoning cases have been reported in humans. Many were the result of use as an antiseptic for irrigating body cavities, treating wounds or as a treatment for conditions such as epilepsy. Such medical uses are now obsolete. Also, accidental misuse in the preparation of baby formula (1 – 14 g in boric acid in the formula) and the topical use of pure boric acid powder for infants has led to poisonings in the past.

3.3.1.3. Acute inhalation toxicity

Low acute inhalation toxicity was observed in those borates tested. In an inhalation study in which rats were exposed to boric acid at actual concentrations of 2.12 mg (0.37 mg B)/L (highest attainable concentration) for 4 hours no deaths were observed.

3.3.2 Irritation and corrosivity

3.3.2.1. Skin irritation

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not classified as skin irritants.

EU, 2009a

3.3.2.2. Mucous membrane irritation

No classification is indicated for boric acid under the current EU guidelines (67/548/EEC) or under the GHS guidelines.

Disodium tetraborate pentahydrate, disodium tetraborate decahydrate, and disodium tetraborate anhydrous are classified as eye irritant R36 under current EU guidelines (67/548/EEC) and as Category 2 Irritating to Eyes under GHS.

EU, 2009a

3.3.3. Skin sensitisation

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are neither skin nor respiratory sensitisers.

EU, 2009a

3.3.4. Dermal / percutaneous absorption

Draize and Kelley (1959) found no increase in urinary boron in a volunteer after topical application of powdered boric acid (15 g) to the forearm and held under occlusion for 4 hours. Friis-Hansen *et al.* (1982) reported no evidence of boron absorption in 22 newborn infants treated dermally with ointment containing 3% boric acid for 4-5 days (total dose of approximately 16 mg B); plasma boron levels fell over the 5-day study period, as expected for neonates, and did not differ from 10 untreated controls. Vignec and Ellis (1954) found minimal difference in blood or urinary boron levels in twelve 1 to 10 month old infants exposed to talcum powder containing 5% boric acid 7-10 times per day for at least 1 month (estimated daily dose of 2.33 g boric acid or 407 mg B) compared with an equal number of untreated controls. An additional group of 12 infants with mild to moderate diaper rash during the test period was continued on the powder regimen for 48 – 72 hours after rashes appeared. Their boron blood levels were similar to controls.

There is evidence that boron can be absorbed through more severely damaged skin, especially from an aqueous vehicle. Blood and urinary boron levels were increased in six male volunteers with severe skin conditions (e.g. psoriasis, eczema, urticaria) following topical application of an aqueous jelly containing 3% boric acid (Stuttgen *et al.,* 1982). However, urinary boron levels did not increase in skin-damaged volunteers given 3% boric acid in an emulsifying ointment.

Studies in laboratory animals have produced similar results. Boron was not absorbed across intact or mildly abraded skin in rabbits topically administered boric acid as the undiluted powder or at 5% in talc or aqueous solution (1.5 hr/day under occlusion for 4 days; 10-15% of body surface exposed) (Draize and Kelley, 1959). However, boron was readily absorbed across severely damaged skin in rabbits in proportion to the exposure concentration. Rats with intact skin treated topically with 3% boric acid (ointment or aqueous jelly) did not

absorb boron, but urinary boron was increased 4- to 8-fold (to 1% of dose) following exposure to boric acid ointment and 34-fold (to 23% of dose) following exposure to aqueous boric acid in rats with damaged skin (Nielsen, 1970).

Wester *et al.* (1998) reported *in vivo* percutaneous absorption of boric acid, borax and octaborate tetrahydrate in man. Human volunteers (8 per group) were dosed (non-occluded) on a 900 cm^2 area (30 cm x 30 cm) of the back with ^{10}B enriched boric acid or sodium tetraborate decahydrate (5% in aqueous solution) or disodium octaborate tetrahydrate (DOT) (10% in aqueous solution). Twenty-four hours later the residual dose was removed by washing. Boron was measured in the urine. It was concluded that 0.23 $\pm$ 0.13 % boric acid, 0.21 $\pm$ 0.19 % sodium tetraborate decahydrate , and 0.12 $\pm$ 0.11 DOT of the applied dose were absorbed.

The total recovery of the applied dose ranged from 48.8 - 63.6%, therefore 36.4-51.2% of the applied dose is not accounted for. The authors suggested that this may be due to loss to outside clothing and bedding. However, part of the lost dose may be located in the body or in the skin at the application site, which in that case should be considered as being absorbed.

In vitro, borax dosed at 5.0% (1.0 ml/cm^2) resulted in 0.41% absorbed and DOT at 10% (1.0 ml/cm^2) resulted in 0.19% absorbed (Wester *et al.,* 1998).

Comment
No dermal absorption studies have been performed according to modern guidelines. During Meetings of the Commission Working Group on the Classification and Labelling of Dangerous Substances it has been stated several times that human skin absorption is less than 0.3%, but may be higher in damaged skin. In the SCCNFP Opinion concerning boric acid, borates and tetraborates adopted 23 September 1998 (SCCNFP/0024/98) the percutaneous absorption was considered to be about 0.2%.

The SCCS considers that the available measurements of dermal absorption have a significant degree of uncertainty. Therefore an absorption of 0.5% will be used in the safety evaluation for the boric compounds discussed in this Opinion (representing the absorption of boric acid + 2 x SD [0.23 + 2 x 0.13%] from the study of Wester *et al.,* 1998). This is in agreement with other recent risk assessment of borates in EU (EU, 2009a, ECHA, 2010). It should be noted that skin absorption is probably higher in case of damaged skin.

The dermal absorption of disodium octaborate tetrahydrate was slightly lower than that for the other boron compounds, however the octaborate was applied at a higher concentration, and the percentage of absorption would probably be higher if lower concentrations had been used.

