Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Chloramphenicol eye drops containing borax and boric acid buffers: review of the use in children under 2 years

MHRA Public Assessment Report
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Contents

1. Plain Language Summary

Key message

Following a thorough review, we have concluded that the benefits outweigh the risks of using chloramphenicol eye drops containing borax and boric acid when indicated for children aged 0 to 2 years. See Drug Safety Update advice, issued in July 2021.

This Public Assessment Report presents the data considered in this review and how we reached these conclusions.

About these medicines

Eye infections (for example, conjunctivitis) are very common in babies and infants and it is important they are treated properly. Chloramphenicol eye drops are an important medicine for treating bacterial eye infections in children and have been used safely for many years.

Some eye drops contain borax and boric acid, which are sources of boron. These ingredients are included as buffers to make sure the medicine is not too acidic or alkaline and is comfortable when administered to the eye.

Reason for the review and how it was done

Concerns about boron and a possible effect on future fertility led to restrictions in the use of some chloramphenicol eye drop products in children younger than 2 years.

The MHRA has reviewed the available evidence to understand whether there is a risk for children aged 0 to 2 years. We sought independent expert advice to understand the risk for infants when these products are used as recommended, for what is likely to be a short period of time.

Conclusions of the review

Chloramphenicol eye drops are used infrequently and for a short amount of time. The small amount of liquid that can be absorbed through the eyes of young children and the way these products are prescribed mean that the daily exposure to children would be well below the calculated safety limits for most patients. These products can be safely given to children younger than 2 years as advised by a doctor or other prescriber.

We have asked for the removal of restrictions and associated warnings about boron exposure in children aged 0 to 2 years from the product information (Summary of Product Characteristics and Patient Information Leaflets) for UK chloramphenicol eye drop products. See Drug Safety Update, July 2021 – Chloramphenicol eye drops containing borax or boric acid buffers: use in children younger than 2 years.

2. Summary of review and conclusions

Boric acid and its salts are used in ophthalmic (eye) preparations as buffering agents to control pH and to maintain isotonicity.

In October 2017, warnings for boric acid (and borates) were introduced into the 'Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' SANTE-2017_11668' by the European Medicines Agency (EMA). The guidance document is applicable in the UK, being referred to in the Human Medicines Regulations 2012.

The EMA's Committee for Human Medicinal Products (CHMP) introduced the warnings with an accompanying 'Questions and answers document on boric acid and borates used as excipients in medicinal products for human use'.

As there was an implementation period of 3 years for marketing authorisation holders to update their product information in line with the 2017 guidance, manufacturers changed their product information at the end of 2020.

The European guidance requires strong warnings not to give children boron-containing products if certain exposures are exceeded. Future impaired fertility is the reason given. The European guidance documents elaborate that testicular toxicity and sterility at high levels of exposure is the main concern.

With restrictions introduced on the use of some products in children younger than 2 years old, concerns were raised by clinicians in the UK regarding the applicability of the warning and the lack of suitable alternatives to chloramphenicol eye drops.

The MHRA therefore undertook a review of the interpretation of the European guidance on boric acid and borates in the 0–2 years age group. We sought independent expert advice from the Paediatric Medicines Expert Advisory Group of the Commission on Human Medicines.

For some chloramphenicol eye drop products, exposure has been calculated using the boron concentration in the product and assuming a full drop size of around 40µl and maximum doses. These calculations may lead to an assumption that the exposure to boron exceeds the 1 milligram (mg) per day threshold. However, an eye drop is normally considered an excess, as some liquid will be blinked out. The maximum volume that can be accommodated in the conjunctival sac of a child aged 0 to 2 years of age is considered by experts to be between 10µL and 20µL. Taking this volume into account, a typical regime of one drop to both eyes 4 times daily would result in a daily exposure well below 1mg per day, even if 100% absorption is assumed. It should also be noted that chloramphenicol eye drops are used infrequently on a short-term basis.

The EMA/CHMP threshold for boron is based on a pregnancy-related effects following oral exposure in adult rats (reduced fetal weights). The uncertainty factors used in the derivation of this permitted daily exposure (PDE) are based on toxicokinetic data and bodyweight data from pregnant rats and humans. Therefore, it was concluded that the current PDE is not relevant to infants aged 0 to 2 years. There are no data indicating clinical relevance to children 0 to 2 years of age at present, therefore the assumption of potential risk to future fertility was considered precautionary.

Given the toxicological data and the calculation of daily exposure from a typical dosing regime, it has been concluded that the benefit-risk balance of chloramphenicol eye drops containing boron and boric acid remains positive for children 0 to 2 years of age.

Key messages from the review:

- Although concerns have been raised about boron and a possible effect on future fertility, these products can be safely given to children aged 0 to 2 years as advised by a doctor or other prescriber
- Chloramphenicol eye drop products remain an important medicine in children and have been used safely for many years
- We have reviewed the available evidence and sought independent expert advice to understand whether there is a risk for children aged 0 to 2 years when using these products within the licensed indication, for what is likely to be a short period of time
- For some chloramphenicol eye drop products, exposure had been calculated assuming a drop size of around 40µl – this may over-estimate exposure since it is known that some of the drop will be blinked out and lost in tears; a typical regime of one drop to both eyes 4 times daily would result in a daily exposure well below 1mg per day, even if 100% absorption is assumed.
- Calculations of the safety margins based on no-observed-adverse effect-level (NOAELs) for acute and chronic male reproductive toxicity indicates safety margins ranging from 29-fold to 200-fold
- There are no data indicating clinical relevance to adults and children at present, therefore the assumption of potential risk to future fertility of infants is precautionary – this, combined with the safety factors, should permit the use of chloramphenicol products in 0 to 2 year olds
- Product information for the affected products has been updated to reflect the revised advice that these products can be safely administered to children 0 to 2 years old

3. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates. The Commission on Human Medicines (CHM) advises government ministers and the MHRA on the safety, efficacy and quality of medicines takes into account the advice from its various Expert Advisory Groups.

