Annex Section (e) – Exposure Information

This annex contains data, analyses and references to support the information provided in Section (e) of the WCC Submission for Pentachlorobenzene (PeCB)

1. Exposure Information

1.1 Assessment of Exposure and Effects

The attached information outlines several approaches for evaluating the 'significant adverse effect' criterion for PeCB. Based upon the available evidence, each of the three approaches suggests that the existing data for PeCB do *not* meet the 'significant adverse effect' criterion. This is based on the following key conclusions from the various approaches:

- Approach 1: Studies of Canadian lake sediments in both rural and remote sites show typical PeCB organic carbon concentrations are *at least three orders of magnitude lower* than Environment Canada's "estimated no effect value" ($ENEV_{sed}$) for freshwater benthic organisms. (Section 1.2)

- Approach 2: PeCB concentrations in various animal species represent particular dose levels to predator organisms. For example, a piscivorous mammal, i.e., mink, consuming 15% of its own body weight in food each day (a consumption rate based on data from Vorkamp, 2004), and ingesting food with an average PeCB level of 1 ng/g wet weight (based on gull egg data), would be exposed to only a small fraction of the US EPA Integrated Risk Information System's reference dose. (A reference dose is an estimate of a daily oral exposure to humans, including sensitive subgroups, likely to be without appreciable risk of deleterious effects over a lifetime). (Section 1.3)

- Approach 3: Biomonitoring studies of polar bears indicate PeCB levels are much lower than concentrations necessary to produce adverse health effects. Reported values of PeCB levels in polar bears represent a margin of exposure of *at least* 460. (A margin of exposure is a ratio of a no-observed adverse-effect-level to an estimated exposure dose.) (Section 1.4)

1.2 Approach 1: Assessment Based on Comparison with Guidelines

Sediment was the most sensitive compartment for excessive PeCB concentrations in the environment found in the Canadian process for Priority Substances List under the Canadian Environmental Protection Act listing of chemicals. Environment Canada calculated an estimated no effect value ($ENEV_{sed}$) for freshwater benthic organisms exposed to PeCB of 25 µg/g (25,000 ng/g) organic carbon (Environment Canada, 2003). This PeCB ng/g-OC concentration was exceeded in 1994 in Canada only at a location near a single site of industrial contamination, which has since undergone remediation activities.

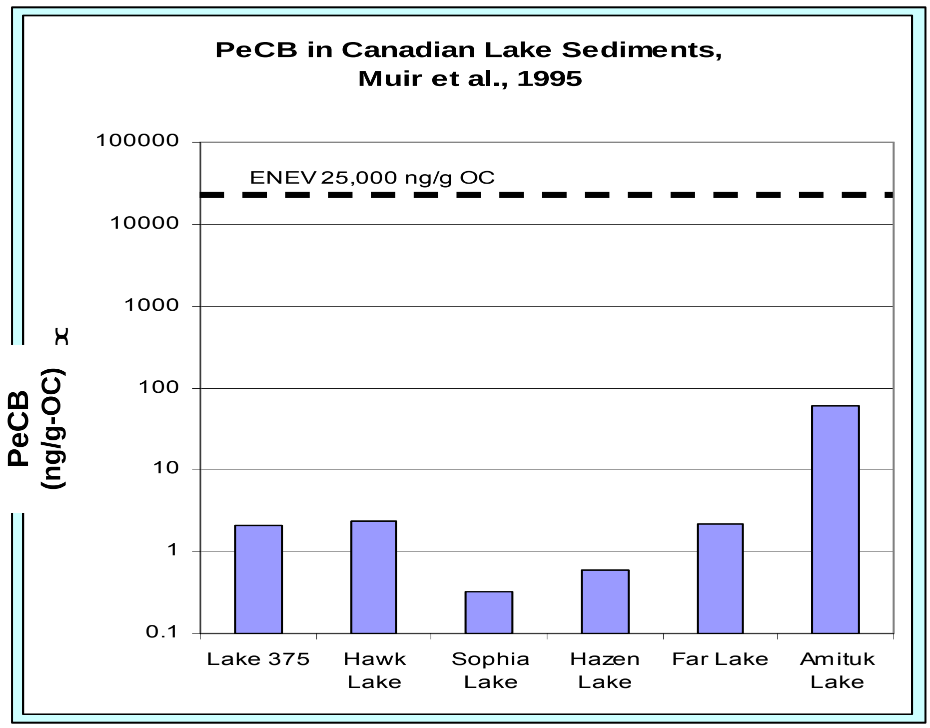
Rural and remote sites which have been studied for long range transport have PeCB ng/g-OC concentrations typically more than three orders of magnitude less than, or 1/1000, of the $ENEV_{sed}$. For example, Muir et al. (1995) report sediment surface layer concentrations of PeCB in northern Canada lake sediments of less than 0.01 to 0.73 ng/g sediment between 1979 and 1988. The sediment concentration of PeCB has been converted to its concentration in the organic carbon, ng PeCB/g-OC, by dividing by the fraction of organic carbon in the sediment. This was then divided by the $ENEV_{sed}$ to show how far below the $ENEV_{sed}$ the environmental PeCB concentrations are. Table 1 presents these values adjusted for the organic carbon content of the sediments and calculated ENEV quotients.

