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SWP response to CMDh questions on chlorobutanol

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2.1. Assessment of data

Chlorobutanol (synonyms: trichloro-2-methyl-2-propanol, chlorbutol, chloreton, chloretone, chlortran) is used as preservative due to its antibacterial and antifungal properties. As excipient it is used up to concentrations of 0.5% in injectables (e.g. methadone, epinephrine, oxytocin, morphine, desmopressin, thiamine), ophthalmic (e.g. pilocarpine, epinephrine, phospholine iodide), otic (e.g. Cresylate, Cerumenex) and cosmetic products.

Due to its sedative and hypnotic effects, it is also used as active ingredient in oral sedatives marketed outside the EU (e.g. Seducaps: 150 mg chlorobutanol/300 mg salicylamide). In addition, topical anaesthetics may also contain chlorobutanol.

Results of a Japanese OECD TG 422 Combined Repeat-dose toxicity study with the reproduction/developmental toxicity screening test which had not been taken in account in previous assessment procedures, was received and evaluated for deriving a PDE of chlorobutanol.

2.1.1. Human data

Human data from controlled studies on pharmacologic/toxicologic effects are not available in the public domain. However, there are several published case reports on the use of chlorobutanol either as medication, as preservative in medicinal preparations or from poisonings. The reported pharmacological and toxicological effects include CNS effects such as somnolence, drowsiness, slow speech, dysarthria, sluggish reflexes, disorientation, coma, generalised hypertonia, hyperreflexia, hypersalivation and trismus. In addition, chlorobutanol has been demonstrated to induce hypersensitivity reactions, low blood pressure and may have the potential to prolong the QT interval (Valentour et al., 1975; Borody et al., 1979; Dux et al., 1981; Itabashi et al., 1982; Hofmann et al., 1986; Vaillancourt et al., 1992; Bowler et al., 1986; Nordt et al., 1996; Brun et al., 2010; Woosley et al., 2019).

Preclinical data with regard to neurotoxicity could not be identified. However, preclinical data on cardiotoxicity are available (see 2.1.3).

Limited data on human pharmacokinetics are available from one published study (Tung et al., 1982). In this study 600 mg chlorobutanol was orally administered to four healthy male subjects (aged 20–30) on two occasions, where the second dose was administered at least 2 months after the first dose. Chlorobutanol displayed a high volume of distribution and low plasma clearance with a long half-life of 10 days. Peak plasma concentrations of ~4–5 µg/mL were reached 15–60 min after administration.

A plasma half-life of 13.2 days has been reported in a case of high doses of chlorobutanol as sedative (Seducaps, chlorobutanol 150 mg in combination with salicylamide 300 mg). Repeated ingestion of large amounts (6–10 capsules per day corresponding to 900–1500 mg/d chlorobutanol) were leading to plasma levels of ~100 µg/mL (Borody et al., 1979).

Overall, these studies suggest that chlorobutanol might accumulate in humans when administered repeatedly.

The oral lethal human dose of chlorobutanol is estimated to be 50–500 mg/kg (Nordt et al., 1996).

2.1.2. Antiplatelet effect

Some in vitro studies with human plasma indicated that chlorobutanol inhibits human platelet aggregation and release. Chlorobutanol produced potent concentration-dependent inhibition of platelet aggregation and release of platelet-rich plasma. It exhibited a significant inhibitory activity towards several aggregation inducers in a concentration- and time-dependent manner (Chen SL et al., 1990). However, it was concluded that the antiplatelet effect of chlorobutanol was most likely due to its generalized adverse effect on the arachidonic acid pathway. In addition, its action was found to be readily reversible.

Conclusion

Chlorobutanol was considered most likely not to have an unspecific toxic effect on platelets in vivo (Chen SL et al., 1990).

2.1.3. Cardiotoxicity

A published study (Hermsmeyer K et al., 1976) reported that chlorobutanol exerts a direct myocardial membrane excitation action and depressed contractility in vitro on toad, frog, or rat myocardium. Chlorobutanol (500 µg/ml ~2.8 mM) caused a 30% decrease in contraction amplitude and a 20% increase in action-potential duration. These effects produced by chlorobutanol were rapid in onset, appearing within 15sec and reaching steady state within 5–10 min. The amplitude of the isometric contraction remained depressed during continued perfusion with chlorobutanol solution and returned to control level within 10 mins after chlorobutanol washout. The mechanism by which chlorobutanol exerted its negative inotropic effect involved conduction disruption and desynchronization of contraction. Chlorobutanol lowered conduction velocity and induced conduction failure and automaticity within isolated ventricular muscle strips.