The aim of our Safety Public Assessment Reports is to present evidence-based assessments of safety issues for a particular drug or drug class.

This report provides a summary of our review of the use of chloramphenicol eye drops containing borax and boric acid buffers in children younger than 2 years of age. A glossary is provided for an explanation of the terms used in this report (see section 12).

The information and analyses contained in this report reflect evidence that was available at the time of the review in 2021. The MHRA will continue to monitor the safety of all medicines. The information in this report will not be actively updated with new data or studies unless major new safety information is available that results in critical changes.

Parents and caregivers should contact their healthcare professionals if they are concerned about their child's health or medicines.

4. Background

Chloramphenicol is a broad-spectrum antibiotic used in both adults and children for the treatment of bacterial conjunctivitis and other superficial eye infections. Chloramphenicol eye drops are an important medicine for children, including the very youngest.

Chloramphenicol eye drops contain borax and boric acid buffers, which are a source of boron. In accordance with the European guidance, marketing authorisation holders (MAH) for chloramphenicol eye drops at the end of 2020 introduced warnings for boron, resulting in chloramphenicol eye drops being contraindicated in children under 2 years old. This meant that this useful therapy would no longer be available for children under 2 years of age, with detrimental consequences for public health.

The European guidance 'Questions and answers on boric acid and borates used as excipients in medicinal products for human use' (Annex I) states that if the threshold of 1mg boron per day is exceeded the following warning should be included in the package leaflet: '*Do not give to children less than 2 years old as this medicine may impair fertility in the future*'.

In April 2021, the Royal College of Ophthalmologists raised concerns, stating "*Whilst a theoretical risk to future fertility from boron-containing excipients in chloramphenicol eyedrops should not be dismissed lightly, a decision to stop using chloramphenicol eyedrops in children also carries risks…*" and "*At the present time, the College believes that the benefits of chloramphenicol eyedrops in paediatric ophthalmic practice for appropriate indications and with courses of appropriate duration outweigh the possible risks posed by boron ingestion*" (see 'Safety Alert: Boron additives in Chloramphenicol drops; should ophthalmologists be concerned?').

The MHRA undertook a review of the interpretation of the European guidance on boric acid and borates as relates to children aged 0 to 2 years. We systematically reviewed the available quality, clinical and toxicological evidence, including the published literature and guidance on these aspects. We sought independent expert advice from the Paediatric Medicines Expert Advisory Group of the Commission on Human Medicines to understand the risk for infants when these products are used within the licensed indication for what is likely to be a short period of time.

5. Excipient guidance

For some years the European Medicines Agency (EMA) has been updating guidance for warning labels for excipients that appear in the Package leaflet.

Historically there were no warnings for boric acid and borates. On 9 October 2017 warnings for boric acid (and borates) were introduced into the 'Annex to the European Commission guidance on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668)' as replicated in Table 1:

Table 1: Warnings for boric acid (and borates), adapted from Annex to the European guidance on 'Excipients in the labelling and package leaflet of medicinal products for human use; rev. 1. EMA/CHMP/302620/2017'.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet
Boric acid (and borates)	9 October 2017	All	1mg 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.
Boric acid (and borates)	9 October 2017	All	3mg 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.
Boric acid (and borates)	9 October 2017	All	7mg B/day*	Do not give to a child less than 18 years old as this medicine contains boron and may impair fertility in the future. If you are pregnant, talk to your doctor before taking this medicine as it contains boron which may be harmful to your baby.

Amount of boron that may impair fertility if exceeded

<2 years 1mg B/day
<12 years 3mg B/day
<18 years ** 7mg B/day
≥18 years ** 10mg B/day

See Q&A document (EMA/CHMP/619104/2013) for further calculations. *1 mg B (Boron) = 5.7 mg boric acid. **This amount may also cause harm to the unborn child.

The October 2017 warnings were introduced with an accompanying questions and answers document ('Questions and answers on boric acid and borates used as excipients in medicinal products for human use' or 'Boric acid and borates'). The EMA/CHMP also wrote a background review in 2015 (see 'Background review for the excipient boric acid').

As the implementation period was 3 years, variations to marketing authorisations were submitted in 2020 to update product information.

6. Review of Pharmaceutical Quality Information

6.1 Quantity of boron in chloramphenicol eye drops

It should be noted that the guidance considers the quantity of elemental boron. The European guidance 'Questions and answers on boric acid and borates used as excipients in medicinal products for human use' document states that "*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. 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)*".

In the chloramphenicol eye drop products in question there are 2 boron-containing compounds (borax and boric acid), which are used as buffers in the eye drops. The European guidance provides the following Table 2 of doses of boric acid, borax and borax anhydrous corresponding to the thresholds determined for boron.

Table 2: Doses of boric acid, borax and borax anhydrous corresponding to the thresholds determined for boron, adapted from EMA/CHMP/619104/20139; October 2017

Boron (B)	**Boric acid***	**Borax****	**Borax anhydrous*****
1mg	5.7mg	8.8mg	4.7mg
3mg	17.1mg	26.5mg	14.0mg
7mg	40.0mg	61.9mg	32.6mg
10mg	57.1mg	88.5mg	46.5mg

*Equivalent dose of boric acid, calculated according to the following conversion factor: dose of boric acid × 0.175 = equivalent dose of boron.
**Equivalent dose of borax, calculated according to the following conversion factor: dose of borax × 0.113 = equivalent dose of boron.
***Equivalent dose of anhydrous borax, calculated according to the following conversion factor: dose of anhydrous borax × 0.215 = equivalent dose of boron.