Absorption for oral and inhalation routes are assumed to be 100% (ECHA, 2010)

3.3.5. Repeated dose toxicity

Sprague-Dawley rats received in a 2-year feeding study (Weir, 1966a,b, Weir and Fisher, 1972) boric acid and disodium tetraborate decahydrate (0, 117, 350, or 1170 ppm; 0, 5.9, 17.5, or 58.5 mg/kg bw/day as boron equivalent) in the feed. The dosing started with weanling rats. The control group consisted of 70 males and 70 females, while the dosed group consisted of 35 males and 35 females. Clinical signs included coarse hair coats, hunched position, and inflamed bleeding eyes, desquamation of the skin of the tail and the pads of the paws which were also swollen, marked respiratory involvement, shrunken appearance of the scrotum were observed in all males of the high dose group. In addition a reduction in body weight was observed in males and females in the high dose group accompanied by decreased food consumption.

Decreased red cell volume and haemoglobin were observed in boric acid and disodium tetraborate decahydrate treated rats. Blood samples were taken after 30, 60, 90, 180, 365, and 545 days and at the end of the study. At the end of the study the values in all dosed animals were reduced compared to control. Significant reduction of red blood cell volume and haemoglobin was mainly observed in high dosed males treated with boric acid (at the end of the study 5% to 21% and 7% to 19% reduction compared to control, were observed for red blood cell volume and haemoglobin, respectively), but also in the females treated with boric acid a significant reduction of haemoglobin at all dose groups was detected at the last measurement (between 8% and 13%).
For disodium tetraborate decahydrate blood of the high dosed animals showed reduced values for both endpoints in males and females at several time points. It is noted in EU (2009) that, as described in Muller *et al.* (2006), reduction of haemoglobin of 20% is a stand alone adverse effect, reductions of 10% must be supported by further effects like extramedullary haematopoiesis or haemosiderin deposition. However, these endpoints were not examined in the study and since only 5 animals per group were sampled the statistical power is low.

Testicular atrophy and seminiferous tubule degeneration was observed at 6, 12 and 24 months at the highest dose level with both boric acid and disodium tetraborate decahydrate. Microscopic examination of the tissue revealed atrophied seminiferous epithelium and decreased tubular size in the testes. No effects were observed in the control and low dose groups.

Based on the clinical and haematological effects and the testicular atrophy observed at the highest doses tested (58.5 mg B/kg bw/day) of both boric acid and disodium tetraborate decahydrate the NOAEL for the effects of boron was set at 17.5 mg B/kg bw/day (EU, 2009a).

Comment
SCCS notes that several repeated dose studies are available on boron compounds. These studies are in general agreement with the one above used to derive the NOAEL and will not be discussed in this Opinion.

3.3.6. Mutagenicity / Genotoxicity

All available *in vitro* data indicate no mutagenic activity. In addition, the only *in vivo* study on boric acid (a mouse bone marrow micronucleus study) also indicated no mutagenic activity. Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are considered non-mutagenic.

EU, 2009a

3.3.7. Carcinogenicity

A chronic rat feeding study was conducted by Weir and Fisher (1972). The study was, however, not designed as a cancer bioassay. Only a limited number of tissues were examined histopathologically, and the report failed to even mention tumour findings.

The chronic mouse study conducted by NTP (1987) was adequately designed, but the results are difficult to interpret. Boric acid was added to the feed in concentrations of 0, 2500, or 5000 ppm. The average amount of boric acid consumed per day was approximately 400-500 mg/kg bw or 1100-1200 mg/kg bw for low dose and high dose mice respectivly. There was an increase in hepatocellular carcinomas and subcutaneous tumours in low-dose, but not high-dose male mice. However, the increases were within the range of historical controls. The authors concluded that under the conditions of the study, there was *no evidence of carcinogenicity.* Low survival in both the low- and high-dose male groups (60 and 40%, respectively) may have reduced the sensitivity of this study for evaluation of

carcinogenicity. Testicular atrophy and interstitial cell hyperplasia were observed in high dose male mice.

The chronic mouse study conducted by Schroeder and Mitchener (1975) was inadequate to detect carcinogenicity because only one, very low dose level was used (0.95 mg B/kg-day) and the MTD was not reached.

No data were found regarding a possible association between cancer and boron exposure in humans.

Comment
The studies available in animals were inadequate to ascertain whether boron has the potential to cause cancer.

3.3.8. Reproductive toxicity

Below, only the experiments used by EU and US EPA for determination of the NOAELs for effects on fertility and developments will be discussed. The text is in part cited from U.S. EPA (2004) and EU (2009a).

3.3.8.1. Fertility

In a multigeneration study, Weir and Fisher (1972) administered 0, 117, 350, or 1170 ppm boron (approximately 0, 5.9, 17.5, or 58.5 mg B/kg bw/day) as boric acid or disodium tetraborate decahydrate in the diet to groups of 8 male and 16 female Sprague-Dawley rats. No adverse effects on reproduction or gross pathology were observed in the rats dosed with 5.9 or 17.5 mg B/kg bw/day that were examined to the F3 generation. Litter size, weights of progeny, and appearance were normal when compared with controls. The test groups receiving 58.5 mg B/kg bw/day boron from either compound were found to be sterile. In these groups, males showed lack of spermatozoa in atrophied testes, and females showed decreased ovulation in the majority of the ovaries examined. An attempt to obtain litters by mating the treated females with the males fed only the control diet was not successful. A LOAEL of 58.5 mg B/kg bw/day and a NOAEL of 17.5 mg B/kg bw/day were identified from this study.

