immunologic glomerulonephritis, acute renal failure, pulmonary edema, and cardiovascular collapse were reported (Mahajan, 2007).

Inhalation, oral, or dermal exposure to elemental mercury vapours or inorganic mercury has resulted in erythematous and pruritic skin rashes. Other dermal reactions to mercury exposure include heavy perspiration and reddened and/or peeling skin on the palms of the hands and soles of the feet, typically associated with acrodynia (ATSDR, 1999).

The central nervous system is probably the most sensitive target for elemental mercury vapour exposure. A wide variety of cognitive, personality, sensory, and motor disturbances have been reported. Prominent symptoms include tremors, emotional lability, insomnia, memory loss, neuromuscular changes, headaches, polyneuropathy, and performance deficits in tests of cognitive function. Some long-term exposures to elemental mercury vapour have resulted in unsteady walking, poor concentration, tremulous speech, blurred vision, performance decrements in psychomotor skills, decreased nerve conduction, and other signs of neurotoxicity(IPCS 2003).

Renal dysfunction can be also prominently indicated by the asymptomatic proteinuria (e.g., elevation of ß2-microglobulin or N-acetyl-D-glucosaminidase), oliguria, anuria or nephrotic syndrome. Although the dose-effect relationships is uncertain, the detectable changes in renal function begin to occur at urinary mercury concentrations of >5-10 µg/g creatinine, with "clear toxicity" at 35 µ/g creatinine (Holmes et al., 2009).

Several studies have demonstrated that some mercury from amalgam fillings is absorbed, but no relationship was observed between the mercury release from amalgam fillings and the mercury concentration in basal brain (Maas et al., 1996) or brain more generally (Saxe et al., 1999). In a cross-sectional study, Saxe et al. (1995) reported that cognitive function among 129 Catholic nuns, 75–102 years of age, was not related to the number or surface area of occlusal dental amalgams. However, in a study involving dentists (mean urinary Hg 3.3 µg/L, SD=4.9) and dental assistants (mean urinary Hg 2.0 µg/L, SD=2.3), significant associations were found between urinary mercury level and scores on a variety of tests of attention, concentration, visual memory, executive functions, fine motor function, and sensory function (Echeverria et al., 2006).

Although some studies of occupational exposure have suggested associations between inorganic mercury exposure and some cancers, the data are limited, and IARC has classified inorganic mercury compounds in Group 3 (not classifiable as to their carcinogenicity to humans).

Regulatory assessments

Recommendations, Regulations and Guidelines applicable to Inorganic Mercury

Agency	Description	Information	Reference
Carcinogenicity classification			
IARC	Carcinogenicity classification for Mercury and inorganic mercury compounds	Group 3 (not classifiable as to humans)	IARC, 1993
Oral Administration			
USP	Oral permitted daily exposure (PDE) Oral Daily Dose PDE Oral Components Limit	0.3 μg /kg/day 15 μg /day 1.5 μg/g(ppm)	USP, 2010
U.S. ATSDR	An Acute oral minimal risk level An intermediate-duration oral minimal risk level	0.007 mg Hg/kg/day 0.002 mg Hg/kg/day *(Based on nonclinical data)*	ATSDR, 1999
IPCS	elemental mercury and inorganic mercury compounds TDI	 2μg/kg bw/day	IPCS 2003
Parenteral Administration			
USP	USP Component Limit	0.15 ppm	USP, 2010
U.S. ATSDR	A chronic inhalation minimal risk level	0.0002 mg/m3 (metallic vapor)	ATSDR, 1999
Water			
WHO	Drinking water quality guidelines for Mercury TDI Guideline value	 2 μg/kg bw/day (inorganic) 0.006 mg/L (inorganic)	WHO, 2004
Food			
FAO/WHO	A provisional tolerable weekly intake (PTWI) (withdrawn in 2010)	5 μg/kg bw/week (total mercury)	FAO/WHO (JECFA), 1972
FAO/WHO	A provisional tolerable weekly intake (PTWI)	4 μg/kg bw/week (inorganic)	FAO/WHO (JECFA), 2010
JP - FSC	Tolerable daily intake (TWI)	0.7 μg/kg bw/day	JP-FSC, 2011

<注：会議資料としての提案文書のため、最終的に合意されたプレステップ2文書のPDE値とは異なります。>

Conclusion

Inorganic mercury compounds show significantly lower oral bioavailability compared to organic mercury and induce different toxicological effects including neurological, corrosive, haematopoietic, renal effects and cutaneous disease (acrodynia). However, only limited information on the dose or exposure levels are available in human studies. While there is some genotoxic evidence both in vitro and in vivo studies, although inorganic mercury is not considered to be involved in direct DNA interaction and/or damage. In addition, in a well conducted chronic bioassay with mercuric chloride (HgCl2), there was only equivocal evidence for carcinogenicity. IARC classified mercury and inorganic mercury compounds as group 3. Most sensitive effects of non-carcinogenic effects by mercuric chloride is considered to be renal effects of nephropathy in rodents studies. The oral PDE should be estimated by using the dose-response data from these studies.