6.2 Volume accommodated by the eye

The volume of an eye drop is generally considered an excess. Aulton's 'Textbook of Pharmaceutics' states "*It has been found that the conjunctival sacs are capable of accommodating only 20µl TO 30µl of added fluid temporarily without spilling; however, the typical drop volume from eye drop bottles made by different manufacturers ranges*

from 34µl to 63µl. Not only is this variability large but it also exceeds the volume that can be accommodated by the eye if several drops are administered at once".

Exposure calculations were generally not provided by MAHs adding boron warnings, but it is thought that some MAHs have based their calculations on the full drop size of around 40µl. This might be considered an excess as the ocular capacity of the adult eye is said to be 20µl to 30µl. This is perhaps even more of an excess if considering the eye of a child aged 0 to 2 years.

Urtti and Salminen (1993) state "*The kinetics of eyedrops on the ocular surface are well known: the solutions spread over the ocular surface, some spills out of the eye, and the rest is diluted with tear fluid and flows rapidly into the puncta……The typical volumes delivered by the commercial eye droppers are 25-56µl. However, the extra solution volume that can be held in the conjunctival sac is less than the typical eye drop volume. Thus, part of the eye drop may spill over from the conjunctival sac onto the skin of the lids and cheek. The capacity of the conjunctival sac may depend on blinking, position, and technique of instillation…*"

The EMA/CHMP's 'Background review for the excipient boric acid' points out that boron is well absorbed orally stating: "*Boric acid is readily absorbed from the gastrointestinal tract in rats and humans. At least 92% of a single oral dose of boric acid was recovered in the urine of human volunteers".* Boron in eye drops expelled via the lacrimal puncta may be absorbed by the nasal mucosa and the gastrointestinal tract if swallowed.

Boric acid and borax are not significantly absorbed by skin. The EMA/CHMP's 'Background review for the excipient boric acid' (Executive Summary) states that "*Cutaneous absorption is negligible if the skin is intact".* Borax is converted to boric acid in solution, so this statement is relevant to both excipients. The reference given in the European guidance states the following:

'Dermal' – "In a report by Vignec & Ellis (1954), infants 1.25-10 months old received applications of a talcum powder containing 5% boric acid 7-10 times/day for at least 1 month. The authors calculated that the infants were exposed to an estimated dose of 2.33 g boric acid/day (408 mg boron/day). The boron concentrations in a test group composed of 12 infants were 0.04 ± 0.04 mg/100 ml in blood and 0.16 ± 0.14 mg/100 ml in the urine. An additional group of 12 treated infants, who had developed a mild to moderate diaper rash, had an average blood boron concentration of 0.03 ± 0.04 mg/100 ml. Although Vignec & Ellis (1954) did not analyse the data statistically, the range of the values obtained indicates that, at most, only traces of boric acid penetrated the skin, even in infants with moderate diaper rash.

Further reassurance that boron is not significantly absorbed by the skin of neonates is provided by the 'EC Scientific Committee on Consumer Safety (SCCS) Opinion on Boron compounds' (SCCS/1249/09 Revision of 28 September 2010), which states *"Friis-Hansen and colleagues (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 [boron])".*

Although the formulations studied are different to eye drops there seems evidence that boric acid is not significantly absorbed by undamaged skin. Eye drop expelled onto the skin of the lids and cheek need not be included in exposure calculations, even for neonates.

The eye of a child 0 to 2 years of age is smaller than an adult eye. Patton and colleagues (1976) considered the dimensions of the eye and stated that "*It is possible to calculate that the eye undergoes an almost three-fold volume change from ages 0-14 years*". Other authors have noted that "*increased systemic exposure observed in paediatric patients has been attributed to absorption of eye drops into the systemic circulation where the reduced size of the patient results in higher plasma concentrations of circulating drug*" (Batchelor and colleagues, 2015). "*Customised paediatric delivery devices to provide smaller doses of topically applied ophthalmic preparations*" have been called for by Farkouh and colleagues (2016). However, the volume of eye drop that neonates are capable of accommodating in the eye or the amount of systemic exposure that may result from an eye drop in the 0 to 2 years age group does not seem well defined.

Lynch and colleagues (1987) looked at systemic exposure from 2.5% phenylephrine eye drops in neonates using two volumes. The authors gave 8 infants an 8µl drop volume in both eyes, while 9 infants received a 30µl drop in both eyes. The drops were delivered with a calibrated micropipette and administered to each eye every 2 minutes for 3 doses. The mean plasma phenylephrine level at a single 10-minute time point after the last drop was 0.9 nanogram (ng) per ml for the 8µl-drop group and 1.9ng/ml for the 30µl drop group. The author states that "*Thus, the 30µl drop volume resulted in a mean systemic level of phenylephrine more than twice the level achieved with the 8µl drop. The difference between the groups was statistically significant (p=0.01)".* These results would suggest that neonates are capable of absorbing more than 8µl via the ocular route.

