Proposed Toxicological Reference Values for Lead (Pb)

ENVIRONMENT
Revised June 2012
Summary

The following toxicological reference values (TRVs) for lead (Pb) exposure for application in risk assessment have been revised from the original draft prepared January 2012 (Wilson and Richardson, 2012):

› Adults, including women of childbearing age: 1.3 µg/kg bw/day; and
› Infants and children (≤ 11 years of age): 0.6 µg/kg bw/day.

It is recommended that these TRVs be applied to risk assessment without consideration of a soil allocation factor less than 1, owing to their derivation from dose-response slope factors considering Pb as a non-threshold toxicant. These values are recommended only for individual site risk assessment and that other approaches (particularly those that incorporate the epidemiological literature with blood lead and soil concentration relationships) could be considered for wide-area sites.

Details of the approach used to develop these TRVs are provided below.
1. Introduction

In order to undertake a risk assessment of lead (Pb) exposure, and to derive risk-based guidelines for Pb in dust or soil, it is necessary to determine, either from a review of the literature or from regulatory health agencies, the dose of Pb that is considered tolerable, acceptable or of “essentially negligible” risk (a toxicological reference value or TRV). In December 2009, the Contaminated Sites Division (CSD) of Health Canada (HC) notified federal departments that federal sites contaminated with Pb should no longer be assessed for risks on the basis of HC's dated tolerable daily intake (TDI) of 3.6 µg/kg bw/day and recommended instead the interim use of the Ontario Ministry of Environment’s intake level of concern of 1.85 µg/kg bw/day (HC, 2009a). However, CSD is now revising this advice (CSD personal communication to GM Richardson), and will recommend consideration of other sources of suitable toxicological information and reference exposure levels for Pb. HC will no longer recommend a specific TDI but instead will recommend that risk assessors weigh the available information to arrive at a suitable TRV based on sound professional judgment.
2. Lead Toxicology

A thorough review of the toxicology of Pb was recently completed on behalf of HC (Azimuth, 2009). A review of this subject is also provided by the United States Agency for Toxic Substances and Disease Registry (US ATSDR, 2007) and the World Health Organization (WHO, 2011). Therefore, a detailed review of the toxicology of Pb will not be presented herein. The adverse health outcomes of Pb exposure have been well documented in the literature for a wide variety of tissues, organs and organ systems. These include the neurological system, cardiovascular system, reproductive system, hematopoietic system (blood), immune system and renal system (kidneys). Of these various target organs and systems affected by Pb, developmental neurotoxicity is considered the key effect in children (manifested as decrements in intelligence quotient {IQ} with increasing blood lead levels). In adults, cardiovascular toxicity is the key effect, manifested as increasing systolic blood pressure (SBP) with increasing blood lead levels.

2.1 IQ Effects

No threshold for the toxic effects of Pb has yet been determined, with toxic effects being observed to the lowest levels of exposure that have been measured in multiple studies, particularly in relation to the neurodevelopmental effects and IQ in children (HC 2011; US EPA, 2006; California Environment Protection Agency {Cal EPA}, 2009; Cal EPA, 1997; World Health Organization {WHO}, 2009). For children, Cal EPA has established a reference blood Pb level of 1 µg/dL, which they predict is associated with a 1 IQ point decrement (Cal EPA, 2009). HC (2011) has defined an approximate effect range of 1 to 2 µg/dL that may be associated with a 1 IQ point decrement. WHO (2010;2011) has indicated the 2 µg/dL may be associated with a 1 IQ point decrement.

One of the sources of information which HC (2011) refers to is a recent review conducted by the World Health Organization/Food And Agriculture Organization Of The United Nations (WHO/FAO) Joint Expert Committee on Food Additives and Contaminants (JECFA) (WHO, 2010; 2011). HC is a member of JECFA and the Food Directorate of HC employs JECFA reference doses (RfDs) or tolerable daily intake values (TDIs) for risk assessment of ingestion exposures from foods.

In the case of IQ effects, the JECFA evaluation of lead determined the following (see WHO, 2010; 2011):

› A chronic lead dose of 0.3 μg/kg bw/day was determined to be associated with a population decrease of 0.5 IQ points; and
› A chronic lead dose of 1.9 μg/kg bw/day was determined to be associated with a population decrease of 3 IQ points.

From these, it is apparent that the dose-effect scaling is approximately linear, so the dose associated with a 1 IQ point decrement (the accepted impact level by Cal EPA) is 0.6 μg/kg bw/day.