Mechanistically, chlorobutanol inhibits hERG currents at therapeutically relevant millimolar concentrations (the IC_{50} values are 4.4–7.4 mM (Kornick et al., 2003; Friemel and Zünkler 2010). For comparison, plasma concentrations of about 0.5 mM (~88 µg/mL) chlorobutanol were reported in a patient receiving IV morphine preserved with 0.5% (about 30 mM) chlorobutanol (DeChristoforo et al., 1983). The ratio of the IC_{50} value for the block of hERG currents (4.4–7.4 mM) to the plasma concentration of chlorobutanol is below the margin of 30 and might indicate a torsadogenic potential of chlorobutanol according to the criteria developed by Redfern et al. (2003). However, the torsadogenic potential induced by block of hERG currents can be counterbalanced by effects on other types of cardiac ion channels (e.g. Na^+ and L-type Ca^{2+} channels), and further in vitro and in vivo electrophysiological studies are required to test the torsadogenic potential of chlorobutanol.

In addition, interactions between chlorobutanol and a hERG channel blocker binding inside the central cavity (terfenadine) of the channel produce synergistic inhibitory effects on hERG currents (Friemel and Zünkler, 2010). Depending on both the site and the speed of injection, it is likely that the concentration of chlorobutanol in the heart may approach the level (2.5 mM ~439 µg/mL) at which synergistic inhibitory effects on hERG currents with simultaneously administered pore blockers of the hERG channel can be observed.

A recent review addresses the question, which IV drug formulations on the US market contain chlorobutanol and if they are associated with Torsade de Pointes (TdP) arrhythmias (Woosley et al., 2019). Nine drugs (methadone, epinephrine, papaverine, oxytocin, vasopressin, testosterone,

estradiol, isoniazid, and desmopressin) containing 2.5 mg/mL or 5.0 mg/mL chlorobutanol were identified. For all nine drugs QT prolongation or TdP were reported in the FDA's Adverse Event Reporting System (FAERS) and for five the same was reported in PubMed. Two of the nine drugs had positive signals (by disproportionality analysis) for TdP in FAERS (EB_{05} 2.88 and 23.81, respectively) and four were reported in published articles as the suspect drugs in cases of TdP. Exposure at the recommended dose ranged from 2–500 mg/d chlorobutanol (Table 1).

Table 1. Drugs on the US market that contain chlorobutanol in an IV formulation and associated reports of QT prolongation and TdP (source: Woosley et al., 2019)

Drug name	FAERS data						Medical literature (PubMed)			Chlorobutanol	
	QT prolonged			TdP			QT prolonged	TdP	hERG/I_{KR} block (IC_{50} µm)	Conc. (mg/mL)	Exposure at rec. dose (mg/day)
	Reports (*n*)	EBGM	90% CrI	Reports (*n*)	EBGM	90% CrI					
Methadone	328	9.77	9.08–10.50	264	25.88	23.81–28.09	✓	✓	9.8	5	25–500
Epinephrine	58	1.87	1.53–2.27	37	3.75	2.88–4.82	✓	✓	Inactive	5	5
Estradiol	50	0.66	0.52–0.81	9	0.25	0.15–0.40			Inactive	5	10
Vasopressin	5	1.49	0.76–2.70	7	3.38	1.86–5.79	✓	✓	Inactive	5	20
Testosterone	14	0.34	0.23–0.48	1	0.12	0.03–0.39			Inactive	5	10
Papaverine	7	3.18	1.82–5.26	2	3.25	1.15–9.00	✓	✓	Inactive	5	2–40
Oxytocin	2	0.58	0.18–1.48	1	0.74	0.16–2.40	✓		Inactive	5	20
Isoniazid	18	0.80	0.55–1.13	0					Inactive	2.5	7.5–22.5
Desmopressin	11	0.89	0.56–1.35	0					Inactive	5	35

90% CrI 90% credible interval, lower and upper bounds designated as EB_{05}–EB_{95}, *Conc.* concentration, *EBGM* empirical Bayesian geometric mean, *Exposure at rec. dose* estimated exposure to chlorobutanol if drug formulation is administered at the recommended daily dose, *FAERS* FDA's Adverse Event Reporting System, *hERG* human ether-a-go-go related gene, IC_{50} concentration of drug that produces 50% block of I_{KR}, I_{KR} rapid component of the cardiac delayed rectifier potassium current, *n* number of spontaneous reports to FAERS, *TdP* torsades de pointes

The authors conclude that the pharmacologic profile of chlorobutanol (synergistic hERG block) and its association with reports of TdP and QT prolongation suggest the need for a full evaluation of its cardiac safety when used as a preservative in IV drug and vitamin formulations.