3.3.8.2. Developmental toxicity

Price et al. (1996a) administered boric acid in the diet (0, 0.025, 0.050, 0.075, 0.1, or 0.2%) to time-mated CD rats, 60 per group, from gd 0 – 20. Throughout gestation, rats were monitored for body weight, clinical condition, and food and water intake. This experiment was conducted in two phases, and in both phases offspring were evaluated for post-implantation mortality, body weight and morphology (external, visceral, and skeletal).

Phase I of this experiment was considered the teratology evaluation and was terminated on gd 20 when uterine contents were evaluated. The calculated average dose of boric acid consumed for Phase l dams was 19, 36, 55, 76, and 143 mg/kg bw/day (3.3, 6.3, 9.6, 13.3, and 25 mg B/kg bw/day). During Phase I, no maternal deaths occurred and no clinical symptoms were associated with boric acid exposure. Maternal body weights did not differ among groups during gestation, but statistically significant trend tests associated with decreased maternal body weight (gd 19 and 20 at sacrifice) and decreased maternal body weight gain (gd 15 – 18 and gd 0 – 20) were indicated. In the high-dose group, there was a 10% reduction (statistically significant in the trend test $p<0.05$) in gravid uterine weight when compared with controls. The authors indicated that the decreasing trend of maternal body weight and weight gain during late gestation reflected reduced gravid uterine weight. Corrected maternal weight gain (maternal gestational weight gain minus gravid uterine weight) was not affected. Maternal food intake was only minimally affected at the highest

dose and only during the first 3 days of dosing. Water intake was higher in the exposed groups after gd 15. The number of ovarian corpora lutea and uterine implantation sites, and the percent preimplantation loss were not affected by boric acid exposure.

Offspring body weights were significantly decreased in the 13.3 and 25 mg B/kg bw/day dose groups on gd 20. The body weights of the low- to high-dose groups, respectively, were 99, 98, 97, 94, and 88% of control weight. There was no evidence of a treatment-related increase in the incidence of external or visceral malformations or variations when considered collectively or individually. On gd 20, skeletal malformations or variations considered collectively showed a significant increased percentage of foetuses with skeletal malformations per litter. Taken individually, dose-related response increases were observed for short rib XIII, considered a malformation in this study, and wavy rib or wavy rib cartilage, considered a variation. Statistical analyses indicated that the incidence of short rib XIII and wavy rib were both increased in the 13.3 and 25 mg B/kg bw/day dose groups relative to controls. A significant trend test ($p<0.05$) was found for decrease in rudimentary extra rib on lumbar I, classified as a variation. Only the high-dose group had a biologically relevant, but not statistically significant, decrease in this variation. The LOAEL for Phase I of this study was considered to be 0.1% boric acid (13.3 mg B/kg bw/day) based on decreased foetal body weight. The NOAEL for Phase I of this study was considered to be 0.075% boric acid (9.6 mg B/kg bw/day).

In Phase II, dams were allowed to deliver and rear their litters until postnatal day (pnd) 21. The calculated average doses of boric acid consumed for Phase II dams were 19, 37, 56, 74, and 145 mg/kg bw/day (3.2, 6.5, 9.7, 12.9, and 25.3 mg B/kg bw/day). This phase allowed a follow-up period to determine whether the incidence of skeletal defects in control and exposed pups changed during the first 21 postnatal days. Among live born pups, there was a significant trend test for increased number and percent of dead pups between pnd 0 and 4, but not between pnd 4 and 21; this appeared to be due to an increase in early postnatal mortality in the high dose, which did not differ significantly from controls and was within the range of control values for other studies in this laboratory. On pnd 0, the start of Phase II, there were no effects of boric acid on the body weight of the offspring (102, 101, 99, 101, and 100% of controls, respectively). There were also no differences through termination on pnd 21; therefore, foetal body weight deficits did not continue into this postnatal period (Phase II). The percentage of pups per litter with short rib XIII was still elevated on pnd 21 in the 0.20% boric acid dose group (25.3 mg B/kg bw/day), but there was no incidence of wavy rib, and none of the treated or control pups on pnd 21 had an extra rib on lumbar 1. The NOAEL and LOAEL for phase II of this study were 12.9 and 25.3 mg B/kg bw/day, respectively.

In addition to the rat studies, the developmental effects of boric acid were also studied in mice and rabbits. Heindel et al. (1994, 1992) and Field et al. (1989) identified a NOAEL and LOAEL of 43.3 and 79 mg B/kg-day, respectively, for decreased foetal body weight in mice exposed to boric acid in the feed. Increased resorptions and malformations, especially short rib XIII, were noted at higher doses. Price et al. (1996b) and Heindel et al. (1994) identified a NOAEL and LOAEL of 21.9 and 43.7 mg B/kg-day for developmental effects in rabbits. Frank effects were found at the LOAEL, including high prenatal mortality and increased incidence of malformations, especially cardiovascular defects.

More recent investigations of the developmental effects of boric acid (Wery et al., 2003) have produced evidence supporting a role of altered gene expression in boron's developmental effects. These data indicate that boric acid administration during the normal period of expansion of hox gene expression results in rib and vertebrae alterations, coincident with altered hox gene expression.

General comments

One of the most sensitive targets of boron that has been identified is the developing foetus (rats, mice and rabbits) carried by the pregnant female. Another sensitive target of boron

that has been identified is the testis of the male. A study in dogs provided a LOAEL of 29 mg B/kg-day and a NOAEL of 8.8 mg B/kg-day, based on histopathological effects (Weir and Fisher, 1972). Thus, the sensitivity to boron exposure does not appear to differ markedly for these two targets, although there is some uncertainty in this determination due to the less comprehensive design of the dog study.