Table 1. Concentration of PeCB in Lake Sediments

Lake	PeCB (ng/g)	% OC	PeCB (ng/g-OC)	PeCB ng/g-OC $ENEV_{sed}$
Lake 375	0.28	13.4	2.1	0.000084
Hawk Lake	0.32	13.5	2.4	0.00010
Sophia Lake	0.01	3.0	0.33	0.000013
Hazen Lake	0.01	1.7	0.59	0.000024
Far Lake	0.21	9.4	2.2	0.000088
Amituk Lake	0.73	1.2	61	0.0024

These very low quotients combined with the declining environmental concentrations clearly show that current long range transport of PeCB is unlikely to cause significant adverse effects to the environment. The same information is presented graphically in Figure 1 below using a logarithmic scale for PeCB concentrations to accommodate the wide ranges in concentrations.

Figure 1: PeCB Levels in Canadian Lake Sediments are Well Below the Environment Canada Estimated No Effect Value in Sediment for Benthic Organisms



1.3 Approach 2: Assessment Based on Integrated Risk Information System (IRIS)

The PeCB concentrations reported in prey organisms can represent a particular dose of PeCB to a predator. There are limited toxicological data specific to polar bears for PeCB. However, one can use the U.S. EPA Integrated Risk Information System (IRIS) RfD[1] process to make a reasonable estimation of an expected level likely to be without appreciable risk to polar bears. When deriving the RfD, U.S. EPA applied a 10-fold safety factor to the LOAEL to derive the NOAEL; applied an added 10-fold factor for subchronic to chronic effects; applied a 10-fold factor to extrapolate chronic effects for rats to other mammal species; and another 10-fold factor from average individuals (mammals) to sensitive animals for a lifetime exposure. This human health criterion is applied here to other species.

Vorkamp et al. (2004) report the sums of PeCB and 1,2,3,4-tetrachlorobenzene (TeCB) concentrations in a large variety of animal species in Greenland. Using the sums of these two chemicals in this discussion is conservative since the concentration of PeCB alone will be lower. Table 2 shows selected data from Vorkamp et al.

Table 2. Conversion of Tissue Concentration from Lipid Weight to Wet Weight

Species	Concentration (sum of PeCB and TeCB in ng/g-lipid)	Percent Lipid	Adjusted to wet weight (in ng/g wet weight)
Ring seal blubber	approx 8.6 ng/g lw	95	6.1 ng/g ww
Kittiwake liver	approx 10.8 ng/g lw	5.7	0.62 ng/g ww
Musk ox blubber	approx 0.33 ng/g lw	89.8	0.30 ng/g ww
Atlantic salmon	approx 3 ng/g lw	9.2	0.28 ng/g ww
Arctic Char	approx 2.3 ng/g lw	1.8	0.04 ng/g ww

Source: Excerpt from Vorkamp et al., (2004)

The numbers in column 2 are the concentrations of PeCB+TeCB on a lipid weight basis and are adjusted to wet weight basis (shown in column 4) by multiplying the concentration by the fraction of lipid as listed in Vorkamp et al (2004). The many other species analyzed by Vorkamp et al. have similar PeCB+TeCB concentrations. The amount of PeCB potentially ingested by a predator animal or human can be calculated by multiplying the food consumption rate by the concentration of PeCB. Using this calculation, a piscivorous mammal, such as mink, consuming 0.15 its own body weight of salmon each day (Environment Canada, 2003), would be exposed to a small fraction of the RfD for PeCB.