Kidney effects are consistently observed in various experimental species (weight changes, proximal tubule damage and progressive nephropathy). Relative kidney weight increases observed in rats following exposure to HgCl2 are also associated with a dose-dependent increase in renal mercury accumulation and with significant changes in the renal cortex, including increases in both proximal tubule and glomerular volumes. Therefore, the working group of Q3D considered it appropriate to model kidney weight changes, which generally occurred at doses similar to or lower than other renal effects. By using data on relative kidney weight increases from the 6-months rat study, the lowest $BMDL_{10}$ of 0.11 mg Hg/kg bw/day was selected as a point of departure.

The modifying factors as fellows, F1 (Inter-species difference): 5(rat study); F2(Intra-Individual difference) :10; F3(duration of exposure): 2 (6 month study); F4(Nature of toxicity) :1; F5(Quality of data):1. The oral PDE is calculated as below.

PDE = (0.11 mg Hg/kg bw/day x 50 kg) / (5 x 10 x 2 x 1 x1) = 0.05 mg/day (round figure)

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BORON (B)

Introduction

Boron is never found in the elemental form in nature. It exists as a mixture of the 10B (19.78%) and 11B (80.22%) isotopes (Budavari et al., 1989). Boron is a naturally-occurring element that is widespread in nature at relatively low concentrations (Woods, 1994). Boron concentrations in rocks and soils are typically less than 10 ppm, although concentrations as high as 100 ppm have been reported in shales and some soils.

Boric acid and sodium salts of boron (primarily borax, or disodium tetraborate decahydrate) are widely used for a variety of industrial purposes including manufacture of glass, fiberglass insulation, porcelain enamel, ceramic glazes, and metal alloys. These compounds are also used as fire retardants in cellulose insulation, laundry additives, fertilizers (boron is an essential element for plants), herbicides (at high concentrations, boron is toxic to certain plant species) and insecticides (Woods, 1994). Elemental boron has only limited industrial applications. The most important source of exposure for human populations is ingestion of boron from food (primarily fruits and vegetables) (WHO, 1998). Occupational exposure to borate dust and exposure to borates in consumer products (e.g., cosmetics, medicines, insecticides) are other potentially significant sources.

Elemental boron exists as a solid at room temperature, either as black monoclinic crystals or as a yellow or brown amorphous powder when impure. Boron is a relatively inert metalloid except when in contact with strong oxidizing agents.

Boric acid is a weak acid with a pKa of 9.2, It exists primarily as the undissociated acid (H3BO3) in aqueous solution at physiological pH, as do the borate salts (Woods, 1994). Sodium perborates are persalts, which are hydrolytically unstable because they contain characteristic boron–oxygen–oxygen bonds that react with water to form hydrogen peroxide and stable sodium metaborate ($NaBO_2 \cdot nH_2O$).

The toxicological properties of these compounds and other borates are expected to be similar on a molar boron equivalent basis when dissolved in water or biological fluids at the same pH and low concentration. Boron oxide will also produce similar effects because it is an anhydride that reacts exothermically with water in the body to form boric acid (WHO, 1998).

Dietary Intake

The richest sources of boron are fruits, vegetables, pulses, legumes and nuts. Dairy products, fish, meats and most grains are poor sources of boron (United Kingdom Expert Group on Vitamins and Minerals, 2002). Estimations of daily intakes of boron by various age and sex groups have been made based on analyses of foods and food products (WHO, 1998). Based on the United Kingdom total diet study in 1994, the dietary intake of boron was estimated as an average population intake of 1.5 mg/day and an upper 97.5th-percentile intake of 2.6 mg/day (United Kingdom Expert Group

on Vitamins and Minerals, 2002). This is similar to the assessment by the United States Institute of Medicine (2001), which determined that the mean intake of boron in women of childbearing age and pregnant women was 1.0 mg/day (median 1.05 mg/day; 1.27 mg/day for lactating women).

The majority of Earth's boron occurs in the oceans, with an average concentration of 4.5 mg/l (Weast, Astle & Beyer, 1985). Concentrations of boron in groundwater throughout the world range widely, from <0.3 to >100 mg/l. High concentrations of boron can be found in many parts of the world, particularly in highly mineralized, naturally carbonated groundwaters. Concentrations of boron found in drinking-water from Chile, Germany, the United Kingdom and the USA ranged from 0.01 to 15.0 mg/l, with most values below 0.5 mg/l. These values are consistent with ranges and means observed for groundwater and surface water (WHO, 1998).

