



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 October 2017
EMA/CHMP/619104/2013
Committee for Human Medicinal Products (CHMP)

Questions and answers on boric acid and borates used as excipients in medicinal products for human use

Draft agreed by Excipients Drafting group	16 June 2015
Adopted by CHMP for release for consultation	23 July 2015
Start of public consultation	31 July 2015
End of consultation (deadline for comments)	31 October 2015
Agreed by Excipients Drafting group	16 June 2016
Adopted by CHMP	21 July 2016
Date of publication	9 October 2017

Keywords	<i>Excipients, Package leaflet, Boric acid, Borates, Boron, Borax</i>
-----------------	---

This document should be read in the context of the revision of the Annex of the European Commission guideline 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/3026202017) [1].



Questions and answers on boric acid and borates used as excipients in medicinal products for human use

Table of contents

Table of contents.....	2
1. What is boric acid and why is it used as an excipient?.....	3
2. Which medicinal products contain boric acid?	3
3. What are the safety concerns?	3
4. What are the reasons for updating the information in the package leaflet?	4
5. Proposal for new information in the package leaflet	5
Annex - Doses of boric acid, borax and borax anhydrous corresponding to the thresholds determined for boron.....	6
References	7

1. What is boric acid and why is it used as an excipient?

Boron, which is the characteristic element of boric acid, is a widely occurring element found mainly in minerals in sediments and sedimentary rock. It is found in the environment primarily combined with oxygen in compounds called borates, and is never found as the free element. Common borate compounds include boric acid, salts of boric acid (e.g. sodium tetraborate, also referred to as borax), and boron oxide [2].

Boric acid is used as an antimicrobial preservative and is used as a buffering agent to control the pH. Additionally, it can have the function as tonicity-adjusting agent.

2. Which medicinal products contain boric acid?

Boric acid can be found in products such as:

- Ophthalmic preparations, containing boric acid or its salts used as buffer and/or isotonicity agents,
- Ears drops,
- Homeopathic dilutions containing boric acid, its salts and esters.

3. What are the safety concerns?

Metabolism of inorganic borates by biological systems is not feasible owing to the excessive energy required to break the boron-oxygen bond. Inorganic borates, in low concentrations, convert to boric acid at physiological pH in the aqueous layer overlying mucosal surfaces prior to absorption. This is supported by the evidence in both human and animal studies, where more than 90% of the administered dose of borate is excreted as boric acid [22]. Therefore, systemic effects observed in animal studies with boric acid are relevant for inorganic borates. That is why, dose levels are also expressed as mg boron/kg (mg B/kg).

Following single-dose administration, the target organs identified in the mouse, rat and dog were the kidneys (glomerular and tubular lesions) and nervous system (cerebral cortex, spinal marrow). In the mouse and rat the oral LD₅₀ ranges approximately from 2200 to 4000 mg/kg (400–700 mg boron/kg) [22]. These data are consistent, from a qualitative point of view, with the neurological toxicity suggested for boric acid after analysis of the pharmacovigilance cases over a 10-year period. In the repeated-dose studies in the mouse and rat (90 days, 2 years), the testes were the target organ [13, 21]. The rat is the most sensitive species. The NOAEL of boric acid was 100 mg/kg/day in the 2-year rat study [21].

The testicular toxicity was confirmed by the fertility studies. The latter showed, after a single oral exposure in the rat, reversible changes in testicular histology and sperm parameters [11]. Following repeated oral dosing in the male mouse and rat, impairment of spermiation and sperm quality was observed and resulted in a partial reduction in fertility or complete sterility, depending on the dose [5, 20, 21]. In female rats, following oral administration, a decrease in ovulation was observed and resulted in a decrease in reproductive performance at high dose levels [21]. The effects on fertility occurred at dose levels not inducing any other marked toxic effects. In the rat, the NOAEL of boric acid is 100 mg/kg/day (equivalent to 17.5 mg B/kg/day) [21].

No genotoxic or carcinogenic potential of boric acid was evidenced. The compound is not a cutaneous or ocular irritant in the rabbit. The compound does not induce cutaneous sensitisation in an appropriate test in the guinea pig.

In the mouse, rat and rabbit, boric acid administered during gestation was fetotoxic and fetolethal (at high doses). Malformations were reported in the 3 species, particularly costal malformations. In the rabbit, cardiovascular abnormalities were observed in the heart and main vessels. In the rat, the most sensitive species, fetotoxic and teratogenic effects were evidenced at dose levels not inducing maternal toxicity [8, 14, 15]. In the rat, the fetal NOEL was 55 mg/kg/day (equivalent to 9.6 mg B/kg/day) [14, 15].