Effects on the pregnant females themselves are seen only at considerably higher doses (no clearly adverse maternal effects even at 94.2 mg B/kg-day in the same study used to derive the NOAEL and LOAEL values for the developing foetus reported above). A specific target of boron toxicity has not been identified in non-pregnant females, who are markedly less susceptible to boron than males. Data are inadequate to assess differences in gender susceptibility with regard to non-reproductive, non-developmental effects.

3.3.8.3. EU conclusions on reproductive toxicity

Summary of the Discussion of the Technical Committee on Classification and Labelling of Dangerous Substances (Arona, 08.09.06) and the Specialised Experts, leading to the recommendation by the Technical Committee on Classification and Labelling regarding the classification of Borates (ECB, 2006).

Animal data

Studies investigating the effects of exposure to boric acid on fertility in the rat and mouse identified males being more sensitive than females. Acute exposure to boric acid results in changes in sperm parameters and histopathological changes in the testes of the male rat. The effects were irreversible at higher doses. Repeated exposure to boric acid can affect the spermatogenisis and sperm quality of the male adult rat, mouse and dog, resulting either in partial reduction in fertility or sterility depending on the dose. Reproductive performance was also affected in female rats during repeated exposure to high doses (caused by decreased ovulation). These effects occur at doses well below 1000 mg/kg bw/day which do not produce marked signs of other toxicity and which are not a secondary consequence of other toxicity. A NOAEL of 100 mg/kg bw/day *(17.5 mg B/kg bw/day)* can be established.

Exposure to boric acid during pregnancy (given either throughout gestation or only during major organogenesis) resulted in decreased foetal body weight, and foetal cardiovascular and rib malformations in the rat, mouse and rabbit. The rat appears the most sensitive species for developmental toxicity, since the developmental effects were observed at a dose which did not induce any significant maternal toxicity. A NOAEL for pre-natal effects in all 3 species has been established at 55 mg/kg bw/day *(9.6 mg B/kg bw/day)*.

The effects observed across species were very similar, both in nature and effective doses (mg B/kg bw/day). The evidence from different animal species therefore shows that boric acid and the borates have an adverse effect on fertility (rat, mouse, dog) and development (rat, mouse, rabbit), which is not a consequence of general systemic toxicity.

Human Data

The epidemiological studies in humans are insufficient to demonstrate the absence of an adverse effect on fertility. The available studies do not have a sufficient sample size, do not demonstrate sufficient sensitivity to account for confounders, do not study all the relevant effects and do not provide adequate information about exposures. The relevance for humans of the animal data is therefore not put in doubt based on the available human data.

Relevance for Humans

The available data on toxicokinetics do not indicate major differences between laboratory animals and humans. It is not known whether there are significant differences in the toxicodynamics between humans and laboratory animal models and in the absence of such knowledge it must be assumed that the effects seen in animals could occur in humans. On

the basis of toxicokinetic and toxicodynamic considerations it is assumed that the animal data are relevant to humans.

Comment
Based on the available data, boron compounds were classified in the EU as toxic to reproduction Cat. 2; R60-61 (R60; May impair fertility, R61; May cause harm to the unborn child).

The SCCS endorses the assessment summarised above and will use the NOAEL of 9.6 mg B/kg bw/day will in the safety evaluation of boron compounds.

3.3.9. Toxicokinetics

Boron is readily absorbed following oral exposure in both humans and animals (>90%). Studies in male mine workers and rats have shown that boron is also absorbed during inhalation exposure. Studies suggest that boric acid and borate compounds in the body exist primarily as undissociated boric acid, which distributes evenly throughout the soft tissues of the body, but shows some accumulation in bone. There is no evidence that boron compounds are metabolized in the body. More than 90% of an orally administered dose of boron as boric acid is excreted in a short time in both humans and in animals.

Boric acid is not further metabolised. Borates are distributed rapidly and evenly through the body, with concentrations in bone 2 - 3 higher than in other tissues. Boron is excreted rapidly, with elimination half-lives of 1h in the mouse, 3h in the rat and < 27.8 h in humans, and has low potential for accumulation. Boric acid is mainly excreted in the urine.

Because of the extent to which boron's residence time in the body and pharmacokinetic profile are influenced by urinary elimination, a more thorough investigation of the urinary clearance of boron has been undertaken to determine the difference in the urinary clearance of boron in pregnant and nonpregnant rats and humans. Reports from studies (U.S. Borax, 2000; Pahl *et al.,* 2001; Vaziri *et al.*, 2001) indicated that the renal clearance of boron from female rats was greater than in humans, and that pregnant rats and pregnant women cleared boron slightly more efficiently than nonpregnant rats and women. The magnitude of the difference (rat:human) between average clearance values was approximately 3.6-fold and 4.9-fold for pregnant and nonpregnant individuals, respectively, in close agreement with differences in kinetic parameters predicted by allometric scaling (approximately 4-fold). The variance of boron clearance in humans was slightly greater than in rats (0.35%), but the coefficient of variation was 4-fold higher in humans than in rats. Overall, the available pharmacokinetic data support a high degree of qualitative similarity (lack of metabolism, highly cleared through renal filtration mechanisms, and apparently consistent extravascular distribution characteristics) between the relevant experimental species and humans. After accidental boric acid uptake in 9 patients, the mean half-life of boric acid was determined to be 13.4 hours (range, 4.0 to 27.8) (Litovitz *et al.,* 1988).

There is no substantiated evidence of boron accumulation in humans or other animals although bone contains higher levels than other tissues and boron is slowly eliminated from bone (Chapin et al., 1997). A poisoning case with boric acid in a pregnant woman suggested that borates might cross the placenta (Grella et al., 1976). The foetus was delivered early due to accidental poisoning of the mother with boric acid. However, since no boric acid fetal blood or amniotic fluid concentrations were measured, it is not possible to definitely conclude that boric acid passed the placenta. No information was presented on possible reproduction parameters.