Toxicological Data

< KINETICS AND METABOLISM>

Numerous studies have shown that boric acid and borax are absorbed from the gastrointestinal tract and from the respiratory tract, as indicated by increased levels of boron in the blood, tissues or urine or by systemic toxic effects in exposed individuals or laboratory animals.

Boron is well absorbed (84-94%) from the gastrointestinal tract in humans. Studies in animals have shown that boron is readily absorbed following oral exposure in rats, rabbits, sheep and cattle (US EPA 2004). Studies in male mine workers and rats have shown that boron also is absorbed during inhalation exposure (Culver et al., 1994; Wilding et al., 1959).Absorption is poor through intact skin in human and laboratory animals but is much greater through damaged skin (WHO, 1998; US EPA, 2004).

Examinations in rats have revealed a fairly uniform distribution of boron outside the blood compartment across various tissues. Notable exceptions were that consistently lower concentrations of boron were found in fat and consistently higher concentrations were observed in bone (Ku et al., 1991). When the kinetic data from rodents are compared with the data available for humans (plasma elimination half-life reports and high volume of distribution of 104.7 mL/100 g body weight), it seems reasonable that the distribution of boron to human tissues parallels that observed in rodents (US EPA, 2004).

Because of the extent to which boron's residence time in the body and pharmacokinetic profile are influenced by urinary elimination, a more thorough investigation of the urinary clearance of boron was undertaken to determine the difference in the urinary clearance of boron in pregnant and nonpregnant rats and humans. Reports from studies (U.S. Borax, 2000; Pahl et al., 2001; Vaziri et al., 2001) indicated that the renal clearance of boron from female rats was greater than in humans, and that pregnant rats and pregnant women cleared boron slightly more efficiently than nonpregnant rats and women. The magnitude of the difference (rat:human) between average clearance values was approximately 3.6-fold and 4.9-fold for pregnant and nonpregnant individuals, respectively, in close agreement with differences in kinetic parameters predicted by allometric

scaling (approximately 4-fold) (US EPA, 2004).

Overall, the available pharmacokinetic data support a high degree of qualitative similarity between the relevant experimental species and humans.

<ACUTE TOXICITY>

The oral median lethal doses (LD50 values) for boric acid and borax in mice and rats are in the range of about 400–700 mg/kg bw as boron (Pfeiffer, Hallman & Gersh, 1945; Weir & Fisher, 1972). Oral LD50 values for boron in the range of 250–350 mg/kg bw for boric acid or borax exposure have been reported for guinea-pigs, dogs, rabbits and cats (Pfeiffer, Hallman & Gersh, 1945; Verbitskaya, 1975). Signs of acute toxicity for both borax and boric acid in experimental animals given single large doses orally include depression, ataxia, convulsions and death; kidney degeneration and testicular atrophy are also observed (Larsen, 1988).

<SUBCHRONIC TOXICITY>

In a 13-week study, mice were fed diets containing boric acid at approximately 0, 34, 70, 141, 281 or 563 mg/kg bw/day as boron. At the two highest doses, increased mortality was seen, and there was a dose-related decrease in body weight gain. Degeneration or atrophy of the seminiferous tubules was observed at a boron dose of 141 mg/kg bw/day. In all dose groups, extramedullary haematopoiesis of the spleen of minimal to mild severity was seen (NTP, 1987).

In a 90-day study in rats receiving boron (as boric acid or borax) at approximately 0, 2.6, 8.8, 26, 88 or 260 mg/kg bw/day in the diet, all animals at the highest dose died within 3–6 weeks. Body weights in males and females were reduced at a dose of 88 mg/kg bw/day, and absolute organ weights, including the liver, spleen, kidneys, brain, adrenals and ovaries, were also significantly decreased. A pronounced reduction in testicular weights in males in the 88 mg/kg bw/day group was also observed. Microscopic examination revealed complete testicular atrophy at 88 mg/kg bw/day group in all males fed borax or boric acid, and partial testicular atrophy at 26 mg/kg bw/day group in four males fed borax and in one male fed boric acid. (Weir & Fisher, 1972).

The findings that boron can cause testicular atrophy in rodents at doses of a similar order of magnitude following short-term exposure have been confirmed by other workers (Fukuda et al., 2000; Kudo et al., 2000).