Lynch and colleagues (1987) also state "*For several reasons, infants may develop higher systemic levels from eye drops compared with adults. First, it is likely that the tear film volume in an infant is much smaller than that of an adult. With a smaller tear film, more of an eye drop may be pumped into the lacrimal system and be available*…." and "*because topical medication is usually administered to infants in the supine position, the eye drop 'pools' in the tear film. Thus, less medication spills onto the cheek and more*

drug is available for systemic absorption through the nasolacrimal system". Lynch and colleagues (1987) also considered that *"The tear film volume in neonates and infants is not known".*

In calculating exposure, MAHs assumed that the full volume of a drop is absorbed. It is understandable that MAHs take a cautious approach, but this volume seems an excess given that the adult eye is capable of accommodating only 20µl to 30µl temporarily without spilling.

6.3 Calculating Exposure from Posology

The posology of chloramphenicol eye drops varies across products, but is generally similar to the BNF for Children (BNF-C) which gives the posology of chloramphenicol eye drops as

"Superficial eye infections
To the eye using eye drop
For Child
Apply 1 drop every 2 hours then reduce frequency as infection is controlled and continue for 48 hours after healing, frequency dependent on the severity of the infection. For less severe infection 3–4 times daily is generally sufficient."

Calculations are based on a typical concentration of boron in eye drops of approximately 3mg/ml.

Experts have advised that in the 0 to 2 years age group, a dose of one drop 3 or 4 times a day is the usual dose (8 drops a day if used in both eyes). The more frequent 2 hourly drops, although specified in the BNF-C and the Summary of Product Characteristics (SmPCs) of some eye drops, are infrequently used in this age group. The SmPCs of products also usually limit the duration of this higher dose to 48 hours.

In Table 3 (below), exposure to boron is estimated. Infants will blink much of the eye drop out but as the volume absorbed is difficult to estimate, exposure has been calculated using three exposure volumes – 10µl, 20µl and 30µl. It should be noted that in expert opinion, the maximum volume that can be accommodated in the conjunctival sac of a child younger than 2 years is between 10µl and 20µl.

Table 3: Daily boron exposure (8 drops per day) at three exposure volumes 10µl, 20µl and 30µl

	Exposure volume 10µl per drop	Exposure volume 20µl per drop	Exposure volume 30µl per drop
Volume per day calculation	8 drops × 10µl = 80µl or 0.080ml per day	8 drops × 20µl = 160µl or 0.16ml per day	8 drops × 30µl= 240µl or 0.24ml per day
Estimated Boron Exposure, assuming 3mg boron per ml	0.24mg	0.48mg	0.72mg

As can be seen from Table 3, if a dose frequency of 4 times a day is assumed, then one drop into each eye 4 times a day (8 drops in 24 hours) will result in boron exposures that are less than the EMA/CHMP's 1mg per day threshold, even assuming a worst-case exposure volume of 30µl.

Table 4 shows exposures if the higher dose with 2-hourly drops is used in both eyes (24 drops per day).

Table 4: Daily boron exposure (24 drops per day) at three exposure volumes 10µl, 20µl and 30µl

	Exposure volume 10µl per drop	Exposure volume 20µl per drop	Exposure volume 30µl per drop
Volume per day	24 drops × 10µl = 240µl or 0.24ml per day	24 drops × 20µl = 480µl or 0.48ml per day	24 drops × 30µl= 720µl Or 0.72ml per day
Estimated boron exposure, assuming 3mg boron per ml	0.72mg	1.44mg	2.16mg

The European guidance threshold of 1mg boron per day could be exceeded, in some cases, based on these calculations, and would trigger the warning "*Do not give to a child less than 2 years old as this medicine contains boron and may impair fertility in the future*". In some cases, the threshold is only just exceeded. Considering expert opinion

estimates that the maximum volume that can be accommodated in the conjunctival sac of a child younger than 2 years is between 10µL and 20µL, the EMA/CHMP's threshold might not necessarily be exceeded. It should be noted that these exposure estimates assume 100% absorption of boron. Absorption may not be 100%, reducing these figures further.

Overall, considering a short course of treatment, the maximum volume that can be accommodated in the conjunctival sac of a child younger than 2 years (between 10µl and 20µl) and the most usual dosage regime (3 to 4 drops per eye per day) exposure to boron is likely to be below the EMA/CHMP's threshold of 1mg boron per day.

6.4 Prevalence (Frequency of treatment)

In the UK, infective conjunctivitis accounts for approximately 1% of all GP consultations (NICE infective conjunctivitis Clinical Knowledge Summary).

Cumberland and colleagues (2010) reviewed the prevalence of eye disease in early childhood in the UK and determined that the incidence of "nasolacrimal conditions and infection" was about 1% at 3 years of age based on maternal interviews. Therefore, only occasional use of chloramphenicol eye drops would be expected in children aged 0 to 2 years.

7. Review of Non-Clinical Information

The safety of boron has been reviewed extensively by multiple regulatory bodies including the European Union (EU) European Food Safety Authority (EFSA) and Scientific Committee on Consumer Safety (SCCS), US Environmental Protection Agency (EPA) and US Agency for Toxic Substances and Disease Registry (ATSDR – public health agency). The developing embryo/fetus and the testes have been identified as the most sensitive toxicological targets of boron.

7.1 US Environmental Protection Agency (EPA 2004)

Studies in laboratory animals conducted by oral exposure have identified the developing fetus and the testes as the 2 most sensitive targets of boron toxicity in multiple species (Weir and Fisher, 1972; Seal and Weeth, 1980; NTP, 1987; Fail and colleagues, 1991; Price and colleagues, 1996A, 1996B; Field and colleagues, 1989).