There are several epidemiological studies in workers. Boron exposure data were measured in the workplace and in biological samples [16, 19] the Scientific Committee on consumer Safety concluded that the design of such studies are insufficient to demonstrate an effect or an absence of effect on fertility [18].

A permitted daily exposure (PDE) for adult patients was derived from the MRL (minimal risk level) determined by the ATSDR based on its developmental toxicity in rodents [17].

$$\text{PDE} = 0.2 \text{ mg B/kg/day} \times 50 \text{ kg} = 10 \text{ mg B/day}$$

This limit is consistent with the Scientific Committee on Consumer Safety opinion on Boron compounds which is set the Upper Intake Level (UL) in food for at 10 mg boron/person/day in adults and consider that this UL also applies to pregnant and lactating women. The SCCS 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 [18].

4. What are the reasons for updating the information in the package leaflet?

As per the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1) [6] there is no information in the package leaflet. Boron compounds are classified as toxic to reproduction (CMR Repr. cat. 2) [17]. Therefore, it is considered necessary to include appropriate information in the package leaflet of boron-containing medicinal products especially for the most sensitive populations, i.e. pregnant women and children.

5. Proposal for new information in the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments										
Boric acid (and borates)	All routes of administration	1 mg B/day*	Do not give to a child less than 2 years old as this medicine contains boron and may impair fertility in the future.	<p>* 1 mg B (Boron) = 5.7 mg boric acid</p> <p>See Q&A document [link to be inserted] for further calculations.</p> <p>Amount of boron per age group which may impair fertility if exceeded:</p> <table border="1"> <thead> <tr> <th>Age</th> <th>Safety limit</th> </tr> </thead> <tbody> <tr> <td>< 2 years</td> <td>1mg B/day</td> </tr> <tr> <td>< 12 years</td> <td>3 mg B/day</td> </tr> <tr> <td>< 18 years**</td> <td>7 mg B/day</td> </tr> <tr> <td>≥ 18 years**</td> <td>10 mg B/day</td> </tr> </tbody> </table> <p>** This amount may also cause harm to the unborn child.</p>	Age	Safety limit	< 2 years	1mg B/day	< 12 years	3 mg B/day	< 18 years**	7 mg B/day	≥ 18 years**	10 mg B/day
		Age	Safety limit											
		< 2 years	1mg B/day											
< 12 years	3 mg B/day													
< 18 years**	7 mg B/day													
≥ 18 years**	10 mg B/day													
3 mg B/day*	Do not give to a child less than 12 years old as this medicine contains boron and may impair fertility in the future.													
7 mg B/day*	<p>Do not give to a child less than 18 years old as this medicine contains boron and may impair fertility in the future.</p> <p>If you are pregnant, talk to your doctor before taking this medicine as it contains boron which may be harmful to your baby.</p>													

Further scientific background is available in the report entitled 'Boric acid and borates used as excipients' [3].

Annex - Doses of boric acid, borax and borax anhydrous corresponding to the thresholds determined for boron

Boron (B)	<i>Boric acid^a</i>	<i>Borax^b</i>	<i>Borax anhydrous^c</i>
1 mg	<i>5.7 mg</i>	<i>8.8 mg</i>	<i>4.7 mg</i>
3 mg	<i>17.1 mg</i>	<i>26.5 mg</i>	<i>14.0 mg</i>
7 mg	<i>40.0 mg</i>	<i>61.9 mg</i>	<i>32.6 mg</i>
10 mg	<i>57.1 mg</i>	<i>88.5 mg</i>	<i>46.5 mg</i>

^a equivalent dose of boric acid, calculated according to the following conversion factor: "dose of boric acid × 0.175 = equivalent dose of boron" [22];

^b equivalent dose of borax, calculated according to the following conversion factor: "dose of borax × 0.113 = equivalent dose of boron" [22];

^c equivalent dose of anhydrous borax, calculated according to the following conversion factor: "dose of anhydrous borax × 0.215 = equivalent dose of boron" [22].