Conclusion

Chlorobutanol is a hERG blocker, which acts synergistically with simultaneously administered pore blockers. US Pharmacovigilance and published data indicate a risk of QT prolongation or TdP arrhythmias for several IV applied drugs preserved with chlorobutanol (dose range 2–500 mg/d chlorobutanol, 0.04–10 mg/kg bw/d respectively). As preclinical in vivo data and clinical QT studies with chlorobutanol are lacking, no firm conclusion on cardiac safety can be drawn. However, based on the available data a cardiotoxic risk of chlorobutanol containing IV formulations especially when given in conjunction with hERG blocker such as methadone cannot be excluded.

2.1.4. Repeat-dose toxicity

In previous procedures, oral administration to rats with 300 mg chlorobutanol/kg body weight/d for up to 28 days or 500 mg/kg body weight/d for 14 days caused liver enlargement, higher liver enzyme activity and ascorbic acid levels, an increased urinary ascorbic acid excretion and changes in blood biochemical parameters including an increase in serum cholesterol levels. (Toxicity profile Chlorobutanol. Bibra toxicology advice & consulting. JCLC/SL/ February 1989 (1). p.290.) However, no assessment with regard to a possible No Observed (Adverse) Effect Level (NO(A)EL) had been made in previous procedures and the details of the study from the corresponding literature could not be retrieved.

2.1.5. Genotoxicity and Carcinogenicity

One published study describing genotoxicty testing of chlorobutanol is available (Gocke et al., 1981). In this study chlorobutanol was tested in an Ames assay, a mutation test on fruit flies (Drosophila melanogaster) and an in vivo micronucleus test on mouse bone marrow.

While no carcinogenicity studies with chlorobutanol are available, results of the genotoxicity tests are shown in the table below.

Table 2: Genotoxicity tests with chlorobutanol

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria / Gocke E. et al, 1981/ No	S. typhimurium TA 1535, TA 1537, TA1538, TA 98 and TA 100 +/- rat S9	5 concentrations, top dose: 3600 µg/plate Chlorobutanol was tested in two different media: ZLM and VB. The concentration of citrate was 3.5 higher in VB medium than ZLM medium. The concentrations of the other ions are up to 2-fold higher in VB medium.	**Positive** in TA1535 –S9 in ZLM medium. However, **negative** in TA1535 in standard VB medium and in all other strains +/-S9
Basc test on Drosophila detecting sex-linked recessive lethal mutations / Gocke E. et al, 1981/ No	Berlin K (wild-type) and Basc Drosophila melanogaster strains	2.5 mM, 3.75 mM and 5 mM were applied by the adult feeding method in 5% saccharose. About 1200 X chromosomes were tested per experiment in each of 3 successive broods (3-3-4 days). In repeat experiments, sometimes only single broods were tested. F2 progeny cultures with 2 or fewer wild-type males were routinely retested in the F 3 generation to confirm X-linked recessive lethal mutations (RLs).	**Negative**
Micronucleus test in vivo / Gocke E. et al, 1981/ No	NMRI mice, 2-4 mice/sex/dose, 1000 PCEs per mouse	0, 93.25, 186.5, 373 mg/kg i.p. twice 24 h apart, sample collection 30 h after last dose	**Negative**

VB medium: Vogel-Bonner medium; ZLM medium: modified minimal medium for E. coli

Conclusion

The published studies were not conducted under GLP conditions. Description of the used methods is in parts incomplete. Nevertheless, the studies were published in a recognised peer-reviewed journal and description of results is sufficiently detailed. Chlorobutanol was only positive in one salmonella strain (TA1535) without metabolic activation under specific medium conditions (ZLM) but negative in TA1535 when using the standard medium (VB) for Salmonella strains in the AMES assay. The effect in ZLM medium is probably a secondary effect due the difference in salt concentration and therefore not considered relevant. Chlorobutanol was negative in all other tester strains. In addition, chlorobutanol was negative in the Drosophila Basc test and in the micronucleus test in vivo in mice up to 373 mg/kg i.p. twice.

Based on the available data and the overall weight of evidence, chlorobutanol can be considered as non-genotoxic.