The testicular effects that have been reported include reduced organ weight and organ: bodyweight ratio, atrophy, degeneration of the spermatogenic epithelium, impaired spermatogenesis, reduced fertility and sterility (Weir and Fisher, 1972; Seal and Weeth, 1980; NTP, 1987; Fail and colleagues, 1991; Dixon and colleagues, 1979; Linder and colleagues, 1990; Treinen and Chapin, 1991; Ku and colleagues, 1993). The mechanism for boron's effect on the testes is not known, but the available data (as reviewed by Fail and colleagues, 1998) suggest an effect on the Sertoli cell, resulting in altered physiological control of sperm maturation and release.

The developmental effects that have been reported following boron exposure include high prenatal mortality; reduced fetal bodyweight; and malformations and variations of the eyes, central nervous system, cardiovascular system, and axial skeleton (Price and colleagues, 1996A, 1996B; Field and colleagues, 1989). Increased incidences of short rib XIII (a malformation) and wavy rib (a variation), and decreased incidence of rudimentary extra rib on lumbar I (a variation), were the most common anomalies in both rats and mice. Cardiovascular malformations, especially interventricular septal defect, and variations were the frequent anomalies in rabbits. Fail and colleagues (1998) attributed reduced fetal growth, the most sensitive developmental endpoint, to a general inhibition of mitosis by boric acid, as documented in studies on the mammalian testis, insects, yeast, fungi, bacteria, and viruses (Beyer and colleagues, 1983; Ku and colleagues, 1993).

7.2 EU Scientific Committee on Consumer Safety (SCCS 2010) - Opinion on boron compounds (SCCS/1249/09)

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).

7.2.1 Animal data

Studies investigating the effects of exposure to boric acid on fertility in the rat and mouse identified males as 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 spermatogenesis 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 1000mg/kg bodyweight (bw) per day which do not produce marked signs of other toxicity, and which are not a secondary consequence of other toxicity. A NOAEL of 100mg/kg bw/day (17.5 mg boron (B) per kg bw/day) can be established.

Exposure to boric acid during pregnancy (given either throughout gestation or only during major organogenesis) resulted in decreased fetal bodyweight, 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 prenatal effects in all 3 species has been established at 55mg/kg bw/day (9.6mg 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.

7.2.2 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.

7.2.3 Toxicokinetics

Boron is readily absorbed following oral exposure in both humans and animals (more than 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 metabolised 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 to 3 higher than in other tissues. Boron is excreted rapidly, with elimination half-lives of 1 hour in the mouse, 3 hours in the rat and less than 27.8 hours 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, studies of the urinary clearance of boron aimed to determine the difference in the urinary clearance of boron in pregnant and non-pregnant rats and humans. Reports from these studies (US Borax, 2000; Pahl and colleagues, 2001; Vaziri and colleagues, 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 non-pregnant 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 non-pregnant 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 oral boric acid intake in 9 patients, the mean half-life of boric acid was determined to be 13.4 hours (range 4.0 to 27.8; Litovitz and colleagues, 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 and colleagues, 1997). A poisoning case with boric acid in a pregnant woman suggested that borates might cross the placenta (Grella and colleagues, 1976). The fetus 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 less than 24 hours in humans and animals. Boron is slowly eliminated from bone (Chapin and colleagues, 1997). Following oral intake of an aqueous solution of boric acid, the urinary recovery was 94% (Jansen and colleagues, 1984); more than 50% of the oral dose was eliminated in the first 24 hours, consistent with the 21-hour half-life in the intravenous study. Sutherland and colleagues (1998) showed in a boron balance study that only 8% of dietary boron is excreted in faeces. Absorption for oral and inhalation routes is assumed to be 100%.

7.3.4 Conclusion/discussion of the SCCS Opinion on boron compounds

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.

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.

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

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 bodyweight, 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 3 species has been established at 55mg boric acid/kg bw/day (9.6mg 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 Europe as toxic to reproduction Cat. 2; R60-61 (R60; May impair fertility, R61; May cause harm to the unborn child). A NOAEL of 9.6mg B/kg bw/day is used in the safety evaluation.

7.4 European Food Safety Authority (EFSA 2013) Review: Fertility and boron levels

Testicular lesions have been observed in rats, mice, and dogs administered boric acid or sodium tetraborate in food or drinking water (Truhaut and colleagues., 1964; Weir and Fisher, 1972; Green and colleagues, 1973; Lee and colleagues, 1978; NTP, 1987; Ku and colleagues, 1993, as reported in International Programme on Chemical Safety (IPCS), 1998).

The IPCS (1998) and Expert Group on Vitamins and Minerals (2003) summarised that male reproductive effects from boron have been noted in mice, rats, and dogs and included inhibition of spermiation in stage IX and X tubules, followed by germ cell loss, changes in epididymal sperm morphology and caput sperm reserves, decreased serum testosterone levels, and testicular atrophy. Male reproductive effects have been reported in 2 year oral exposure studies using boric acid or sodium tetraborate at doses of 29mg boron/kg bw/day in dogs (Weir and Fisher, 1972) and in rats the lowest-observed-adverse-effect level (LOAEL) for reproductive toxicity was 58.5 mg boron/kg bw/day (IPCS, 1998). The NOAEL for the three-generation rat study was reported as 17.5 mg boron/kg bw/day (Weir and Fisher, 1972).

Furthermore, the Panel agreed with ECETOC (1995) that dogs are not an appropriate model for reproductive studies and, therefore, did not take into account the data from the 2-year dog study for risk assessment given the low number of animals involved and the large variability of the dogs.

8. EU Permitted Daily Exposure (PDE) for Boron

Embryofetal development and the male reproductive tract are the main toxicological targets of boron. However developmental toxicity is the most sensitive toxicological effect of boron, and therefore the endpoint selected by numerous international regulatory bodies (for example, EMA/CHMP, EU CSSC, EU FSA, EU REACH, US ATSDR, EPA) for the establishment of relevant health based thresholds, focusing on data from the studies by Price and colleagues 1996 and Heindel and colleagues 1992.