The U.S. EPA estimated risks to predators (eagles and mink) by combining feeding rates with levels of HCBD in prey and comparing these daily intake values to a NOAEL (USEPA, 1992, as cited in Lecloux, 2004, p.30). A similar approach could be used to assess risks associated with other chemicals such as PeCB for the polar bear.

Polar bear diet is comprised principally of the ringed seal, with supplementation by other seal species (bearded, harp), certain whales (e.g., white, narwhal), walrus, reindeer, sea birds, carrion, and vegetation (EZNC, 2006). In terms of seal consumption, the polar bear first consumes the skin and blubber, and then possibly the meat; a 500 kg bear can consume 75 kg of food every few days (Mikepolarbear, 2004). Polar bears require an average of 2 kg of fat per day to survive (Stirling, 1988). The estimate for body weight of 300 kg may be on the high end of the

[1] The RfD is an estimate of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD for PeCB is 8E-4 mg/kg-body weight/day or 0.8 µg/kg-body weight/day.

range of body weight for female polar bears (150-300 kg) but on the small side for males (300-800 kg) (Gunderson, .2002).

If we assume that a polar bear consumes 2 kg of ringed seal blubber per day and using the wet weight adjusted concentration of PeCB + TeCB (Table 2) the following equation and input parameters can be used to estimate doses to the polar bear via a diet of ringed seal, where:

$$(0.28\ \text{ng/g}) * \frac{(0.15\ \text{body weight prey in kg/day})}{(\text{body weight predator in kg/day})} * (1000\ \text{g/kg}) = 42\ \text{ng/kg/d or } 0.04\ \mu\text{g/kg/d}$$

This is about 1/20 of the RfD calculated to protect sensitive populations of humans.

Similarly, a polar bear consuming 1% of its body weight per day of ringed seal blubber as its only food would receive less than 10% of the RfD:

$$(6.1\ \text{ng/g}) * \frac{(0.01\ \text{body weight prey in kg/day})}{(\text{body weight predator in kg/day})} * (1000\ \text{g/kg}) = 61\ \text{ng/kg/d or } 0.06\ \mu\text{g/kg/d.}$$

1.4 Approach 3: Assessment Based on Critical Tissue Concentrations

Advances in analytical chemistry, in combination with a recognition of the substantial uncertainties involved in estimating environmental exposures, have resulted in a shift toward assessing humans' exposures to chemicals through biomonitoring. Biomonitoring may be defined as measuring the concentration of chemicals or their metabolites in blood, urine, breast milk, hair and other biological samples. Biomonitoring has the potential to decrease the uncertainty inherent in estimating exposures by conventional exposure assessment methods and to provide a more biologically relevant measure of true exposure. Conventional environmental exposure assessments typically incorporate conservative assumptions designed to provide upper bound estimates of possible intake rates. However, the accuracy of the estimates may not easily be determined, and in many cases may overestimate actual exposures, sometimes by orders of magnitude (Gosselin et al., 2005; Ewers et al., 1996; Ewers et al., 2004). Biomonitoring can provide a direct measure of an individual's exposure and can integrate exposures from multiple pathways and sources, although it cannot, by itself, identify the specific sources or pathways of exposures or the relative contributions from multiple sources. Because biomonitoring is an indicator of internal dose, it may provide exposure estimates that are more directly related to the concentration of the active agent at the target site or organ. This is a key determinant of toxicity and/or pharmacological response, compared to estimated intakes or measures of concentration of a chemical in soil, water or air. For these reasons, biomonitoring is gaining popularity as a means for assessing environmental exposures to chemicals for both humans and animals.

1.4.1 Comparison of Critical Body Residues with Observed Concentrations of PeCB in Biota in Remote Areas

Critical tissue resides (CTR) and the internal dose approach have been used as a way to identify not effect levels of substances having PBT and POP-like properties, which can normally not be assessed reliably in standard toxicity tests. For PeCB several CTRs have been published in the literature. These have been compiled in a database by jarvinen and Ankley (1999). Four values in this database were derived from studies where effects were observed. The CTR found were: earthworm: 325 μg/g; sand crab: 861 μg/g; and guppies (two species): 528 and 636 μg/g. In a recent 28 day study Schuler et al., (2007) found 165 μg/g in juvenile fathead minnow was associated with reduce growth.