2.1.6. Embryotoxicity

Embryotoxic effects of chlorobutanol were reported in vitro in a study in cultured mouse embryos (Smoak, 1993). In this study mouse embryos were exposed to chlorobutanol during two stages of organogenesis, neurulation stage (3–6 somites, day 8.5) and early limb-bud stage (20–25 somits, day 9.5). Final chlorobutanol concentrations in culture were 0 (control), 10 (only neurulation stage), 25, 50, 100, and 200 µg/mL. Embryos were exposed to chlorobutanol for 24 h. At neurulation stage embryos were malformed at a rate of 14% (3/21) in 10 µg/mL chlorobutanol, 31% (5/16) in 25 µg/mL chlorobutanol, 56% (10/18) in 50 µg/mL chlorobutanol, 83% (20/24) in 100 µg/mL chlorobutanol and 100% (9/9) in 200 µg/mL chlorobutanol compared to control with 3% (1/37). Increases in the incidence of malformations at concentrations ≥ 25 µg/mL where statistically significant. Early limb bud stage embryos were not significantly affected up to chlorobutanol concentrations of 25 µg/mL. The observed decline in sensitivity with increasing embryonic age is typical for many other teratogens. According to Smoak (1993) chlorobutanol concentrations associated with abnormal embryonic development are within the range of human blood levels measured following multiple doses of 900 mg or more chlorobutanol (see 2.1.1 human data). The use of chlorobutanol containing medicinal preparations should therefore be handled with caution during pregnancy, particularly in case of repeated dosing with potential accumulation of chlorobutanol (Smoak, 1993).

Placental transfer of chlorobutanol was studied in pregnant mice. In this study chlorobutanol serum levels were measured in maternal animals in a time course study 10 min, 20 min, 1, 2, 4, 8, 12, 24, or 36 h post dose and for placental transfer in embryos 2 h post dose. For the time course study pregnant mice were dosed by gavage with 80 mg/kg chlorobutanol and for the placental transfer study with 0, 8, 40, or 80 mg/kg chlorobutanol on gestation day 9.5. Embryonic tissue concentrations of chlorobutanol (ng/mg protein) increased with maternal dose and serum levels (µg/ml). At the lowest dose (8 mg/kg) chlorobutanol was not detectable in embryonic tissues whereas increase at the highest dose was over proportional compared to maternal serum levels. Serum levels in mice followed a time course similar to humans, with rapid absorption and slow elimination. Placental transfer into the embryo was demonstrated and it is assumed that embryonic accumulation of chlorobutanol may potentially occur. Due to the similarity of exposure time course post dosing in humans and mice placental transfer and embryonic accumulation may also be assumed to potentially occur in humans. (Smoak et al., 1997).

In the studies by Smoak et al. (1993 and 1997) chlorobutanol was not detectable in embryonic tissue after treating maternal animals with a single dose of 8 mg/kg, but chorobutanol content was measureable and increased over proportionally at and above doses of 40 mg/kg. The long half-life and the tendency of accumulation in humans was measured at relatively high doses of chlorobutanol as well. However, due to lack of appropriate data it cannot be excluded that also at lower doses chlorobutanol concentrations in human plasma may increase when repeatedly dosed over a longer period of time.

In addition to the literature data already assessed in previous procedures, an additional study could be identified.

Reproduction and developmental toxicity of chlorobutanol was evaluated in an OECD TG 422 study (Combined Repeated Dose and Reproductive/Developmental Toxicity Screening Test of 1,1,1-Trichloro-2-methyl-2-propanol by Oral Administration in Rats. N. 0696, March 28, 2008). The study was GLP compliant and submitted in Japan to the Ministry of International Trade and Industry (MITI). A study report fact sheet, a brief study summary (in English) and the complete study report (in Japanese) can be found online (see references). The study was performed in 2007 in Crl:CD (SD) male and female rats. Animals were 10 weeks old at initiation of dosing. In the DRF 5 animals per sex/dose group were given chlorobutanol in olive oil at doses of 0, 10, 30, 100, or 300 mg/kg/d by oral gavage for 14 days.

At 300 mg/kg/d all animals died. At 100 mg/kg/d kidney and liver weights were increased in both sexes and at 30 mg/kg/d kidney weights were increased in male and female animals. 10 mg/kg/d was the no effect dose in the DRF. For the main study rats were dosed with 0, 10, 30, or 100 mg/kg/d by oral gavage. 12 animals/sex/dose were treated from 14 days before mating until day 4 of lactation. Satellite groups of 5/sex in control and 100 mg/kg/d dose groups for recovery investigations were dosed daily for 42 days with an additional 14 days recovery period without treatment. Parental animals were sacrificed on day 5 of lactation (females) or day 43 of treatment (males). Satellite groups were sacrificed on day 15 of recovery. All offspring was sacrificed on day 4 post birth.