8.1 Derivation of the EMA/CHMP PDE for boron

The current European guidance PDE from EMA/CHMP (see 'Annex 1 of Questions and answers on boric acid and borates used as excipients in medicinal products for human use') for boron was adopted from the minimal risk level (MRL) for reduced fetal bodyweights established by the US Agency for Toxic Substances and Disease Registry (ATSDR, 2010, Appendix A, A-8) .

The ATSDR did not use a NOAEL to establish the MRL; instead they selected the 95% lower confidence limit on the benchmark dose associated with 5% reduction in fetal bodyweight (benchmark dose level; $BMDL_{05}$) of 10.3mg boron per kg per day (Allan and colleagues,1996) as the point of departure for calculating the MRL. Allan and colleagues (1996) developed the BMD using data pooled from the studies by Heindel and colleagues (1992) and Price and colleagues (1996). The reduction in fetal bodyweights, which was reported at the same dose as the skeletal effects in the paper by Price and colleagues was shown to be the most sensitive toxicological response of the 2 developmental effects during the derivation of the BMD. Boron is a topoisomerase inhibitor and appears to disrupt the patterning of the axial skeleton. Studies indicate that the somites in the developing embryo are affected

The ATSDR used uncertainty factors (outlined below) to derive the MRL of boron, 2 of which were chemical specific uncertainty factors that were based on pregnancy data. The others were default values. The variability in boron toxicokinetics between pregnant rats and pregnant humans was assessed using renal clearance as the kinetic factor (glomerular filtration rate [GFR] as a surrogate for renal clearance) because boric acid is not metabolised but is almost completely eliminated in urine in both species. In addition, interspecies differences in GI tract absorption and pregnant bodyweights were used to derive the rat to human toxicokinetic factor. The toxicokinetic assessment of variability between human pregnant women took into account differences in mean GFR of healthy women and those with compromised renal function (in other words, 3–5% of women with pre-eclampsia in the US with potentially reduced GFR). The value at 3 standard deviations below the mean GFR was chosen to account for women with very low GFR.

Box: Derivation of the uncertainty factors

Based on these analyses, the total uncertainty factor applied to the $BMDL_{05}$ of 10.3mg boron per kg is derived as:

$UF_{TOTAL} = (AF_{AK} \times AF_{AD} \times AF_{HK} \times AF_{HD} \times UF)$
$= (3.3 \times 3.16 \times 2.0 \times 3.16 \times 1)$
$= 66 \times$

Total uncertainty factor of x66 was used to account for:
AF_{AK}=rat-to-human extrapolation of toxicokinetics (3.3) (pregnancy chemical specific accounting for differences in mean bodyweights and renal clearance between pregnant women and pregnant rats; and gastrointestinal absorption fractions for humans and rats)
AF_{AD}=rat-to-human extrapolation of toxicodynamics (3.16) (default value)
AF_{HK}= human toxicokinetic variability (2.0) (pregnancy specific accounting for variability in renal clearance between women with normal and low GFR)
AF_{HD}=human toxicodynamic variability (3.16) (default value)
UF =Other uncertainty factors (for example, use of a LOAEL instead of a NOAEL)

Reference: Appendix A, A-8, ATSDR 2010 https://www.atsdr.cdc.gov/toxprofiles/tp26.pdf

Overall an uncertainty factor of x66 was applied to the $BMDL_{05}$ of 10.3mg/kg/day resulting in an adult MRL of 0.2mg B/day which was adopted in the European excipients guidance and multiplied by the adult bodyweight of 50mg/kg/day (recommended in ICH Q3C) resulting in a PDE of 10mg B/day.

($BMDL_{05}$ 10.3 mg/kg/day) / (total uncertainty factor 66) = oral MRL of 0.2mg B/kg/day

PDE = (oral MRL: 0.2 mg B/kg/day) × (Adult bodyweight: 50kg) = 10mg B/day

8.2 Age extrapolation of the PDE

For the derivation of the European Boron PDE, the value of 0.2mg/kg/day was adopted and multiplied by the following bodyweights to achieve the PDEs for adults and children:

Adult older than 18 years	50kg × 0.2 mg/kg/day = 10mg B/day
Age 12–17 years	35kg × 0.2 mg/kg/day = 7mg B/day
Age 2–11 years	15kg × 0.2 mg/kg/day = 3mg B/day
Age 0–2 years	5 kg × 0.2 mg/kg/day = 1mg B/day

8.3 Issues arising from the application of the European Boron PDE for infants aged 0 to 2 years with some of the chloramphenicol eye products

The extrapolation of the adult PDE to children has resulted in a threshold of 1mg per day for 0 to 2 year olds, which may be exceeded by the concentrations of boric acid present in chloramphenicol eye products, leading to their contraindication of use in 0 to 2 year olds. However as discussed above, the adverse effect upon which the PDE in the European guidance is based (reduced fetal weights) and the uncertainty factors used in the derivation of the PDE are only relevant to calculations for pregnant woman and women of childbearing potential, not infants aged 0 to 2 years. It is therefore proposed that in this instance the use of this PDE should not be applied to children aged 0 to 2 and a risk assessment based on exposures of boron in the chloramphenicol eye products and the fertility NOAEL of 17.5mg/kg B/day is used to evaluate the safety of the use of these products in the 0 to 2 year old age-range. See below.