In both humans and animals, boron is excreted in the urine regardless of the route of administration. It is excreted with a half-life of < 24 hours in humans and animals. Boron is slowly eliminated from bone (Chapin *et al.,* 1997). Following oral intake of an aqueous solution of boric acid, the urinary recovery was 94% (Jansen *et al*., 1984); more than 50 %

of the oral dose was eliminated in the first 24 hours, consistent with the 21 hour half-life in the i.v. study. Sutherland *et al.* (1998) showed in a boron balance study that only 8% of dietary boron is excreted in faeces.

3.3.10. Photo-induced toxicity

No data submitted

3.3.11. Human data

Boron exposure/dose data were measured in workplace inhalable dust, dietary food/fluids, blood, semen, and urine from boron workers and controls. Three groups were established; boron workers (n = 66), community comparison (n = 59), and control comparison (n = 67). Correlations between boron and semen parameters (total sperm count, sperm concentration, motility, morphology, DNA breakage, apoptosis and aneuploidy) were assessed (Robbins *et al*., 2010). Blood boron averaged 499.2 ppb for boron workers, 96.1 and 47.9 ppb for workers from high and low environmental boron areas ($p < 0.0001$). Boron concentrated in seminal fluid. No significant correlations were found between blood or urine boron and adverse semen parameters. Exposures did not reach those causing adverse effects published in animal toxicology work but exceeded those previously published for boron occupational groups.

A recent study of nearly 1000 men working in boron mining or processing in Liaoning province in northeast China has been published in several Chinese and a few English language papers. The study of Scialli *et al*. (2010) included individual assessment of boron exposure, interview data on reproductive experience and semen analysis. Employed men living in the same community and in a remote community were used as controls. Boron workers (n = 75) had a mean daily boron intake of 31.3 mg B/day, and a subset of 16 of these men, employed at a plant where there was heavy boron contamination of the water supply, had an estimated mean daily boron intake of 125 mg B/day. Estimates of mean daily boron intake in local community and remote background controls were 4.25 mg B/day and 1.40 mg/day, respectively. Reproductive outcomes in the wives of 945 boron workers were not significantly different from outcomes in the wives of 249 background control men after adjustment for potential confounders. There were no statistically significant differences in semen characteristics between exposure groups, including in the highly exposed subset, except that sperm Y:X ratio was reduced in boron workers. Within exposure groups the Y:X ratio did not correlate with the boron concentration in blood, semen and urine. In conclusion, while boron has been shown to adversely affect male reproduction in laboratory animals, there is no clear evidence of male reproductive effects attributable to boron in studies of highly exposed workers.

Comment
SCCS notes that in the high exposure group, the dose was about 20% of the NOAEL for reproductive effects in the rat.

For the general population, the greatest exposure to boron comes from food. The mean daily intake of boron in the diet is assumed to be near 1.2 mg per day (WHO, 1998). Vegetarian diets (Nielsen, 1992) and consumption of wine and mineral water could raise boron intake (WHO, 1998).

To derive a tolerable upper intake level (UL) of boron (sodium borate and boric acid), the NOAEL for decreased foetal weight in rats (9.6 mg/kg bw/day) was extrapolated to humans by dividing by an uncertainty factor of 60 (to allow for variability between rats and humans and between-person variability in humans), giving an UL of 0.16 mg/kg bw/day, which is equivalent to an UL of 10 mg boron/person/day in adults. This UL also applies to pregnant and lactating women. UL values for children were derived by extrapolating from the UL for adults on a body surface area basis, giving values (mg/day) of 3, 4, 5, 7, and 9 mg

boron/person/day for children aged 1-3, 4-6, 7-10, 11-14 and 15-17 years of age, respectively. These UL values apply only to the intake of boron as boric acid and borates (EFSA, 2004).
Data on boron intake in EU countries are limited. In the UK mean intake in adults from food is estimated at 1.5 mg/day, with the 97.5 percentile of 2.6 mg/day, while mean intake from water is estimated to be in the range of 0.2-0.6 mg/day. The main dietary sources of boron are plant foods, and foods rich in boron include fruits, leafy vegetables, mushrooms, nuts and legumes, as well as wine, cider and beer (EFSA, 2004).

3.3.12. Special investigations

3.3.12.1. Setting specific concentration limits for substances toxic to reproduction

The specific concentration limit (SCL) concept allows a fine tuning of the contribution of a certain hazardous substances to the classification of mixtures based on the potency of the substances. SCLs have been established for most of the substances discussed in this Opinion. There is no detailed and accepted guidance developed for the setting of specific concentration limits (SCLs) for reproductive toxicity, as is the case for e.g. carcinogenic substances. Such guidance like the T25 concept for carcinogens covering all relevant aspects would be needed to be able to derive SCLs for reproductive toxicants in a standardized manner. This is due to the fact that reproductive toxicity is a complex hazard class for which SCL setting is difficult. In conclusion, the possibility to set SCL for reproductive toxicity is therefore currently not considered possible in the process of self-classification as there is no standardized methodical approach available which adequately takes into account all relevant information. An EU expert group (linked to ECHA) is currently working on a concept for the setting of specific concentration limits (SCLs) for reproductive toxicity. This will probably be finalised in 2010.

A method named "the German method" has previously been used for two substances toxic for reproduction. The method is not validated.

The specific concentration limit according to the German method is calculated from the formula:

SCL = NOAEL x 100/1000

Concentration limits in preparations are derived by applying § 4.2.3.3 of Annex VI of Directive 2001/59/EC to preparations analogously, i.e. 1,000 mg/kg of a preparation should contain amounts of the developmentally toxic substance which correspond at maximum to the NO(A)EL of a relevant animal toxicity test (ECB, 2003).