An initial comparison of these CTRs with observed PeCB concentrations in biota is presented in Section D of these comments. As the POPs Review Committee Intercessional Working Group on PeCB prepares its risk profile, we urge that it look at the available data on CTRs.

1.4.2. Comparison of Tissue Concentrations in a Health Context Using Biomonitoring Equivalent Approach

The traditional paradigm for human health risk assessment of environmental chemicals compare estimated daily doses (calculated by combining intake assumptions with exposure media concentrations) to health-based criteria for acceptable, safe, or tolerable daily intakes (e.g., reference doses or minimal risk levels) to provide a quantitative (the result of absorption, distribution, metabolism and excretion of administered doses) rather than estimated intake doses.

A rather straightforward means of interpreting biomonitoring data in a health risk context is to calculate the concentration of the chemical in the body (e.g., blood, urine, adipose tissue etc.) that would be predicted to occur as a result of an exposure equivalent to an established safe exposure in test animals such as a No Observed Effect Level (NOEL) or Lowest Observed Effect Level (LOEL), etc. This value has been termed the Biomonitoring Equivalent (BE) (Hays et al., 2007). Once calculated, it can then be used to interpret biomonitoring data in animals or humans in a health risk context.

BEs are calculated for chemicals based on a quantitative understanding of the pharmacokinetics (PK) of that specific chemical in the species of interest (either the specie that was used in the critical study used to derive the safe exposure limit) or in humans. A quantitative understanding of the PK of a chemical can be obtained from various types of data, including animal and/or human PK studies. Simple extrapolation procedures and one-compartment models can be employed to calculate steady-state behavior of chemicals based on these types of data or more complex physiologically-based pharmacokinetic (PBPK) models can be employed to calculate BEs when sufficiently robust data is available. The robustness of a BE will be dependent upon the extent of PK data available.

A risk assessment for a chemical can be conducted using the BE approach by dividing a calculated BE by a measured biomonitoring level to provide a type of Margin of Exposure (MOE) for interpreting biomonitoring data.

$$MOE = \frac{BE}{Measured\ Biomonitoring\ Level}$$

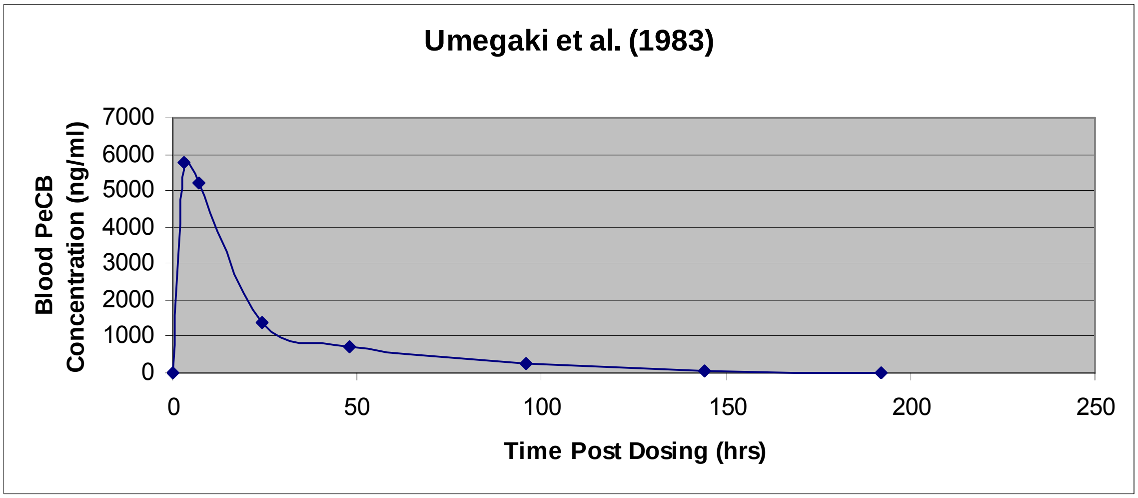
The pharmacokinetics of PeCB have been fairly well studied, especially following high oral doses in rats. Umegaki and coauthors have studied the kinetics of PeCB in blood and tissues of rats given a single oral dose by gavage of either 15 mg or 20 mg (Umegaki et al. 1993; Umegaki et al., 1995). In an unpublished study, Thomas and coauthors have performed a pharmacokinetic study of PeCB in rats given either a single oral dose or seven continuous days of doses of 5 mg/day.

Using the published data of Umegaki et al., 1993, an Area Under the Curve (AUC) of PeCB in blood following the single 15 mg oral dose was calculated as 2.6 µg/ml-hr (see Figure 4). It has been shown that for a simple first-order pharmacokinetic system, the steady-state concentration achieved following repeated dosing can be related to the AUC following a single oral dose of the same dose level (mg/kg) using the relationship;

$$Css = \frac{AUC\_1}{\tau}$$

Where Css is the steady-state concentration following repeated dosing to a specified dose used in a single dose study, AUC_1 is the AUC following the same single oral dose, and tau (τ) is the dosing interval. If the dosing interval is once daily (1 /day), the steady-state concentration will equal the AUC_1. Therefore, assuming steady-state exposures of single daily oral doses of 15 mg (or 77 mg/kg), the steady-state blood concentration of PeCB would be predicted to be 2.6 µg/ml in rats. Extrapolating from 77 mg/kg-day to the LOAEL of 8.3 mg/kg-day found in the Linder et al (1980) study assuming linear kinetics in this dose range, the steady-state blood concentration of PeCB would be predicted to be 0.28 µg/ml. Since PeCB partitions predominantly in the lipid portion of blood and adipose tissue, the concentration of PeCB in blood lipid fraction would be predicted to be approximately 46 µg/g lipid (0.28/0.006 – source for lipid fraction of blood – Patterson et al., 1988).

Figure 4: Plot of blood PeCB concentrations in rats following a single oral dose of 15 mg (see Table 5 in Umegaki et al., 1983)



The Biomonitoring Equivalent approach relies on predicted blood concentration of a compound associated with exposures at a NOEL, LOEL or RfD, RfC, etc. to provide context for interpreting biomonitoring data in a health risk context. Since it has long been known that tissue or blood concentration of a compound is more closely related to the toxic moiety than the actual oral dose, the use of an internal dose metric reduces some uncertainty in the risk assessment paradigm. To the degree that a rat is useful for deriving TDIs and RfDs for human exposures, the same should also apply for predicting some health risks in polar bears or any other mammal. Therefore, the BE associated with the LOEL from the Linder et al. study in rats of 46 ug/g lipid will be used to compare to biomonitoring data for PeCB in animals and humans exposed in Arctic regions.

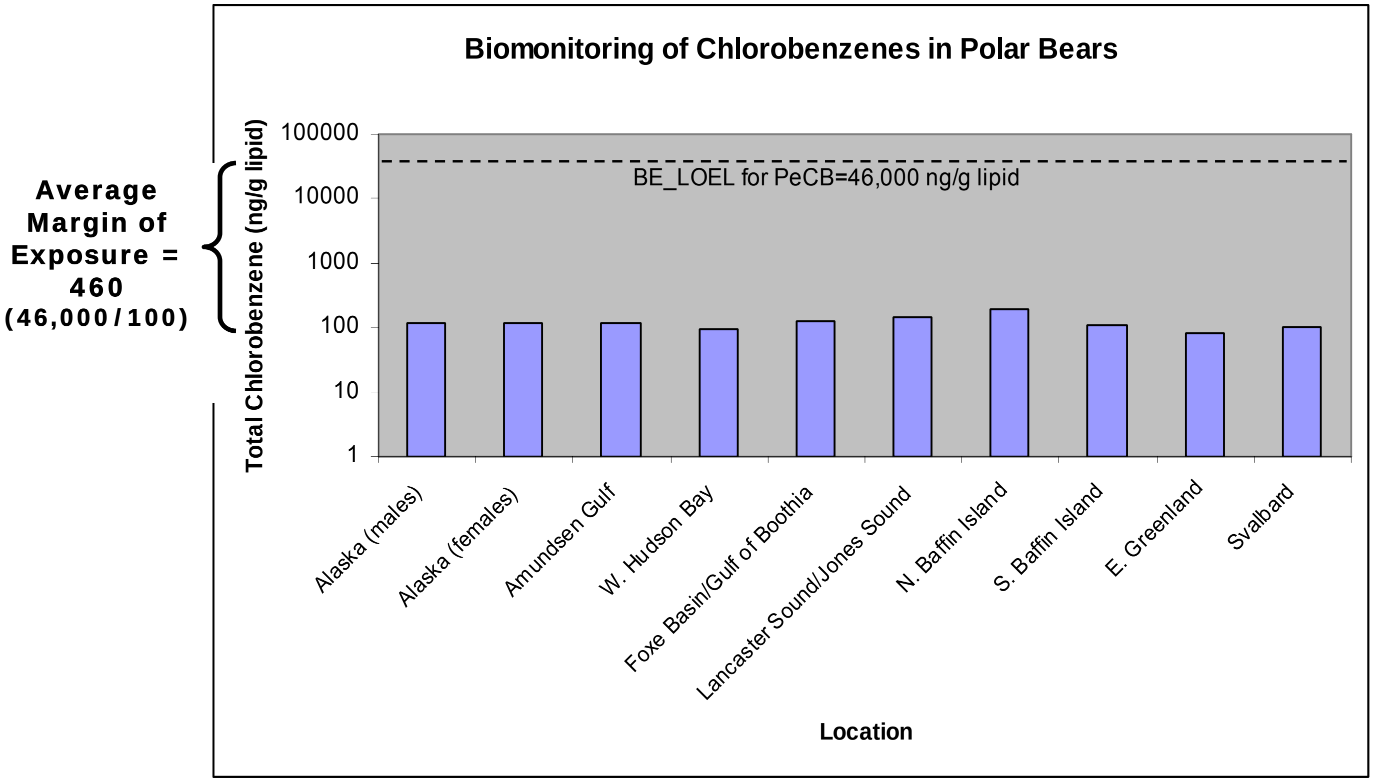
Biomonitoring Data for PeCB in Polar Bears

Biomonitoring studies of polar bears have found approximately 100 ng/g lipid of total chlorobenzenes (reported as the sum of 1,2,3,4-tetraCB, pentaCB, and hexaCB) with a range of approximately 26 – 344 ng/g lipid (Verreault et al., 2005). Compared to the biomonitoring equivalent calculated above, these reported values in polar bears represent a margin of exposure (MOE) of approximately 460 (range: 134 – 1769). Since the biomonitoring levels are the sum of 1,2,3,4-tetraCB, pentaCB and hexaCB concentrations, the actual MOE for PeCB in polar bears is likely significantly larger.*

$$MOE = \frac{46{,}000}{100} = 460$$

* Personal communication with Dr. Robert Letcher of the University of Windsor (May 25, 2006) indicates PeCB actually constitutes no more than approximately one-quarter of the total chlorobenzene levels shown in Figure 5.

Figure 5: Total Chlorobenzene Levels in Polar Bears from Various Arctic Regions are below PeCB Biomonitoring Equivalent Level



Note: This graph uses a logarithmic scale not a linear scale.

2. National and International Risk Evaluations Data for Derivation of Biomonitoring Equivalents

Both the USEPA and Health Canada have derived a human oral non-cancer regulatory guidance value. The USEPA derived a Reference Dose (RfD) of 8E-4 mg/kg/day and Health Canada derived a Tolerable Daily Intake (TDI) of 1E-3 mg/kg/day, using the following assumptions:

Table 3: Governmental Assumptions to Derive RfD and TDI [2]

Organization Name	**Health Canada**	**U.S.EPA**
Risk Value Name	TDI	RfD
Risk Value (mg/kg-day)	1E-3	8E-4
Year	1992	1988
Basis(EXP) (mg/kg-day)	LOEL 5.2	LOAEL 8.3
Basis(ADJ) (mg/kg-day)	N/A	N/A
Uncertainty Factor	5000	10,000
Critical Organ or Effect	liver	liver, kidney
Species	mouse	Rat
Study	NTP,1991	Linder et al., 1980

Source: International Toxicology Estimates for Risk (ITER) database.

In both of these studies, effects to the test group were observed to be mild when observed at the LOELs.

2 Additionally, in the 1993 Priority Substances List Assessment Report for PeCB, Health Canada and Environment Canada used the NTP 1991 study and apply a 10,000 uncertainty factors, (at page 20) to get a TDI of 5E-4 mg/kg-bw/d.

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