9. Review of the Fertility Safety Margin

9.1 Fertility NOAEL

9.1.1 Chronic

The fertility NOAEL identified in the review of boron conducted by the EMA/CHMP, and in agreement with multiple international regulatory bodies, is based on the multigeneration study by Weir and Fisher (1972). In this study, 0 parts per million (ppm), 117ppm, 350ppm, or 1170ppm boron (approximately 0, 5.9, 17.5, or 58.5 mg B/kg bw/day, respectively) was administered 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 5.9mg B/kg bw/day or 17.5mg 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 that received 58.5mg 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 58.5mg B/kg bw/day and a NOAEL of 17.5mg B/kg bw/day were identified in this study.

9.1.2 Acute

Adverse effects on the male reproductive tract has also been observed following acute exposures. Reversible changes to rat fertility were seen up to 350mg B/kg following the administration of a single oral dose.

The European guidance (section 3.5.1 ‘Fertility’) states “*After a single oral dose, testicular histopathological changes and changes in spermatozoid parameters (morphology, count, motility) were observed in rats. The effects were reversible at up to 2000mg/kg, the highest dose tested*”. It should be noted that a single dose 2000mg boric acid per kg is equivalent to 350mg boron/kg.

The single dose fertility NOEL is 90mg B/kg (rounded up from 87.5mg B/kg), based on rat studies.

The European guidance mentions another single dose study (Linder and colleagues, 1990), where 0, 250, 500, 1000 and 2000 mg boric acid/kg was administered to rats. Changes similar to the previous mentioned study were seen at 1000mg/kg and 2000mg/kg but effects were not seen at 250mg/kg and 500mg/kg boric acid (this is equivalent to approximately 45mg and 90mg of boron respectively based on the conversion set out in the European guidance (replicated in Table 5 below). The no-effect level was 500mg/kg boric acid (Linder and colleagues, 1990).

Table 5: Doses of boric acid, borax and borax anhydrous corresponding to the thresholds determined for boron, adapted from EMA/CHMP/619104/20139; October 2017 – recreated here to illustrate the conversion calculations

Boron (B)	Boric acid*	Borax**	Borax anhydrous***
1mg	5.7mg	8.8mg	4.7mg
3mg	17.1mg	26.5mg	14.0mg
7mg	40.0mg	61.9mg	32.6mg
10mg	57.1mg	88.5mg	46.5mg

*Equivalent dose of boric acid, calculated according to the following conversion factor: dose of boric acid × 0.175 = equivalent dose of boron.
**Equivalent dose of borax, calculated according to the following conversion factor: dose of borax × 0.113 = equivalent dose of boron.
***Equivalent dose of anhydrous borax, calculated according to the following conversion factor: dose of anhydrous borax × 0.215 = equivalent dose of boron.

For chloramphenicol eye drops, the EMA/CHMP's threshold 1mg B/day is possibly exceeded for the first 2 days of treatment only. These single dose findings showing that no changes in fertility occur even at very high single doses, equivalent to 90mg boron/kg and are reversible up to 350mg/kg. This may be relevant considering the short exposure time of chloramphenicol eye drops.

9.2 Safety Margin

The concentration of Boron in the formulations of the affected products are similar. However, the safety margin was calculated using the oral exposures associated with the product that contains the highest concentration of boron of all the affected products.

The entire drop size is 40µl, however this is likely to be an excess considering spillage from the eye (and the size of a child's eye) therefore if 30µl is considered the exposure volume and 24 drops per 24 hours the maximum dose is estimated to be 2.16mg B/day, then for children aged 0 to 2 years old with a maximum bodyweight of 5Kg, this will equate to an intake of 0.432mg B/kg/day.

9.2.1 Chronic

Based on 30µl estimate of the volume of eye drops draining into the nasopharynx and assuming a 100% absorption from the GI tract and a bodyweight of 5kg for children aged 0 to 2 years old; a safety margin of 38-fold is calculated for the lowest fertility NOAEL of 17.5 mg B/Kg/day from the rat multigeneration study by Weir and Fisher (1972).

Chloramphenicol eye drops are used for up to 14 days; therefore a 2-year rat study is not representative of short duration of exposures.

9.2.2 Acute

If the NOAEL of 90mg B/kg for adverse effects on fertility from the single dose study in rats (Linder and colleagues, 1990) is used, then the safety margin based on the 30µl eye drop for a 5kg child (the bodyweight used by the EMA/CHMP to calculate the PDE of Boron for the 0 to 2 year age group) is 200-fold and for a 40µl eye drop is 148-fold (Table 6).

Table 6: Safety margins for potential acute and chronic effects on fertility and exposures associated with reduced fetal growth, an endpoint not considered relevant to infants

Droplet size (µl)*	Total daily intake (mg B/kg/day)	Body weight	End point	NOAEL/NOEL used	Safety margin applied
Chronic NOAEL used from a rat multigeneration study for effects on fertility					
20	0.305	5kg	Fertility	17.5mgB/kg/day	**57.0 fold**
30	0.450	5kg	Fertility	17.5mgB/kg/day	**38.0 fold**
40	0.610	5kg	Fertility	17.5mgB/kg/day	**28.9 fold**
Acute NOAEL used from a single dose study in rats for adverse effect on fertility					
20	0.305	5kg	Fertility	90mgB/kg/day	**295.0 fold**
30	0.450	5kg	Fertility	90mgB/kg/day	**200.0 fold**
40	0.610	5kg	Fertility	90mgB/kg/day	**148.0 fold**
Developmental Toxicity Studies in rat using $BMDL_{05}$ of 10.3mg B/Kg/day					
20	0.305	5kg	Developmental	-	**34.0 fold**
30	0.450	5kg	Developmental	-	**22.0 fold**
40	0.610	5kg	Developmental	-	**17.0 fold**

B/kg/day=boron per kg per day. NOAEL=no-observed-adverse effect-level. NOE=no-observed effect-level. $BMDL_{05}$=95% lower confidence limit on the benchmark dose.