Table 3. Major findings in the repeat-dose toxicity and reproductive/developmental screening study in rats

Sex	**Male**				**Female**			
Dose (mg/kg/day)	**10**	**30**	**100**	**R100***	**10**	**30**	**100**	**R100***
Repeat-dose toxicity								
Clinical signs			ataxic gait				death 3/12 ataxic gait, lateral and prone position, reddish tear, soiled eyes, nose, mouth, decreased faeces	
Behaviour			↓grip strength ↓locomotor activity	↓locomotor activity	↓locomotor activity	↓locomotor activity	↓grip strength ↓locomotor activity	
Body weight, food consumption			↑food consumption	↑food consumption			↓body weight gain	
Clinical Chemistry			↓RBC, ↓haematocrit, ↓ketone bodies ↓total cholesterol				↓WBC, ↓AST, ↓Na, ↓Cl, ↑K	
Organ weight		↑a,r kidney	↑a,r kidney, ↑a,r liver	↑r liver		↑r kidney	↑r kidney	↑r heart

Histopathology	↑eosinophilic bodies of renal proximal tubule	↑eosinophilic bodies of renal proximal tubule ↑regeneration of renal proximal tubule	↑eosinophilic bodies of renal proximal tubule ↑regeneration of renal proximal tubule ↑hepatocellular hypertrophy	↑regeneration of renal proximal tubule			↑hepatocellular hypertrophy ↑poor development of mammary gland	
Reproductive and developmental toxicity								
							↓gestation length and index, ↓No. of implantation and index, ↓No. of pups born, delivery index and Life birth index	
Viability of pubs (d 4)							↓No. of pubs alive, viability index	

* Recovery group

↓ significantly decrease $p<0.05$, ↑ significantly increased $p<0.05$

Abbreviations: a, absolute; AST, aspartate transaminase; Cl, chloride; K, potassium; Na, sodium; r, relative; RBC, red blood cell count; WBC, white blood cell count

Three females in the 100 mg/kg group died of dystocia and showed necrosis of proximal tubules. Clinical observations included ataxia in both sexes and lateral and abdominal positions in females in the 100 mg/kg dose group during the early dosing period but diminished in the third week of dosing. Grip strength of limbs was decreased in both sexes and locomotor activity in males in the 100 mg/kg dose group. In females, locomotor activity was reduced in all dose groups. Reduced body weight gain was noted in high dose females during pregnancy and lactation. Decrease in ketone bodies in urine and decrease in RBC count and haematocrit was observed in high dose males, whereas WBC count was decreased in high dose females. Plasma cholesterol was increased in high dose males whereas in females, potassium was increased, and sodium and chloride were decreased in plasma of the high dose group. In males, kidney weights were increased ≥ 30 mg/kg and liver weights at 100 mg/kg. Centrilobular hypertrophy of hepatocytes was observed in both sexes at 100 mg/kg and in males, proximal tubule regeneration was increased ≥ 30 mg/kg and remained at the end of recovery period. Eosinophilic bodies in kidney were increased ≥10 mg/kg in males. In females vacuolic change of proximal tubules and dilatation of tubular lumen was observed at 100 mg/kg.

Reproductive and developmental toxicity were observed in the 100 mg/kg dose group only with prolonged oestrous cycle, increased pairing days to copulation and two pairs failing copulation at all. Number of deaths of maternal animals and pups was noted in the high dose group with a total of 3 pups born alive. The number of implantations, delivery index, birth index and live birth index decreased. The NOEL for reproductive and developmental toxicity is considered to be 30 mg/kg/d.

In this study reproductive and developmental toxicity were only performed as a screening test. No full histopathological examination of pups was provided. Reproductive and developmental toxicity endpoints are not considered the most relevant and sensitive endpoints in this study and therefore cannot be used to derive a PDE.

In contrast, in the repeat-dose toxicity part in this study histopathological examination was performed. Repeat-dose toxicity endpoints evaluated in F0-animals are considered to provide suitable and sensitive data for deriving a PDE. The NOEL for repeat-dose toxicity in maternal and paternal animals is considered to be below the lowest dose of 10 mg/kg/d based on effect on locomotor activity in females and eosinophilic bodies in renal proximal tubules in males.