Boric acid or borax was also fed to Beagle dogs for 90 days or for 2 years. In the 90- days study (weight-normalized doses of 0, 0.44, 4.4 or 44 mg/kg bw/day as boron; five animals per sex per dose), testis weight was significantly lower than in both boric acid and borax experiments at high-dose groups (reduced by 39% and 44%, respectively). Testicular atrophy was observed in all of the dogs in the high-dose group but not in the other groups. In the borax study, testis weights were reduced compared with controls, but the reduction reached significance only in the high-dose group. Hematological effects were also observed in high-dose dogs. Decreases were found for both hematocrit (15 and 6% for males and females, respectively) and hemoglobin (11% for both males and

females) at study termination in borax-treated dogs. No other clinical or microscopic signs of toxicity were reported in any animals (Weir & Fisher, 1972).

<CHRONIC TOXICITY>

In a 2-year study in mice (50 per sex per dose) receiving boric acid at approximately 0, 48 or 96 mg/kg bw/day as boron in the diet, body weights were 10–17% lower in high-dose males after 32 weeks and in high-dose females after 52 weeks. Increased mortality rates were statistically significant in males, with significant lesions appearing in the testes in male mice and with no significant non-neoplastic lesions in female mice (NTP, 1987; Dieter, 1994).

In a 2-year study, rats (35 per sex per dose) were administered weight-normalized boron doses of 0, 5.9, 18 or 59 mg/kg bw/day in the diet. High-dose animals had coarse hair coats, scaly tails, hunched posture, swollen and desquamated pads of the paws, abnormally long toenails, shrunken scrotum, inflamed eyelids and bloody eye discharge. The haematocrit and haemoglobin levels were significantly lower, the absolute and relative weights of the testes were significantly lower, and relative weights of the brain and thyroid gland were higher than in controls. In animals in the middle- and low-dose groups, no significant effects on general appearance, behaviour, growth, food consumption, haematology, serum chemistry or histopathology were observed (Weir & Fisher, 1972).

In the 2-year study, the dogs (four per sex per dose) received the boric acid or borax in the diet at weight-normalized doses of 0, 1.5, 2.9 or 8.8 mg/kg bw/day as boron. Any dose-related findings were not observed in all treatment groups (Weir & Fisher, 1972). An additional group received boron at a dose of 29 mg/kg bw/day for 38 weeks. Testicular atrophy was observed in two test dogs receiving borax at 26 weeks and in the two dogs and one dog, respectively, killed after 26 or 38 weeks of boric acid consumption. The study was terminated at 38 weeks. The number of dogs was small and variable (one or two dogs at each of three time points) and inadequate to allow statistical analysis. All treated dogs at termination had widespread and marked atrophy in the seminiferous tubules, but testicular lesions also occurred in the control group (Weir & Fisher, 1972). Confidence in these studies is low, and they were considered not suitable for inclusion in the risk assessment, as there are other, more recent studies of greater scientific quality with findings at similar levels of intake of boron (Ku et al., 1993; Price et al., 1996a).

< REPRODUCTIVE AND DEVELOPMENTAL TOXICITY>

In a multigeneration study, boron (as borax or boric acid) at doses of 0, 5.9, 17.5 or 58.5 mg/kg bw/day was administered to male and female rats. At the highest dose, rats were found to be sterile, males showed atrophied testes in which spermatozoa were absent, and females showed decreased ovulation. The NOAEL for boron in this study was 17.5 mg/kg bw/day (Weir & Fisher, 1972).

In time–response and dose–response reproductive studies, adult male Sprague-Dawley rats were administered two boron doses in 1 day, with a total boron dose of 0 or 350 mg/kg bw in the

time–response experiment (animals were sacrificed at 2, 14, 28 or 57 days post-treatment) and a total boron dose of 0, 44, 87, 175 or 350 mg/kg bw in the dose–response experiment (animals were sacrificed after 14 days). Adverse effects on spermiation, epididymal sperm morphology and caput sperm reserves were observed during histopathological examinations of the testes and epididymis. The no-observed- adverse-effect level (NOAEL) for boron for male reproductive effects in the dose–response study was 87 mg/kg bw/day (Linder, Strader & Rehnberg, 1990).

To investigate the development of testicular lesions, boric acid was fed at 61 mg/kg bw/day as boron to male F344 rats; sacrifice of six treated and four control rats was conducted at intervals from 4 to 28 days. At 28 days, there was significant loss of spermatocytes and spermatids from all tubules in exposed rats, and basal serum testosterone levels were significantly decreased from 4 days on (Treinen & Chapin, 1991).

In another study, the activities of enzymes found primarily in spermatogenic cells were decreased, and enzyme activities associated with premeiotic spermatogenic cells were significantly increased in SD rats exposed to boron at doses of 60 or 125 mg/kg bw/day for 60 days. Mean plasma follicle-stimulating hormone levels were significantly elevated in a dose-dependent manner in all boron treatment groups (30, 60 or 125 mg/kg bw/day) in this study after 60-day exposures (Lee, Sherins & Dixon, 1978).