Based on the calculations in Table 6, the exposures arising from the use of chloramphenicol eye drops (as outlined in the posology section of the SmPC) have adequate safety margins in place for the developmental $BMDL_{05}$ of 10.3 mg B/kg/day.

9.3 Conclusion of fertility safety evaluation

At present, the use of the eye drops in the first 2 days of treatment leads to the exceedance of the current European PDE value of 1mg B/day for 0 to 2 year olds, a value that had been based on rodent studies showing adverse effects on the developing fetus (Heindel and colleagues,1992; and Price and colleagues 1996). However, this toxicological endpoint is only relevant to pregnant women whose exposures are well within the European PDE values relevant for their age/bodyweights (adults older than 18 years = 10mg B/day; 12 to 17 years = 7mg B/day).

Using a more relevant toxicological endpoint for infants aged 0 to 2 years old (fertility), which itself presents only a theoretical risk of harm to infants, the exposure to boron from use of chloramphenicol eye drops has a conservative safety factor of 29-fold (based on a 40µl droplet size) and an estimated safety factor of 38-fold, based on an eye droplet size of 30µl for the lowest fertility NOAEL of 17.5mg B/kg/day. Based on a NOAEL of 90mg B/kg/day for fertility arising for acute exposures, a safety margin of 148-fold and 200-fold is estimated based on a 40µl and 30µl droplet size, respectively. Therefore it is considered that exposure to boron through use of chloramphenicol eye drops at the present concentrations will not present a risk of harm to infants aged 0 to 2 years old.

Given the lack of data confirming relevance to the paediatric population, and the absence of human data demonstrating clinical relevance in general, the potential risk of effects on future fertility is theoretical, and the application of a PDE and estimation of a safety margin for fertility in humans are precautionary.

10. Overall conclusion

At the time of the review, the European guidance 'Questions and answers on boric acid and borates used as excipients in medicinal products for human use' required the warning "*Do not give to children less than 2 years old as this medicine may impair fertility in the future*" if the threshold of 1 mg boron per day is exceeded.

If exposure is calculated using maximum doses and full drop sizes, the 1mg boron per day threshold would be exceeded. This has led to the contraindication of use in infants aged 0 to 2-year olds. However, expert opinion estimates that the maximum volume that can be accommodated in the conjunctival sac of a child younger than 2 years to be between 10µL and 20µL and dosage regimes typically lower than the maximum. Taking into consideration these practice-based factors, boron exposures would not be expected to exceed the European guidance threshold of 1mg boron per day for infants 0 to 2 years of age.

In addition, as discussed in this report, the European guidance threshold for boron is based on a pregnancy-related effect (reduced fetal weights) following oral exposure in adult rats. The uncertainty factors used in the derivation of this PDE are based on toxicokinetic data and bodyweight data from pregnant rats and humans. Therefore, the current PDE is not relevant to infants aged 0 to 2 years.

Calculations of the safety margins based on NOAELs for acute and chronic male reproductive toxicity indicates safety margins ranging from 29-fold to 200-fold. There are no data indicating clinical relevance to children 0 to 2 years at present, and the assumption of potential risk to future fertility of infants was considered precautionary. Therefore this, combined with the safety factors, should permit the use of chloramphenicol products in infants aged 0 to 2 years.

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12. Glossary of terms

Benchmark Dose (BMD)
The dose expected to result in a specified change of a biological effect (the benchmark response, or BMR), generally 1% to 10% from the untreated population. The BMD is determined by modeling the dose response data in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose, Lower Limit (BMDL)
The lower confidence limit on the benchmark dose. For example, a BMDL10 would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%.

British National Formulary (BNF)
A United Kingdom pharmaceutical reference containing information and advice on prescribing and pharmacology of medicines.

Commission on Human Medicines (CHM)
The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products.

Committee for Medical Products for Human Use (CHMP)
One of the committees responsible for preparing the European Medicines Agency's opinions on questions concerning human medicines.

European Medicines Agency (EMA)
The European Medicines Agency is an agency of the European Union. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union.

Lowest-Observed-Adverse-Effect-Level (LOAEL)
The lowest exposure level at which there is biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.

Patient Information Leaflet
Every medicine pack includes a patient information leaflet (PIL), which provides information on using the medicine safely. PILs are based on the Summaries of Product Characteristics (SPCs) which are a description of a medicinal product's properties and the conditions attached to its use. Available on the MHRA's website.

Marketing authorisation holder
Holder of a marketing authorisation for a medicine. A marketing authorisation allows a company to make the medicine available to patients.

Minimal Risk Level (MRL)
An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

No-Observed-Adverse-Effect-Level (NOAEL)
The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control; some effects may be produced at this dose level, but they are not considered adverse or precursors of adverse effects.

Summary of Product Characteristics (SmPC)
Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use. Available on the MHRA's website.

Uncertainty Factor
A numerical value (often a factor of 3 or 10) used to adjust a NOAEL, LOAEL, or benchmark dose in order to derive an RfC or RfD. Uncertainty factors are applied as needed to account for extrapolation of results in experimental animals to humans, interindividual variability including sensitive subgroups, extrapolation from a LOAEL to a NOAEL, extrapolation of results from subchronic exposures to chronic exposures, and database inadequacies.

Yellow Card scheme
The MHRA's scheme for healthcare professionals and members of the public to report suspected adverse reactions for a medicine or vaccine, as well as medical devices and other products.

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