In the case of boron:

SCL = 9.6 mg/kg bw/day x 100/1000 mg/kg bw/day = 0.96 = 1% calculated as elemental Boron.

3.3.13. Safety evaluation (including calculation of the MoS)

CALCULATION OF THE MARGIN OF SAFETY
Boron

Table 6: *Calculation of systemic daily dose of boron from different cosmetic products. In cases where the allowed concentration of boron calculated as boric acid was higher than 5.5% (according to Annex III/1b), the values have been reduced to 5.5%. A dermal absorption of 0.5% has been used for calculation of the systemic exposure dose of boron.*

Field of application and/or use	Daily use of finished product (g)	Retention factor	Boric acid (%)	Boron (%)	Daily exposure calculated as boron (mg)	Systemic daily dose (mg)
Powder	18	0.1	5	0.88	15.8	0.079
Products for oral hygiene	3.48 (amount considered absorbed)	1	0.1	0.018	0.63	0.63
Other products	18	1	3	0.53	95	0.48
Bath products	10	0.01	5.5	0.96	0.96	0.005
Products for waving hair	8	0.1	5.5	0.96	7.7	0.038
Total						1.232

Total daily systemic exposure dose (SED) of boron from cosmetic products is estimated to be 1.23 mg per day corresponding to (1.2/60) 0.02 mg/kg bw/day.

SED = 0.02 mg B/kg bw/day
NOAEL = 9.6 mg B/kg bw/day
(developmental effects in rats)

Margin of Safety	**NOAEL / SED**	**=**	**480**

The calculation of MOS given above is based on dermal absorption of healthy skin. Skin absorption is probably higher in case of damaged skin and the MOS may be significantly lower if boron compounds are used in cosmetics applied to damaged skin.

Intake of boron also occurs via food and drinking water. Typical daily intake from these sources has been estimated to be 2.3 – 2.74 mg B/day (0.038 – 0.046 mg B/kg bw/day), while a "reasonable worst case" estimate came to 3.5 – 3.94 mg B/day (0.058 – 0.066, mg B/kg bw/day) (Austria 2009). Taking into account these possible additional exposures still a sufficient Margin of Safety (> 100) is obtained for the total dose of boron from cosmetics, food and water.

3.3.14. Discussion

Physico-chemical properties
Boric acid is a weak acid with a pK_a of 9.2 and exists primarily as the undissociated acid (H_3BO_3) in aqueous solution at physiological pH, as do the borate salts. Therefore, the toxicity associated with these compounds is expected to be similar based on boron equivalents. Boron oxide will also produce similar effects because it is an anhydride that reacts exothermically with water in the body to form boric acid. Sodium octaborate tetrahydrate is converted into boric acid//borate upon dissolution in water.

Acute toxicity
Acute human adult quantitative dose response data range from 1.4 to 70 mg B/kg bw. In cases where ingestion was less than 3.7 mg B/kg bw, subjects were asymptomatic.

Skin/eye irritation and sensitisation
Boric acid is not irritant to the skin. Some borates are mild eye irritants. Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are neither skin nor respiratory sensitisers.

Percutaneous absorption
No dermal absorption studies have been performed according to modern guidelines. During Meetings of the Commission Working Group on the Classification and Labelling of Dangerous Substances it has been stated several times that human skin absorption is less than 0.3%, but may be higher in damaged skin. In the SCCNFP Opinion concerning boric acid, borates and tetraborates adopted 23 September 1998 (SCCNFP/0024/98) the percutaneous absorption was considered to be about 0.2%.

The SCCS considers that the available measurements of dermal absorption have a significant degree of uncertainty. Therefore an absorption of 0.5% will be used in the safety evaluation for the boric compounds discussed in this opinion (representing the absorption of boric acid + 2 x SD [0.23 + 2 x 0.13%] from the study of Wester *et al.,* 1998). This is in agreement with other recent risk assessment of borates in EU (EU, 2009a, ECHA, 2010).

The dermal absorption of disodium octaborate tetrahydrate was slightly lower than that for the other boron compounds, however the octaborate was applied at a higher concentration, and the percentage of absorption would probably be higher if lower concentrations had been used.

Absorption for oral and inhalation routes is assumed to be 100%.

Repeated dose toxicity
In the pivotal 2-year rat feeding study haematological effects and testicular atrophy was observed at the highest doses tested (58.5 mg B/kg bw/day) of both boric acid and disodium tetraborate decahydrate. The NOAEL for the effects of boron was 17.5 mg B/kg bw/day.

Mutagenicity/genotoxicity
All available *in vitro* data indicate no mutagenic activity. In addition the only *in vivo* study on boric acid also indicated no mutagenic activity. Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are considered non-mutagenic.

Carcinogenicity
The studies available in animals were inadequate to ascertain whether boron has the potential to cause cancer.

Toxic to reproduction
Studies investigating the effects of exposure to boric acid on fertility in the rat and mouse identified the male as the most sensitive sex. Acute exposure to boric acid results in changes in sperm parameters and histopathological changes in the testes of the male rat. Reproductive performance was also affected in female rats during repeated exposure to high doses (caused by decreased ovulation).

Exposure to boric acid during pregnancy (given either throughout gestation or only during major organogenesis) results in decreased fetal body weight, and fetal cardiovascular and rib malformations in the rat, mouse and rabbit. The rat appears the most sensitive species for developmental toxicity, since the developmental effects were observed at a dose which did not induce any significant maternal toxicity. A NOAEL for pre-natal effects in all three species has been established at 55 mg boric acid/kg bw/day (9.6 mg B/kg bw/day).

The effects observed across species were very similar, both in nature and effective doses (mg B/kg bw/day). The evidence from different animal species therefore shows that boric acid and borates have an adverse effect on fertility (rat, mouse, dog) and development (rat, mouse, rabbit), which is not a consequence of general systemic toxicity.