Reversibility of testicular lesions was evaluated by Ku et al. (1993) in an experiment in which F344 rats were dosed with boric acid at dose of 0, 3000, 4500, 6000 or 9000 mg/kg feed (equivalent to 0, 26, 39, 52 or 78 mg/kg bw/day as boron) for 9 weeks and assessed for recovery up to 32 weeks post-treatment. Inhibited spermiation was exhibited at a dose of 26 / 39 mg/kg bw/day (5.6 μg of boron per milligram tissue), whereas inhibited spermiation progressed to atrophy at a dose of 52 or 78 mg/kg bw/day (11.9 μg of boron per milligram testes); there was no boron accumulation in the testes to levels greater than those found in the blood during the 9-week period. After treatment, serum and testis boron levels in all dose groups fell to background levels. Inhibited spermiation at a dose of 39 mg/kg bw/day was reversed by 16 weeks post-treatment, but focal atrophy, which did not recover up to 32 weeks post-treatment, was detected.

As for developmental toxicity, rats were fed a diet containing boric acid at boron doses of 0, 14, 29 or 58 mg/kg bw/day on gestation days 0–20 (Heindel et al., 1992). An additional group of rats received boric acid at 94 mg/kg bw/day as boron on gestation days 6–15 only. Average fetal body weight per litter was significantly reduced in a dose-related manner in all treated groups compared with controls. The percentage of malformed fetuses per litter and the percentage of litters with at least one malformed fetus were significantly increased at boron doses of ≥29 mg/kg bw/day. Malformations consisted primarily of anomalies of the eyes, the central nervous system, the cardiovascular system and the axial skeleton. The most common malformations were enlargement of lateral ventricles in the brain and agenesis or shortening of rib XIII. The lowest-observed-adverse-effect level (LOAEL) for boron of 14 mg/kg bw/day (based on the shortening of rib XIII and decreased fetal body weights) for rats occurred in the absence of maternal toxicity; a

NOAEL was not found in this study.

Price et al. (1996a) did a follow-up to the Heindel et al. (1992) study in Sprague- Dawley rats to determine a NOAEL for fetal body weight reduction and to determine whether the offspring would recover from prenatally reduced body weight during postnatal development. Boric acid was administered in the diet to rats on gestation days 0–20. Dams were terminated and uterine contents examined on gestation day 20. The intake of boric acid was 0, 3.3, 6.3, 9.6, 13 or 25 mg/kg bw/day as boron. Fetal body weights were 99%, 98%, 97%, 94% and 88% of controls for the low- to high-dose groups, respectively. Incidences of short rib XIII (a malformation) or wavy rib (a variation) were increased in the 13 and 25 mg/kg bw/day boron dose groups relative to control litters. The NOAEL for boron in this study was 9.6 mg/kg bw/day.

Developmental toxicity and teratogenicity of boric acid were investigated in mice exposed to boron during gestation days 0–17 at 0, 43, 79 or 175 mg/kg bw/day in the diet. There was a significant dose-related decrease in average fetal body weight per litter at boron doses of 79 and 175 mg/kg bw/day. In offspring of mice exposed to boron at 79 or 175 mg/kg bw/day during gestation days 0–20, there was an increased incidence of skeletal (rib) malformations. These changes occurred at doses for which there were also signs of maternal toxicity (increased kidney weight and pathology); the NOAEL for boron for developmental effects (based on the decreased fetal body weight per litter) was 43 mg/kg bw/day (Heindel et al., 1992).

Developmental toxicity and teratogenicity of boric acid in rabbits were investigated by Price et al. (1996b) at boron doses of 0, 11, 22 or 44 mg/kg bw/day given by gavage on days 6–19 of gestation. Frank developmental effects in rabbits exposed to boron at 44 mg/kg bw/day included a high rate of prenatal mortality, an increased number of pregnant females with no live fetuses and fewer live fetuses per live litter on day 30. At the high dose, increases in the malformed live fetuses per litter and in cardiovascular defects were observed. The NOAEL for maternal (reduced body weight gain, reduced gravid uterine weight and number of corpora lutea) and developmental effects was 22 mg/kg bw/day as boron.

<GENOTOXICITY>

The mutagenic activity of boric acid was examined in the Salmonella typhimurium and mouse lymphoma assays, with negative results. No induction of sister chromatid exchange or chromosomal aberrations was observed in Chinese hamster ovary cells (NTP, 1987). Sodium borate did not cause gene mutations in the S. typhimurium preincubation assay (Benson, Birge & Dorough, 1984). Borax was not mutagenic in cell transformation assays with Chinese hamster cells, mouse embryo cells or human fibroblasts (Landolph, 1985).