References

1. Annex of the European Commission guideline 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017).
2. ATSDR (Agency for Toxic Substances and Disease Registry), ToxGuide™ for Boron B CAS#7440-42-8, U.S. Department of Health and Human Services - Public Health Service, 2011, Atlanta.
3. Boric acid and borates used as excipients (EMA/CHMP/765436/2012).
4. Chapin, R.E., Ku, W.W., Kenney, M.A., McCoy, H., Gladen, B., Wine, R.N., Wilson, R., Elwell, M.R., 'The effects of dietary boron on bone strength in rats', *Fundam Appl Toxicol.*, Vol. 35, 1997, p. 205–215.
5. Fail, P.A., George, J.D., Seely, J.C., Grizzle, T.B., Heindel, J.J., 'Reproductive toxicity of boric acid in Swiss (CD-1) mice: assessment using the continuous breeding protocol', *Fundam Appl Toxicol.*, Vol. 17, 1991, p. 225–239.
6. Guideline on excipients in the label and package leaflet of medicinal products for human use (CPMP/463/00 Rev.1), July 2003.
7. Harris, M.W., Chapin, R.E., Lockhart, A.C., Jokinen, M.P., 'Assessment of a short-term reproductive and developmental toxicity screen', *Fundam Appl Toxicol.*, Vol. 19, 1992, p. 186–196.
8. Heindel, J.J., Price, C.J., Field, E.A., Marr, M.C., Myers, C.B., Morrissey, R.E., Schwetz, B.A., 'Developmental toxicity of boric acid in mice and rats', *Fundam Appl Toxicol.*, Vol. 18, 1992, p. 266–277.
9. Heindel, J.J., Price, C.J., Schwetz, B.A., 'The developmental toxicity of boric acid in mice, rats, and rabbits', *Environ Health Perspect.*, Vol. 102, Suppl 7, 1994, p. 107–112.
10. Ku, W.W., Chapin, R.E., Moseman, R.F., Brink, R.E., Pierce, K.D., Adams, K.Y., 'Tissue disposition of boron in male Fischer rats', *Toxicol Appl Pharmacol.*, Vol. 111, 1991, p. 145–151.
11. Linder, R.E., Strader, L.F., Rehnberg, G.L., 'Effect of acute exposure to boric acid on the male reproductive system of the rat', *J Toxicol Environ Health*, Vol. 31, 1990, p. 133–146.
12. Murray, F.J., Schlekot, C.E., 'Comparison of Risk Assessments of Boron: Alternate Approaches to Chemical-Specific Adjustment Factors', *Human and Ecological Risk Assessment: An International Journal*, Vol. 10, 2004, p. 57–68.
13. NTP (National Toxicology Program), Toxicology and carcinogenesis studies of boric acid (CAS NO. 10043-35-3) in B6C3F1 mice (feed studies) (No. NTP TR 324), U.S. Department of Health and Human Services - Public Health Service, National Institutes of Health, 1987.
14. Price, C.J., Marr, M.C., Myers, C.B., Seely, J.C., Heindel, J.J., Schwetz, B.A., 'The developmental toxicity of boric acid in rabbits', *Fundam Appl Toxicol.*, Vol. 34, 1996, p. 176–187.
15. Price, C.J., Strong, P.L., Marr, M.C., Myers, C.B., Murray, F.J., 'Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation', *Fundam Appl Toxicol.*, Vol. 32, 1996, p. 179–193.

16. Robbins, W.A., Xun, L., Jia, J., Kennedy, N., Elashoff, D.A., Ping, L., 'Chronic boron exposure and human semen parameters', *Reprod Toxicol.*, Vol. 29, 2010, p. 184–190.
17. SCCS (Scientific Committee on Consumer Safety) Updated, revised request for a scientific opinion following the new classification of some boron compounds as mutagenic and/or toxic to reproduction according to the Commission Regulation 790/2009.
18. SCCS (Scientific Committee on Consumer Safety), Opinion on boron compounds. European Commission, Directorate-General for Health and Consumers, 2010.
19. Scialli, A.R., Bonde, J.P., Brüske-Hohlfeld, I., Culver, B.D., Li, Y., Sullivan, F.M., 'An overview of male reproductive studies of boron with an emphasis on studies of highly exposed Chinese workers', *Reprod Toxicol.*, Vol. 29, 2010, p. 10–24.
20. Treinen, K.A., Chapin, R.E., 'Development of testicular lesions in F344 rats after treatment with boric acid', *Toxicol Appl Pharmacol.*, Vol. 107, 1991, p. 325–335.
21. Weir, R.J., Fisher, R.S., 'Toxicologic studies on borax and boric acid', *Toxicol Appl Pharmacol.*, Vol. 23, 1972, p. 351–364.
22. WHO (World Health Organisation), International Programme on Chemical Safety, Environmental Health Criteria 204: Boron, 1998, Geneva, Switzerland.