Several boron compounds are classified in EU as toxic to reproduction Cat. 2; R60-61 (R60; May impair fertility, R61; May cause harm to the unborn child. A NOAEL of 9.6 mg B/kg bw/day is used in the safety evaluation.

Toxicokinetics
The available pharmacokinetic data on boron compounds support a high degree of qualitative similarity (lack of metabolism, highly cleared through renal filtration mechanisms, and apparently consistent extravascular distribution characteristics) between the relevant experimental species and humans.

4. CONCLUSION

Boron compounds

(1) Based on the current knowledge on the chemistry, biology and toxicology of boron can the SCCS inform the Commission which of the substances listed in the annex II, newly classified substances to this mandate, are covered by the entries 1a and 1b of Annex III, of the Cosmetics Directive 76/768/EEC?

The SCCS is of the opinion that all substances listed in Annex II of this mandate with the exception of dibutyltin hydrogen borate, are covered by the entries 1a of Annex III of the Cosmetics Directive 76/768/EEC. Tetraborates, as identified in table 1 of this opinion, are also covered by entry 1b of the same annex.

(2) Based on the answer to question 1, and taking into account the scientific data used in the classification of these substances, the SCCS is asked if:

(a) the substances that are covered by the entries 1a and 1b of Annex III and which are currently restricted by Directive 76/768/EEC at a maximum use concentration above the specific concentration limits for classification set out in the Commission Regulation 790/2009 are safe when used in cosmetic products below the specific concentration limits set out in the Commission Regulation 790/2009?

The SCCS points out that a threshold can be established for the reproductive toxicity of boron compounds. On this basis boric acid, borates and tetraborates are safe when used under the conditions laid down in entry 1a of Annex III. Moreover, tetraborates are safe under the conditions laid down in entry 1b of Annex III if the maximum authorised concentration in the finished cosmetic products is reduced to < 4.5%. Sodium perborate and perboric acid are discussed in a separate Opinion (SCCS/1345/10).

Exposure to borate compounds from uses other than cosmetics were not taken into account for this risk assessment.

(b) the substances that are not covered by the entries 1a and 1b of Annex III can safely be used in cosmetic products at concentrations levels below the specific concentrations limits laid down the Commission Regulation 790/2009?

In Annex II of this mandate, the SCCS has only identified dibutyltin hydrogen borate that is not covered by entries 1a and 1b of Annex III. No specific concentration limit is given for this substance in Commission Regulation 790/2009, therefore no risk assessment for the use in cosmetic products has been performed.

Octaborates

(3) (a) Based on the current scientific knowledge on the chemistry, biology and toxicology of boron and its compound does the SCCS consider that octaborates are covered by Annex III of the Cosmetics Directive, entry 1a and 1b? If covered, considering that octaborates are not classified, should the current restrictions limits of Annex III entry 1a and 1b be applied for the octaborates?

SCCS is of the opinion that, based on the chemistry, biology and toxicology available, the threshold for the reproductive toxicity of octaborates are similar to that for other boron compounds. On this basis octaborates are safe when used under the conditions laid down in Annex III, entry 1a of the Cosmetics Directive. Moreover, octaborates are safe under the conditions laid down in entry 1b of Annex III if the maximum authorized concentration in the finished cosmetic products are reduced to < 5.5% (by mass as boric acid). The SCCS notes, however, that octaborates are not classified as toxic for reproduction and no specific concentration limits are assigned to them.

(b) if not covered, does the SCCS have any scientific concern about the safe use of octaborates in cosmetic products?

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5. MINORITY OPINION

Not applicable

6. REFERENCES

Austria (2009). Annex XV Transitional Report for Boric acid and Disodium Tetraborate Anhydrous. Prepared according to the provisions of article 136(3) "transitional measures regarding existing substances" of REACH (Regulation (EC) 1907/2006). Chapin RE, Ku WW, Kenney MA, McCoy H, Gladen B, Wine RN, Wilson R, Elwell MR (1997). The effects of dietary boron on bone strength in rats. Fundam. Appl. Toxicol. 35: 205-215.

Draize JH, Kelley EA (1959). The urinary excretion of boric acid preparations following oral administration and topical applications to intact and damaged skin of rabbits. Toxicol Appl Pharmacol 1:267-276.

EC (2009). Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures. 14. May 2009.

ECB (2003). Concentration limits for substances classified as toxic to reproduction/ developmental toxicity in preparations. N-Methylpyrrolidone (nmp) f 034; Cas no. 872-50-4 Dec. 22, 2003/fg-cg0059. ECBI/47/02 Add 7. Ispra

ECB (2006) Draft SUMMARY RECORD from the Session on Classification of Boric Acid and Borates. ECBI/43/05. ECBI/118/04 Add. 90 Part 1. Ispra.

ECHA (2010) Committee for Risk Assessment (RAC). Opinion on new scientific evidence on the use of boric acid and borates in photographic applications by consumers. ECHA/RAC/A77-O-0000001273-82-05/F. Helsinki 29 April 2010.

EFSA (2004). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Boron (Sodium Borate and Boric Acid) (Request N° EFSA-Q-2003-018) (adopted on 8 July 2004). The EFSA Journal 80: 1-22.

EU (2009a). European Union Draft Risk Assessment Report on Disodium Tetraborate, Anhydrous Boric Acid, Boric Acid, Boric Acid, Crude Natural. (http://ecb.jrc.ec.europa.eu/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/boricacidcrudereport423A.pdf)

EU (2009b) Assessment report. Disodium octaborate tetrahydrate (PT 8), 20 February 2009. http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=ein

Field EA, Price CJ, Marr MC, et al (1989). Final report on the developmental toxicity of boric acid (CAS No. 10043-35-3) in CD-1-Swiss Mice. National Toxicology Program, Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC; NTP Final Report No. 89-250.