< CARCINOGENICITY>

Tumour incidence was not enhanced in studies in which B6C3F1 mice received diets containing boric acid at 0, 2500 or 5000 mg/kg feed for 103 weeks (NTP, 1987) and Sprague-

Dawley rats received diets containing boron (as borax or boric acid) at 0, 117, 350 or 1170 mg/kg feed for 2 years (Weir & Fisher, 1972).

<EFFECTS ON HUMANS>

Available human data on boron compounds for routes other than inhalation focus on boric acid and borax. According to Stokinger (1981), the lowest reported lethal doses of boric acid are 640 mg/kg bw (oral), 8600 mg/kg bw (dermal) and 29 mg/kg bw (intravenous injection). Stokinger (1981) stated that death has occurred at total doses of between 5 and 20 g of boric acid for adults and <5 g for infants. A case-series report of seven infants (aged 6–16 weeks) who used pacifiers coated with a borax and honey mixture for 4–10 weeks concluded that exposures ranged from 12 to 90 g, with a very crudely estimated average daily ingestion of boron of 18–56 mg/kg bw/day (O'Sullivan& Taylor, 1983). Although infants appear to be more sensitive than adults to boron compounds, lethal doses are not well documented in the literature. According to the 109 other case-reports of poisoning, in general, boric acid caused chemical irritation primarily at sites of application and excretion and in organs with maximum boron concentrations. The most common central nervous system findings were oedema and congestion of the brain and meninges. Other common findings included liver enlargement, vascular congestion, fatty changes, swelling and granular degeneration. Goldbloom & Goldbloom (1953)

More recent reports suggest that the oral toxicity of boron in humans is milder than previously thought. Litovitz et al. (1988) conducted a retrospective review of 784 cases of boric acid ingestion reported to the National Capital Poison Center in Washington, DC, USA, during 1981–1985 and the Maryland Poison Center in Baltimore, MD, USA, during 1984–1985; approximately 88.3% of the cases were asymptomatic. All but two of the cases had acute (single) ingestion, and 80.2% involved children less than 6 years of age. No severe toxicity or life-threatening effects were noted, although boric acid levels in blood serum ranged from 0 to 340 μg/ml. The most frequently occurring symptoms, which involved the gastrointestinal tract, included vomiting, abdominal pain, diarrhoea and nausea. Other (primarily central nervous system and cutaneous) symptoms occurred in fewer cases: lethargy, rash, headache, light-headedness, fever, irritability and muscle cramps. The average dose ingested was estimated at 1.4 g. According to Litovitz et al. (1988), 21 of the children less than 6 years of age, 15 of whom were less than 2 years of age, ingested the reported potentially lethal dose of 3 g; eight adults ingested the reported potentially lethal dose of 15 g without clinical evidence of lethal effects.

Sayli (1998, 2001) compared reproductive success in highly exposed populations (0.7–29 mg/l as boron) in Turkey—which has some of the highest deposits of boron and hence high boron concentrations in drinking-water—with that in populations in low boron exposure areas (0.05–0.45 mg/l as boron) and found no significant differences. The birth rate and sex ratio were also compared at France among the different concentration in drinking water, and at USA among different occupational exposure levels, no significant differences were observed(Yazbeck et al., 2005;

Whorton et al., 1994).

Since the first findings involving boron deprivation in humans appeared in 1987 (Nielsen et al., 1987), the most convincing findings have come mainly from two studies in which men over the age of 45, postmenopausal women and postmenopausal women on estrogen therapy were fed a low-boron diet (0.25 mg/8.4 MJ) for 63 days and then fed the same diet supplemented with 3 mg of boron per day for 49 days (Nielsen, 1989, 1994; Nielsen, Mullen & Gallagher, 1990; Nielsen, Mullen & Nielsen, 1991; Nielsen et al., 1992; Penland, 1994). Findings from these human experiments show that boron is a dynamic trace element that can affect the metabolism or utilization of numerous substances involved in life processes, including calcium, copper, magnesium, nitrogen, glucose, triglycerides, reactive oxygen and estrogen, although the function of boron remains undefined. The United Kingdom Expert Group on Vitamins and Minerals (2002) concluded that: Boron appears to be an essential nutrient for humans, in that dietary deprivation of boron consistently results in changed biological functions that are detrimental and that can be corrected by increasing boron intake. Similar effects have been shown in animal models. The signs of boron deficiency in animals are variable in nature and severity. Variables affected by dietary boron include plasma and organ calcium and magnesium concentrations, plasma alkaline phosphatase and bone calcification. Consistent signs of deficiency include depressed growth and a reduction in some blood indices, particularly steroid hormone concentrations. However, as yet, no specific biochemical function for boron has been discovered.

Regulatory Assessment

Recommendations, Regulations and Guidelines applicable to Boron

Agency	Description	Information	Reference
USP	Oral permitted daily exposure (PDE)		
EMA	PDE		
MHLW	Drinking water guideline Tolerable daily intake (TDI)	1 mg/L 0.096 mg/kg bw,	MHLW 2003
U.S. EPA	Reference dose for chronic oral exposure (RfD)	Oral; 0.2 mg/kg bw	US EPA 2004
ATSDR	MINIMAL RISK LEVEL (MRL)	Oral, Intermediate 0.2 mg/kg bw	ATSDR 2009
WHO	Drinking quality guideline Tolerable daily intake (TDI)	2.4 mg/L 0.2 mg/kg bw,	WHO 2009

<注：会議資料としての提案文書のため、最終的に合意されたプレステップ2文書のPDE値とは異なります。>

Conclusion

The critical effect is considered to be decreased fetal body weight in rats, for which the NOAEL was 9.6 mg/kg bw/day. Allen et al. (1996) developed a benchmark dose based on the studies of Heindel et al. (1992), Price, Marr & Myers (1994) and Price et al. (1996a). The benchmark dose was defined as the 95% lower bound on the dose corresponding to a 5% decrease in the mean fetal weight ($BMDL_{05}$) and was used by the United States Environmental Protection Agency in its re-evaluation (USEPA, 2004). The $BMDL_{05}$ of 10.3 mg/kg bw/day as boron is close to the Price et al. (1996a) NOAEL of 9.6 mg/kg bw/day.

Dourson et al. (1998) re-evaluated the toxicokinetics of boron for data-derived uncertainty factors and concluded that a data-derived adjustment factor of 6 was appropriate for intra human variability, rather than the default factor of 10, but that additional studies were needed on rats to be able to modify the interspecies uncertainty factor with confidence. The total uncertainty factors were derived following the methodology.

Intraspecies variation (toxicokinetics) for boron relates primarily to variations in clearance. As the critical effect that serves as the basis for the tolerable daily intake (TDI) is developmental toxicity, pregnant women are the subgroup of interest in this regard. Based on pooled individual data from available studies, the mean glomerular filtration rate in 36 healthy women was 145 ± 23 ml/min in early pregnancy and 144 ±32 ml/min in late pregnancy. The standard deviation represented 22% of the mean value in late pregnancy. Based on division of the mean glomerular filtration rate (144 ml/min) by the glomerular filtration rate at two standard deviations below the mean (80 ml/min) to address variability for approximately 95% of the population, the toxicokinetic component of interspecies variation is 1.8 (compared with the default value for this component of 3.2). As there are insufficient data to serve as a basis for replacement of the default value for the toxicodynamic component of the uncertainty factor for intraspecies variation, the total uncertainty factor for intraspecies variation is 1.8 × 3.2 = 5.76 (rounded to 6). Data are inadequate to determine a different uncertainty factor for interspecies variation; therefore, the default value of 10 is used (Dourson et al., 1998), giving a total uncertainty factor of 60.

Therefore, the oral PDE is:

$$PDE = (10.3 \text{ mg/kg bw/day X } 60 \text{ kg}) / 60 = 10 \text{ mg/day}$$

According with the default methodology of derivation of PDE, the oral PDE is calculated by using the factors of F1 (Inter-species difference): 5(rat study), F2(Intra-Individual difference) :10, F3(duration of exposure): 1 (developmental study), F4(Nature of toxicity) :1 and F5(Quality of data):1. In this case, the value of the factor of inter- species difference was supported by the investigation of the urinary clearance of boron between human and rats.

PDE = (10.3 mg/kg bw/day X 60 kg) / (5 x 10 x 1 x 1 x1) = 12 mg/day

Consequently, both approach brought similar guidance values, and by using safety-side assessment, 10 mg/day was estimated as the recommended oral PDE.

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MOLYBDENUM (Mo)

Introduction

Mo is a Group VIB element of the second transition series. Its main oxidation states are IV and VI, the most common forms of which are oxyanions. The predominant form of Mo occurring in soils and natural waters is the molybdate ion, $MoO4^{2-}$ which forms soluble compounds with a variety of cations including K^+, $NH4^+$ and Ca^{2+}. Mo exists in soil in various forms at concentration of 0.1-10 mg/kg. MoO_2 and MoS_2 are insoluble in water.

Molybdenum is used in the manufacture of special steels, in electrical contacts, spark plugs, X-ray tubes, filaments, screens, and grids for radio valves, and in the production of tungsten, glass-to-metal seals, nonferrous alloys, and pigments. Molybdenum disulfide has unique properties as a lubricant additive. Molybdenum compounds are used in agriculture either for the direct treatment of seeds or in the formulation of fertilizers to prevent molybdenum deficiency (WHO, 2003).

Mo metalloenzymes have a vital role in plants and bacteria particularly in respect of nitrate reductase and nitrogenase. In man, Mo containing xanthine oxidase catalyses the oxidation of hypoxanthine and xanthine as part of the degradation pathway of purine nucleic acids to uric acid (Rajagopalan, 1988). Mo deficiency is characterized by night blindness, nausea, disorientation, coma, tachycardia, tachypena and associated with various biochemical abnormalities including high plasma methionine and almost undetectable serum uric acid, has been reported in a patient receiving total parenteral nutrition (Abumrad *et al* NN, 1981). Mo plays an important role in nitrogen fixation in route nodule bacteria with the Fabaceae plants and incorporated into various foods.

Dietary intake

Mean dietary Mo intake is 120 ug/day in UK; 97.5 percentile intake 210 ug/day (Ysart *et al*, 1999) , 75-250 ug/day in US ESADDI (1989) and 230 ug/day in Japan (Hattori *et al* 2004). Safe levels of daietaly intake are recommended as 50-400 ug/day in UK (Department of Health, 1991) and 450 ug/day in Japan (MHLW, 2010).

A maximum level in drinking water of 0.07 mg/l has been recommended by WHO (2003). Intakes of 10-15 mg/day may be associated with altered nucleotide metabolism and impaired Cu bioavailability. According to WHO (1996) the daily requirement is 0.015 to 0.15 mg per day for children and 0.075 to 0.25 mg per day for adults, i.e. about 1-5 µg/kg/day.

Kinetics

Gastro intestinal absorption depends on the chemical form. Absorption of Mo VI from the gastrointestinal tract is reported to be good for soluble compounds (40-85% in the rat; 85-93% in

man). Human bioavailability of VI form Mo was estimated 88- 93 % after oral administration with 22 -1,490 ug/day (Turnlund *et al*, 1995) and that of food containing Mo was 93 % after feeding with 145 – 318 ug/day (Yoshida *et al*, 2006). Absorption and retention of Mo is markedly influenced by interactions with dietary Cu and sulphate. Cu forms insoluble copper thiomolybdate in the digestive tract and high dietary inorganic sulphate is believed to reduce intestinal absorption by blocking the transport of Mo through the cell membrane.

Following gastrointestinal absorption, molybdenum rapidly appears in the blood and most organs. Highest concentrations are found in the liver, kidneys, and bones. Molybdenum crosses the placental barrier. There is no apparent bioaccumulation of molybdenum in human tissues.

In rodents, molybdenum compounds are excreted largely in the urine, and only to a small extent in faeces (WHO, 2003). Urinary excretion controls plasma level of Mo. Initial plasma level in healthy young men is maintained by a daily intake of 115-120 ug/day (Novotny and Turnlund, 2007).

Toxicological data

Human toxicity; there are limited information on toxicological experience of Mo in humans. Lethal doses in humans have not known. Ingestion of Mo is often in far excess of 300 ug/day in Japanese ordinary diet due to foods made from soy beans (Yoshida et al, 2006). However, there is no evidence suggesting that the dietary Mo causes adverse effects to humans including children and pregnant women.

Acute toxicity; In acute study, oral dose with 1.2-6.0 g Mo/kg of MoO3, CaMoO4 or (NH4)2MoO4 is lethal in the rat. Intraperitonial injection of sodium molybdate at 400 mg Mo/kg was lethal to 4 of 27 mice (Titenko-Holland *et al*, 1998).

Subchronic toxicity; Oral LOAELs from 5-13 week toxicological studies in the rat including those done in 1950s and 1960s were 1.6-80 mg/kg/day (Vyskocil and Viau reviewed , 1999). The latest study for 9 weeks duration suggested the LOAEL 1.6 mg/kg/day and NOAEL 0.9 mg/kg/day based on the effects on oestrus cycle, gestation weight and embryogenesis (Fungwe *et al*, 1990).

Genotoxicity; Mo salts provided positive responses in both mice bone marrow micronucleus tests and dominant lethal test at the doses of 200 and 400 mg/kg (Environ Mol Mutagenesis, 1998, 32, 251-259). However, there are various conflicting results ex. MoO3 was negative in Ames and Chromosomal aberration test (NTP, 1982). Overall assessment concluded that Mo was not suggested to be a genotoxic compound (RIVM, 2001).

Carcinogenicity; No neoplastic effects were seen in a 2-year inhalation study in the rat. There was some evidence of carcinogenic activity in mice based on an increased incidence of alveolar/bronchiolar carcinomas or adenomas. Statistically significant increase was seen in the mice exposed to 100 mg/m3 only (NTP, 1997).