Conclusion

After repeat-dose treatment for 42 or 43 days, respectively, kidney and liver could be identified as target organs in both sexes. In addition, reduction of locomotor activity and grip strength may be considered as a sign for sedative effects of chlorobutanol. Since in the lowest dose group only mild effects in the kidney were seen in males, in addition to some sedative effects in females, after chlorobutanol treatment, the LOEL of 10 mg/kg/d is considered suitable for deriving a PDE.

2.2. Determination of a PDE

Based on the animal toxicology studies with chlorobutanol described above the "OECD TG 422 Combined Repeat-dose toxicity study with the reproduction/developmental toxicity screening test" is considered the only study suitable to derive a PDE for chlorobutanol. Based on the LOEL of 10 mg/kg/d and using the procedure for deriving a PDE described in ICH Q3C(R6) a PDE is derived as follows:

LOEL = 10 mg/kg/d

F1 for extrapolation from rat to human = 5

F2 for inter individual variability = 10

F3 for study duration = 10 (short study duration of 42/43 days)

F4 for severe toxicity = 1

F5 for NOEL not identified = 2 (based on very mild effects at LOEL)

$$PDE = \frac{\frac{10\,\frac{mg}{kg}}{d}}{5(F1)\ x\ 10\ (F2)\ x\ 10\ (F3)\ x\ 1\ (F4)\ x\ 2\ (F5)} = \frac{10\ mg/kg/d}{1000} * 50kg = \ 0.5\ mg/d$$

The study used to derive the PDE does not cover cardiotoxic effects, as this endpoint was not monitored. As mentioned in section 2.1.3 a cardiotoxic risk of chlorobutanol containing IV formulations, especially when given in conjunction with hERG blockers, cannot be excluded. US Pharmacovigilance and published data indicate a risk of QT prolongation or TdP arrhythmias for several IV applied drugs preserved with chlorobutanol at a dose range of 2–500 mg/d (Table 1). The PDE of 0.5 mg/d provides a safety margin of 4-fold to the lowest dose of 2 mg/d were cardiac effects were observed in patients. The PDE of 0.5 mg/d might also provide a safety margin to reproductive toxicity (NOEL in rats: 30 mg/kg/d).

2.3. Response to question 1

Question 1

Can the SWP confirm that the levels of chlorobutanol generally used in medicinal products are safe from a toxicological point of view?

SWP Response to question 1

Chlorobutanol levels generally used in medicinal products as excipient can be considered save for lifetime use if they are at or below the derived PDE. For short-term use higher exposures of Chlorobutanol may be acceptable based on case by case. In such cases benefit/risk consideration should be made with greatest care based on the low safety margins identified with respect to the cardiac effects observed in patients (see above 2.1.1. and 2.2 and below SWP response to question 2). For these specific cases, SWP recommend, if feasible, the use of available alternative excipients.

2.4. Response to question 2

Question 2

Is it feasible to determine acceptable intake levels of chlorobutanol?

SWP response to question 2

The published toxicological studies were not considered suitable to derive a PDE for chlorobutanol due to severe limitations of these studies with respect to study design and treatment durations. However, in addition to the published studies, a GLP-conform OECD TG 422 study with chlorobutanol submitted to MITI in Japan could be identified. An English excerpt of the study results, available online, was suitable to assess the study and the data quality. This study was considered adequate to derive a PDE for chlorobutanol. At the lowest dose mild effects on the kidney (eosinophilic bodies in proximal tubules cells) in males and reduced locomotor activity in females were observed. Therefore, a NOEL was not established and the lowest dose was considered to be the LOEL.

A PDE for chlorobutanol was derived according to the method described in ICHQ3C(R6) with

LOEL = 10 mg/kg/d

F1 for extrapolation from rat to human = 5

F2 for interindividual variability = 10

F3 for study duration = 10 (short study duration of 42/43 days)

F4 for severe toxicity = 1

F5 for NOEL not identified = 2

$$PDE = \frac{\frac{10\frac{mg}{kg}}{d}}{5(F1)\ x\ 10\ (F2)\ x\ 10\ (F3)\ x\ 1\ (F4)\ x\ 2\ (F5)} = \frac{10\frac{mg}{kg}/d}{1000} * 50kg = 0.5\ mg/d$$

In conclusion, from this study a PDE of 0.5 mg/d was derived for chlorobutanol for lifetime treatment which provides a safety margin of 4-fold to the lowest dose where cardiac effects were observed in patients after IV administration.

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