Friis-Hansen B, Aggerbeck B, Jansen JA (1982). Unaffected blood boron levels in newborn infants treated with a boric acid ointment. Food Chem Toxicol 20:451-454.

Grella P, Tambuscio B, Suma V (1976). Boric acid and poisoning during pregnancy: Description of one case. Acta Anaestesiol. Ital. 27: 745-748 (in Italian).

Heindel JJ, Price CJ, Field EA, Marr MC, Myers CBM, Moresby RE, Schwetz BA (1992). Developmental toxicity of boric acid in mice and rats. Fundam Appl Toxicol 18: 266–277.

Heindel JJ, Price CJ, Schwetz BA (1994). The developmental toxicity of boric acid in mice, rats and rabbits. Environ Health Perspect 102(Suppl 7):107-112.

Jansen JA, Schou JS, Aggerbeck B (1984). Gastrointestinal absorption and in vitro release of boric acid from water-emulsifying ointments. Fd. Chem. Toxicol. 22: 49-53.

Litovitz TL, Klein-Schwartz W, Oderda GM, Schmitz BF (1988). Clinical manifestations of toxicity in a series of 784 boric acid ingestions. Am. J. Emerg. Med. 6: 209-213.

Muller A, Jacobsen H, Healy E, McMickan S, Istace F, Blaude MN, Howden P, Fleig H, Schulte A (2006). (EU Working Group on Haemolytic Anaemia). Hazard classification of chemicals inducing haemolytic anaemia: An EU regulatory perspective. Regulatory Toxicology and Pharmacology 45: 229-241.

Nielsen, FH (1992). Facts and fallacies about boron. Nutr Today 27:6-12.

NTP (National Toxicology Program) (1987). Toxicology and carcinogenesis studies of boric acid (CAS No. 10043-35-3) in B6C3F1 mice (feed studies). Research Triangle Park, North Carolina, US department of Health and Human Services, Technical Report Series No 324 (NTP TR No. 324).

Pahl MV, Culver BD, Strong PL, Murray FJ, Vaziri ND (2001). The effect of pregnancy on renal clearance of boron in humans: a study based on normal dietary intake of boron. Toxicol Sci 60(2): 252-256.

Price CJ, Strong PL, Marr MC, Myers CB, Murray FJ (1996a). Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Fund Appl Toxicol 32:179-193.

Price CJ, Marr MC, Myers CB, Goldberg MM (1996b). Blood boron concentrations in pregnant rats fed boric acid throughout gestation. Reprod Toxicol 34: 176–187.

Robbins WA, Xun L, Jia J, Kennedy N, Elashoff DA, Pinge L (2010). Chronic boron exposure and human semen parameters. Reprod Toxicol 29: 184–190.

Scialli AR, Bonde JP, Brüske-Hohlfeld I, Culverd BD, Li Y, Sullivan FM (2010). An overview of male reproductive studies of boron with an emphasis on studies of highly exposed Chinese workers. Reprod Toxicol 29: 10–24.

Schroeder HA, Mitchener M (1975). Life-term effects of mercury, methyl mercury, and nine other trace metals on mice. J Nutr 105: 453-458.

Stuttgen G, Siebel T, Aggerbeck B (1982). Absorption of boric acid through human skin depending on the type of vehicle. Arch Dermatol Res 272: 21-29.

Sutherland B, Strong PL, King JC (1998). Determining Human Dietary Requirements for Boron. Biological Trace Element Research. 66: 193-204.

U.S. Borax. (2000) UCI Boric acid clearance study reports and associated data: rat and human studies.

U.S. EPA (2004). Toxicological Review of Boron and Compounds in Support of Summary Information on Integrated Risk Information (IRIS). National Center for Environmental Assessment, Washington, DC. Available online from: http://www.epa.gov/iris.

Vaziri ND, Oveisi F, Culver BD, Pahl MV, Andersen ME, Strong PL, Murray FJ (2001). The effect of pregnancy on renal clearance of boron in rats given boric acid orally. Toxicol Sci 60(2): 257-263.

Vignec AJ, Ellis R (1954). Inabsorbability of boric acid in infant powder. Am J Dis Child 88: 72-80.

Weir RJ (1966a). Two-year dietary feeding study - albino rats. Boric acid. Final Report. Hazleton Laboratories Inc., Falls Church, VA, July 8th, 1966 and Addendum to Final Report, April 10, 1967. Unpublished report to US Borax Research Corporation.

Weir RJ (1966b). Two-year dietary feeding study – albino rats. Borax (Sodium tetraborate decahydrate). Final Report Hazleton Laboratories Inc., Falls Church, VA, July 8th, 1966 and Addendum to Final Report, April 10, 1967. Unpublished report to US Borax Research Corporation.

Weir RJ, Fisher RS (1972). Toxicologic studies on borax and boric acid. Toxicol Appl Pharmacol 23: 351-364.

Wery N, Narotsky MG, Pacico N, Kavlock RJ, Picard JJ, Gofflot F (2003). Defects in cervical vertebrae in boric acid-exposed rat embryos are associated with anterior shifts of hox gene expression domains. Birth Defects Res (Part A) 67: 59-67.

Wester RC, Hui X, Hartway T, Maibach HI, Bell K, Schell MJ, Northington DJ, Strong P, Culver BD (1998). In vivo percutaneous absorption of boric acid, borax and disodium octaborate tetrahydrate in humans compared to in vitro absorption in human skin from infinite to finite doses. Toxicol Sciences 45: 42-51.

WHO (1998). Environmental Health Criteria 204. Boron. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety.