



Scientific Committee on Health and Environmental Risks

SCHER

Assessment of the Tolerable Daily Intake of Barium

The SCHER adopted this opinion at its 16th plenary on 22 March 2012

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ISSN 1831-4775

doi:10.2772/49651

ISBN 978-92-79-30749-2

ND-AR-12-005-EN-N

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ACKNOWLEDGMENTS

The members of the working group are acknowledged for their valuable contribution to the opinion:

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All Declarations of working group members are available at the following webpage:
http://ec.europa.eu/health/scientific_committees/environmental_risks/members_wg/index_en.htm

Keywords: SCHER, scientific opinion, Barium, toys, TDI

Opinion to be cited as: SCHER (Scientific Committee on Health and Environmental Risks), Assessment of the Tolerable Daily Intake of Barium, 22 March 2012.

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1. BACKGROUND

The new Toys Safety Directive (TSD)¹ establishes migration limits of 19 elements from toys or components of toys. The migration limits shall not exceed the listed limits, depending on the toy material used. However, the elements can be used if the toy or components of the toy exclude any hazard due to sucking, licking, swallowing or prolonged contact with the skin when used as intended or in a foreseeable way, bearing in mind the behavior of children.

The migration limits are based on the RIVM study² and opinions of the Scientific Committee. In the SCHER opinion on the evaluation of migration limits for chemical elements in toys, it was noted that SCHER supports the RIVM approach as a starting point for risk assessment of chemical elements in toys, namely the basis for all approaches is a health-based limit value, e.g. TDI. The SCHER also recommended the amount of TDI allocated to the toy to be limited to 10% (SCHER 2010).

RIVM stated in their report that the toxicity of barium and barium compounds has been evaluated by IPCS (2001) and USEPA (2005). RIVM has evaluated the group in 1991 and again in 2001 (scope: derivation of soil intervention values). Further reviews are those by WHO (1996) and ATSDR (2005). Although human data are considered a more relevant basis for deriving a TDI, the pivotal study as used by IPCS (2001) and RIVM (2001) had important flaws (Dallas and Williams 2001). According to USEPA (2005) and ATSDR (2005, 2007) the chronic drinking-water study in mice represents a more reliable basis for a TDI. Following the approach developed by ATSDR for its chronic MRL, in which a benchmark approach was chosen, a TDI of 0.6 mg/kg bw/day is proposed as the most appropriate value by RIVM. After finalisation of the RIVM report ATSDR published an update (2007), in which a TDI of 0.2 mg/kg bw/day is proposed.

The International Programme on Chemical Safety (IPCS) – a joint venture of WHO, ILO and UNEP - published a so-called "Concise International Chemical Assessment Document (CICAD) on barium in 2001:

<http://www.inchem.org/documents/cicads/cicads/cicad33.htm>

2. TERMS OF REFERENCE

SCHER is requested to review the available scientific data and conclusions drawn for barium including those from WHO and RIVM and recommend a TDI which can be applied for toys.

3. SCIENTIFIC RATIONALE

In its opinion on the evaluation of migration limits for chemical elements in toys (SCHER, 2010), SCHER stated that the starting point for any risk assessment should be a health based limit value, e.g. TDI for those elements causing threshold effects, thus supporting the RIVM approach (RIVM Report, 2008). For barium a number of evaluations have been carried out by different agencies in the last decades. This opinion revises and summarizes literature data with the aim of deriving the most appropriate TDI for barium exposure.

¹ Directive 2009/48/EC of the European Parliament and of the Council of 18 June 2009 on the safety of toys, OJ L 170, 30.06.2009, p.1.

² RIVM advisory report of 12 October 2006, Chemicals in toys, A general methodology for assessment of chemical safety of toys with a focus on elements

3.1. Sources of Barium

Humans are exposed to barium from a variety of sources: via the environment where it naturally occurs, via drinking water and the diet, via consumer products, including toys and also occupationally, being used in many industrial applications (i.e. in the production of drilling muds, paints, bricks, glass, rubber, ceramics). Barium toxicity is produced by the free cation; therefore the crucial factor affecting the onset of adverse health effects in humans is the solubility of the barium compound to which the individual is exposed. Indeed, the kinetic behavior of barium in the organisms is compound-dependent: water soluble barium compounds, such as barium chloride, nitrate, or hydroxide, which quickly dissolved in water and body fluids, have a greater potential for absorption, distribution via the bloodstream and toxicity to humans. The only exception to this rule is carbonate, which although relatively insoluble in water, is toxic to humans because it is soluble in the acid milieu of the stomach. The insoluble barium sulfate due to the absence of any systemic toxicity is commonly used in medical applications as a contrast medium.

For the general population, including children, oral exposure would be the predominant route of exposure (US EPA, 2005). In the specific case of toys, it is expected that the major additional source of barium exposure is due to the potential of oral intake through the licking or ingestion of crayons, water colors or toys colored with Ba-containing pigments (Rastogi and Pritzl, 1996). The dermal and inhalation route are not considered significant for this specific scenario. Although the dermal contact with the toys occurs, barium is not expected to cross the intact skin because of the high polarity of the forms in which it is most commonly encountered. However, there is little quantitative information regarding the extent of barium absorption following dermal exposure.

3.2. Absorption of Barium

Oral absorption of soluble Ba²⁺ is highly variable both in animal and humans. There is evidence that gastrointestinal absorption of barium in humans is in the range 3–60% of the administered dose, although higher spotted values are reported (Dallas and Williams, 2001). Studies in rodents and dogs estimated an oral absorption between 7 and 85%. The striking differences in results can be explained with differences in experimental design and methodology used (duration, age, fasting status of the animals, calculation of absorption vs. the background levels).

Experiments in rats have shown that younger animals (22 days old or less) absorb about 10 times more barium chloride from the gastrointestinal tract (63–84%) than older animals do (about 7%) (Taylor et al. 1962). A similar behavior has been described also in dogs (Cuddihy and Griffith, 1972). In the absence of data to the contrary, ATSDR assumed that this information will also be applicable to children (ATSDR, 2007), and the SCHER supports this conclusion. The International Commission for Radiation Protection (ICRP) estimates that the gastrointestinal absorption of barium is 20% in adults, 30% for children aged 1–15 years, and 60% in infants (ICRP, 1993).

In addition to higher absorption, children experience also a higher daily intake (Health Canada, 2005). According to the results obtained in the Canadian Total Diet Study (TDS) of 1993–1999, the average barium intake ranged from 20.7 to 25.2 µg/kg bw/day for 0–4 years old children. For older children (5–11 years), the average daily barium intake decreased to 18.7 µg/kg bw/day and then down to 9.3–11.8 µg/kg bw/day for 12–19 years old boys and girls reaching values typical of adult age (≈9 µg/kg bw/day at 20–39 years and ≈7.5 µg/kg bw/day at >65 years). These values are in agreement with previous reports (Tipton et al. 1966, 1969), indicating the low end of the daily intake range for barium of 9.30 µg/kg bw/day.

In humans, once absorbed, 90% of the barium in the body was deposited into the bone. There is no evidence that barium undergoes biotransformation other than as a divalent cation. The major route of elimination for barium is through the faeces. In humans, faecal excretion of barium was 2–3 times higher than urinary excretion over a 30-day period (Tipton *et al.* 1966; Stoewsand *et al.* 1988). The rate of elimination (clearance in about 2 weeks) is similar in animal and humans.

3.3. Toxicological profile of Barium

Human and animal high-dose exposure to soluble barium compounds results in a number of effects including electrocardiogram (ECG) abnormalities, ventricular tachycardia, hypertension and/or hypotension, muscle weakness and paralysis. These symptoms, cited in a number of case reports after intentional or accidental exposure to barium carbonate or chloride, are consistent with the postulated mechanism of barium toxicity, related to the increases in intracellular potassium levels. Indeed, being a competitive antagonist for potassium channel, barium can block the passive efflux of intracellular potassium, resulting in the increase of intracellular potassium with a consequent decreased resting membrane potential. The muscle fibres become electrically unexcitable leading to paralysis.

Several investigators have examined whether exposure to much lower doses of barium would adversely affect the cardiovascular system. Two community-based studies have evaluated the possible association between elevated levels of barium in drinking water and increased risk of cardiovascular disease (Brenniman and Levy, 1985; Brenniman *et al.* 1979, 1981). They gave contrasting results: the 1984 study found no significant alterations in blood pressure or in the prevalence of hypertension, heart disease, or stroke among residents in areas with elevated (0.2 mg barium/kg/day) or low (0.003 mg barium/kg/day) levels of barium in drinking water; the 1979-1981 study reported significantly higher mortality rates for cardiovascular disease and arterio-sclerosis in the community consuming the tap water containing higher levels of barium. However, these epidemiological studies have significant flaws (no information available on tap water consumption, actual barium intakes from water and food-likely to be the major source of Ba intake-, duration of exposure and confounding factors such as sodium levels in water) and data cannot be used to establish a causal relationship.

In general, animal studies have not found significant alterations in blood pressure or ECG readings following low-dose oral exposure (up to 150 mg barium/kg/day in drinking water for 16 weeks as in McCauley *et al.* 1985) and no histological alterations have been observed in the hearts of rats and mice exposed sub-chronically or chronically to Ba²⁺ up to 200 mg barium/kg bw/day (NTP, 1994). The only exception are some studies on rats exposed to Ba²⁺ in drinking water up to 16 months (Perry *et al.* 1983, 1985, 1989; Kopp *et al.*, 1985). Significant increase in systolic blood pressure, depressed rates of cardiac contraction and cardiac conductivity and decreased cardiac ATP levels were observed: NOAEL of 0.15 mg barium/kg bw/day and LOAEL of 0.69 mg barium/kg bw/day were derived from the study published in 1983, whereas following studies identified 0.69-0.80 mg barium/kg bw/day as the NOAEL. However, these studies were characterized by poor reporting (i.e. no deviations reported) and by the use of a diet deficient in several essential elements (including calcium and potassium) compared with a standard laboratory feed that could have strongly affected the outcome of the studies. Barium exhibits close relationships with calcium in its chemical properties (both being alkaline earth metals): for this reason barium is thought to interact with calcium (IPCS, 1991). The cardiovascular effects seen in rats in the Perry studies could be attributed to the barium/calcium competition together with the potential hypokalemia due to the diet, not just to barium exposure. The relevance of these data is questionable and the weight of evidence built up with all the other available data indicates that the NOAEL/LOAEL

derived from these studies are not reliable enough to be taken into account for the derivation of reference values.

The available animal data provide strong evidence that the kidney is the most sensitive target organ in rats and mice exposed repeatedly to barium chloride in drinking-water. In rodents, there is a steep dose-response curve for the incidence of nephropathy, considering that in the subchronic NTP study in mice (1994) the NOAEL for this end point is 205 mg barium/kg bw/day and the LOAEL (450 mg barium/kg bw/day) 95% of the animals experienced mild to moderate nephropathy.

The LD₅₀ values for barium chloride in rats range from 132 to 277 mg barium/kg bw; when young animals are considered a LD₅₀ = 220 mg barium/kg bw is derived, which is within the range of values obtained with adult rats, indicating that at least for acute effects there is not any age-dependent toxicity (Borzelleca *et al.* 1988; Tardiff *et al.* 1980).

Among the number of available repeated toxicity studies, the most reliable are those carried out by the NTP (1994), treating F344/N rats and B6C3F1 mice via drinking water for 15 days, 13 weeks and 2 years from which is possible to derive a sub-acute, a sub-chronic and a chronic NOAELs and LOAELs (see Table 1)

Table 1. NOAELs and LOAELs based on renal effects from the NTP study (1994)

Duration/ specie	NOAEL mg Ba/kg bw/day	LOAEL mg Ba/kg bw/day	Notes
15 d, mouse	70/85 (M/F)	Not detected	No effects observed
15 d, rat	110 (M&F)	Not detected	No effects observed
13 wk, rat	65 (M&F)	110/115 (M/F)	Increased kidney weight at LOAEL; kidney lesions at higher doses. No significant cardiovascular effects detected.
13 wk, mouse	205/200 (M/F)	450 (M&F)	Chemical-related kidney lesions at LOAEL
2 yr, rat	Not detected	Not detected	Spontaneous nephropathy observed in most animals (including controls) precluding the detection of any treatment-related effect.
2 yr, mouse	75/90 (M/F)	160/200 (M/F)	Chemical-related kidney lesions at LOAEL

In the NTP (1994) 15 day-study, at the highest dose tested no effects was observed in both species (Table 1).

In the NTP (1994) 13-week rat study, kidney lesion (minimal to mild dilatation of the proximal convoluted tubules of the outer medulla and renal cortex) were observed at 180 and 200 mg barium/kg bw/day in males and female, respectively. At the lower dose (65 mg barium/kg bw/day) only a slight increase (7%) in relative kidney weight, without any hystopathological alteration was described, considered not toxicologically significant: therefore it is considered as the NOAEL. In mice, mild to moderate nephropathy (tubule dilatation, regeneration, and atrophy) was observed in 90-100% of animals exposed to

the highest dose; no renal lesions were observed at the next lowest dose level, which is therefore identified as the NOAEL (200 mg barium/kg bw/day).

In the chronic study (NTP 1994), the treatment of rats to doses as high as 60/75 mg barium/kg bw/day did not result in renal effect clearly attributable to barium, being spontaneous lesion in control animals of the same extent (NTP 1994). Groups of 60 B6C3F1 mice per sex were exposed to 0, 30/40, 75/90, and 160/200 mg barium/kg bw/day (M/F, respectively) in drinking water for 2 years. In mice exposed to 160/200 mg barium/kg bw/day, a significant increase in the incidence of nephropathy was observed. The nature of the lesions was the same as described in the sub-chronic study: these changes were morphologically distinct from the spontaneous degenerative renal lesions commonly observed in aging mice (NTP, 1994). The lowest NOAEL was identified as 75 mg barium/kg bw/day. The ATSDR (2007) carried out a benchmark analysis of the incidence data for nephropathy in mice, leading to a benchmark dose (BMD) of 80.06 mg barium/kg bw/day, corresponding to a 5% increase in the incidence of nephropathy; the 95% lower confidence limit on the BMD (BMDL) was 61.13 mg barium/kg/day.

In both rats and mice receiving Ba chloride dehydrate chronically via drinking water no statistically significant increases in neoplasms was observed.

On the basis of this result the US EPA has concluded that barium is not carcinogenic to humans following oral exposure - Group D (IRIS, 2006). The available in vitro data (most of which negative) are inadequate to assess barium genotoxic potential: however, in light of the clear negative results obtained in the carcinogenicity studies on rats and mice, this is not considered relevant for the completeness of the data base.

Morphological alterations in reproductive tissues of rats or mice were not observed in any of the repeated toxicity studies up to doses as high as 450 mg barium/kg bw/day (Dietz *et al.* 1992; NTP, 1994). A reproductive toxicity study found no significant dose-response in gestation length, pup survival, or occurrence of external abnormalities in rats and mice exposed up to 200 mg barium/kg bw/day as barium chloride in drinking water. The highest dose led to a decreased pup birth weight and a non-significant decrease in litter size in the offspring of rats exposed prior to mating. However maternal body weight and water consumption were not reported, therefore it is not possible to check whether the effects on the offspring are secondary to maternal toxicity.

Although it is not possible to make a definitive conclusion about the potential for barium to impair reproductive function, considering that the NOAEL for the potential developmental effects would be 110/115 mg barium/kg bw/day (Dietz *et al.* 1992), the kidney appears to be the most sensitive target following repeated oral exposure to barium, independently on the exposure duration. Indeed, the sub-chronic and the chronic NOAEL (as well as the chronic BMDL₀₅) derived from the NTP study are in the same range. Although the critical end-points for toxicity following exposure to soluble barium compounds are hypertension and renal effects, the available data indicate that the renal effects occur at doses well below those ones reported for cardiovascular effects.

3.4. Derivation of TDI for Barium

For the TDI derivation, SCHER supports the use of the BMDL₀₅ (61 mg barium/kg bw/day) from the chronic study on mice as a point of departure. As explained in the ATSDR report (2007), the BMDL₀₅ was selected over the typically 10% incidence, due to the marked severity of nephropathy and increased mortality seen at the LOAEL, as a consequence to the steepness of the dose-response curve. The SCHER support this approach. By applying an assessment factor of 300 (100 to account for inter- and intra-species variability and a conservative additional factor of 3 to account for deficiencies in the data base), a **TDI of 0.2 mg barium/kg bw/day** is derived. With the same approach EPA (IRIS, 2006) has derived an oral reference dose (RfD) for barium of 0.2

mg/kg/day, based on a BMDL₀₅ of 63 mg/kg/day for nephropathy in male mice (NTP 1994) and an uncertainty factor of 300 (100 to account for inter- and intra-species variability and a conservative additional factor of 3 to account for deficiencies in the data base). A TDI value of 0.6 mg barium/kg bw/day was reported in the RIVM report 'Chemicals in Toys' (RIVM 2008) using the same approach adopted by USEPA (2005) and ATSDR (2007) but applying an assessment factor of 100.

Although data on humans are also available, SCHER does not consider them appropriate to derive the TDI, as WHO did (WHO, 2001). The two studies used as the basis for this approach have indeed some critical limitations, including the absence of any dose-response relationship, since no effects were seen at the highest dose tested. The flaws related to the community-based study by Brenniman and Levy (1984) have already been mentioned. Since no effects were observed, the high-Ba-water content, corresponding to 0.21 mg Ba/kg bw/d (calculated on the basis of the default values for water consumption and body weight) was considered as the NOAEL.

In the other controlled exposure study, 11 healthy male volunteers aged 27–61 years (mean 39.5 years, median 41 years) were exposed to barium chloride in 1.5L drinking water (Wones *et al.* 1990). No barium was added for the first 2 weeks, which served as a control period; drinking-water containing 5 mg barium/L (0.14 mg barium/kg bw/day using reference values of 2 L/day for water consumption and 70 kg for bw) was administered for the next 4 weeks, and drinking-water containing 10 mg barium/L (0.21 mg barium/kg bw/day) was administered for the last 4 weeks of the study. No significant alterations in blood pressure or ECG readings, relative to initial baseline measurements, were found and the highest dose was chosen as the NOAEL. Although the study design tried to take under control many variables (each individual serving as control for himself to reduce variability, no medications, controlled diet-although the dietary Ba²⁺ intake was not reported, maintenance of exercise habits, timing of measuring and urine sampling), the major problems are the small number of enrolled individuals and the short exposure regimen, not sufficient to detect effects at low level of exposure.

On this basis the SCHER considers that the available human studies are inadequate for providing a NOAEL/LOAEL dose-response assessment for Ba, and they should be used as supporting studies. Some well-conducted good quality animal studies are indeed available, showing that renal effects and, at high doses of exposure, also cardiovascular effects are the critical end-points related to Ba toxicity: the relevance of these findings is supported by the number of case reports indicating that the same effects are potentially of concern also in humans. The TDI calculated as described above is supported by the absence of effects at the same level of human exposure and the use of a quite conservative approach should account for additional uncertainties.

4. OPINION

Considering that the SCHER recommends the amount allocated to the toy to be limited to 10% of the migration limits, the portion of the TDI for barium allocated to toy exposure should not exceed **0.02 mg barium/kg bw/day**.

This value is based on 100% oral absorption and does not represent the actual acceptable internal dose. To include correction for oral absorption when calculating the allowed levels in toys, in light of the differences in gastrointestinal absorption existing between young and adult animals, expected to be present also between children and adults, values of gastrointestinal absorption of 30% for children aged 1–15 years, and 60% for infants (ICRP, 1993) are proposed.

5. ABBREVIATIONS

Ba	Barium
Bw	body weight
D	day
CMR	carcinogenic, mutagenic, and reprotoxic
ECG	electrocardiography, electrocardiogram
EURAR	European Union Risk Assessment Report
LOAEL	Lowest Observed Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
IPCS	International Programme on Chemical Safety
TDI	Tolerable Daily Intake
TIE	Toy Industry of Europe
TSD	Toy Safety Directive
WHO	World Health Organization

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