It is noted that we consider the Cal EPA (2009) relationship of blood Pb level of 1 μg/dL corresponding to a 1 IQ point decrement to be a conservative estimate of the potency of Pb. Both the WHO and Cal EPA estimates are based on the Lanphear et al. (2005) pooled dataset; however, the WHO (2011) estimate is based on the consideration of a wider option of models. On the basis of results of Benchmark Dose (BMD) analysis, the European Food Safety Authority (EFSA, 2010) has estimated a similar potent relationship (i.e., concluded that a Pb blood of 1.2 μg/dl \(\text{BMDL}_{0.1}\) corresponding to a 1 IQ point
decrement). On the other hand, Azimuth (2009) indicated that an appreciably more potent relationship should be assumed (i.e., 0.1 µg/dL corresponding to a 1 IQ point decrement). In our review, we note that the Lanphear et al. (2005) analysis had very few children with blood Pb levels less than 2 µg/dL (by our estimate, it appears that there were fewer than 25 children with Pb levels in this range). Certain other larger studies have not reproduced the Lanphear et al. (2005) dose response curve at lower blood Pb levels. For example, Surkan et al. (2007) represents the IQ study with the largest number of children with blood Pb levels at 2 µg/dL or less (i.e., 286 children in Surkan et al. [2007] versus perhaps 25 or so children in Lanphear et al. [2005]) and they found no effect on IQ when concurrent blood Pb levels were less than 4 µg/dL. Nevertheless, we do not consider the dataset to be sufficiently robust to discount the dose response relationship reported by Lanphear et al. (2005) and there are recognized limitations to the Surkan et al. (2007) dataset.

A recent National Toxicology Program (NTP) draft monograph on the health effects of low levels of Pb has indicated that there is sufficient information to conclude that lead may cause a variety of health effects at blood levels below 5 µg/dL. However, the draft NTP (2011) report does not provide recommendations on the shape of the dose response curve or proposed acceptable doses for given risk levels. Consequently, this document could not be further used to establish toxicological reference doses of lead.

Overall, the WHO (2011) analyses and conclusion that 0.6 µg/kg bw/day is associated with a 1 IQ point decrement was considered to be a reasonably conservative approach to use at contaminated sites. This value is recommended only for individual site risk assessment and that other approaches (particularly those that incorporate the epidemiological literature with blood lead and soil concentration relationships) could be considered for wide-area sites.

### 2.2 Blood Pressure Effects

In a review completed for HC (Azimuth 2009), increased systolic blood pressure (SBP) was the most sensitive effect in adults associated with exposure to Pb. In that review, a blood Pb concentration of 1.7 µg/dL was proposed as a blood Pb reference level for adults in the general, non-occupational population that would result in no more than 1% increase in average adult SBP. Although the general toxico-kinetics for Pb may be similar in adults and in children, it is known that absorption is lower in adults. In adults, Pb absorption is estimated to be approximately 40% of the rate in children (US EPA, 2003). As a result, the daily dose of Pb that might be associated with the adult reference blood Pb level of 1.7 µg/dL would be 2.5 µg/kg bw/day for a 1% increase in SBP mmHg when the relationship from Azimuth (2009) was considered along with the other stated adjustments.

In more recent evaluation of blood pressure effects, the JECFA evaluation of lead determined the following (WHO, 2011):

- A chronic lead dose of 1.3 µg/kg bw/day was determined to be associated with a population increase in systolic blood pressure of 1 mmHg.

Overall, the more conservative estimate of the effect of Pb on SBP is provided by WHO (2011). Consequently, a dose rate of 1.3 µg/kg bw/day was considered to be associated with a 1 mmHg increase in SBP.
3. Derivation of Toxicity Reference Values for Lead

3.1 Infants, Toddlers and Children

As mentioned above, clear guidance on a specific TRV for Pb, to apply to risk assessment, is now lacking from HC. However, recognizing that previous TRVs from HC and Ontario Ministry of Environment should no longer be employed for risk assessments at federal sites in Canada and the fact that the Food Directorate of HC routinely applies WHO/JECFA TRVs to risk assessment of ingestion exposures, the daily dose of 0.6 µg/kg bw/day determined from the WHO (2010; 2011) analysis to be associated with a 1 IQ point decrement in infants, toddlers and children was selected as the appropriate TRV for these younger age groups. When expressed as blood Pb levels, it can be considered that a 1 IQ point decrement is associated with a blood Pb level of 2 µg/dL as a reasonably conservative estimate (WHO, 2011). Thus, in children it is postulated that 0.6 µg/kg bw/day is associated with a blood Pb level of 2 µg/dL and this value should in turn be associated with a 1 IQ decrement (a *de minimis* population level effect that could never actually be detected in any individual child).

3.2 Adults

Adults are less sensitive to the effects of Pb than are children, primarily because developmental neurotoxicity is not the primary health concern in adults. WHO (2011) estimated that 1.3 µg/kg bw/day would result in no more than a 1 mmHg increase in average adult systolic blood pressure. Therefore, based on the foregoing discussion, a TRV for adult exposure to Pb was determined as 1.3 µg/kg bw/day.

3.2.1 Women of Childbearing Age

For women of childbearing age, it is prudent to be more conservative with respect to a TRV in order to protect the developing fetus. Considering 2 µg/dL as the target fetal blood Pb level as the basis for TRV development, two factors must be considered to derive the TRV for this population group: 1) the ratio of Pb in cord blood versus maternal blood; and 2) the relative difference in Pb absorption between adults and children.

As discussed above, Pb oral absorption in adults is approximately 40% of the rate in children (US EPA, 2003). With respect to the fetal (cord): maternal blood Pb concentration ratio, this ratio is approximately 0.9 (reviewed by US ATSDR 2007) but ranges from 0.7 (Amaral *et al*. 2010) to 0.93 (Graziano *et al*. 1990). Although cord blood Pb concentration is routinely lower than maternal blood Pb concentration, it is conservatively assumed herein that the cord blood and maternal blood Pb levels were equivalent (i.e., that the ratio of cord:maternal blood Pb concentration = 1). Then, the daily dose in women of childbearing age that should not result in exceeding the cord blood Pb concentration of 2.0 µg/dL is:

\[ 0.6 \text{ µg/kg bw/day}/\text{µg/dL} \div 0.4 = 1.5 \text{ µg/kg bw/day} \]

With respect to effects of Pb on the fetus, fetuses exposed to lead in the womb may be born prematurely and have lower weights at birth. Exposure in the womb may also slow mental development and cause lower intelligence later in childhood. Epidemiological studies (reviewed by ATSDR 2007) report no association of blood Pb with premature birth or reduced birth weight for maternal blood Pb levels ≤ 5 µg/dL. There is no clear association of cord blood Pb levels in the 2 µg/dL range and impairment of neurological development. Therefore, a maternal Pb intake of 1.5 µg/kg bw/day is considered protective.
of reproductive and fetal effects; however, as discussed below, a Pb dose rate of 1.3 µg/kg bw/day for protection of SBP increases may be a slightly more conservative value. Consequently, the dose rate of 1.5 µg/kg bw/day for protection of IQ effects was not used and instead the value of 1.3 µg/kg bw/day was considered to be more appropriate (see below).

3.2.2 Summary for Adults

Based on the foregoing discussions, it is recommended that a TRV for Pb of 1.3 µg/kg bw/day be applied to the assessment of risks posed by Pb exposure in adults. This value is considered to be protective of both blood pressure effects but also effects to the fetus for women who are pregnant or who could potentially become pregnant. This TRV is a reasonable and conservative TRV to apply to the assessment of risks posted by adult exposure to Pb at contaminated sites.

3.3 Conclusions and recommendations for Pb TRVs

3.3.1 Recommended TRVs for Pb

The following TRVs for Pb exposure are recommended for application in risk assessment:

› Adults, including women of childbearing age: 1.3 µg/kg bw/day
› Infants, toddlers and children (≤ 11 years of age): 0.6 µg/kg bw/day

3.3.2 Recommended Soil Allocation Factor

It is recommended that these dose rates can be used to evaluate risks from Pb at contaminated sites without the need of an apportionment factor. Although an apportionment factor of 0.2 is routinely used for evaluation of chemicals with threshold effects, the IQ effects associated with Pb exposure are now clearly viewed as non-threshold in the range of exposures that are being risk managed at contaminated sites. Similar in concept to evaluation of carcinogens, these reference dose rates have been estimated using the slope factors from relevant dose-response analyses rather than from no-observed-adverse-effect-levels (NOAELs) or lowest observed-adverse-effect-levels (LOAELs). It is considered reasonable to allow a 1 IQ point decrement to arise from soil media as this is in actuality a very small response and is within the observed variance (margin of error) for IQ tests. As summarized in Wilson et al. (2005) (see Table 1, below), a child’s IQ can be affected up to 20-25 IQ points by factors that include: socioeconomic status; parent’s education; family size and position in family; enriched preschool; and whether or not a child was breastfed. Recently, researchers have indicated that heavy consumption of processed foods in early childhood may result in a 1.7 IQ point decrement (Northstone et al., 2011). The standard error of measurement for IQ tests is generally in the range of ±2.8 IQ points (Sattler, 2001). Consequently, use of 1 IQ point as the maximum allowable decrement due to Pb from soil is considered to be reasonable and would account for less than 5% of the total potential for IQ effects due to environmental factors.
3.4 General Limitations and Confidentiality

This report has been prepared by SNC-Lavalin Inc. (SLI) as an internal reference document to assist SLI in assessing the toxicity of the subject chemical and establishing environmental quality guidelines in respect thereof pursuant to specific client engagements SLI may enter into from time to time. The findings are untested and SLI does not make recommendations or accept any liability or responsibility regarding any such assessment or guidelines.

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4. References


## Table 1: Environmental Correlates of Children’s IQ and Estimated Size of Effect (from Wilson *et al.*, 2005)

<table>
<thead>
<tr>
<th>Environmental Correlates of Children’s IQ</th>
<th>Magnitude of Potential Effect on IQ (IQ points)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Socio-economic status (SES)</td>
<td>± 12</td>
</tr>
<tr>
<td>Parent’s education</td>
<td>± 15</td>
</tr>
<tr>
<td>Family size and child’s position in family</td>
<td>± 8</td>
</tr>
<tr>
<td>Enriched pre-school</td>
<td>± 15</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>± 3-5</td>
</tr>
<tr>
<td>Approximate error rate on children’s IQ tests</td>
<td>± 3 **</td>
</tr>
</tbody>
</table>

* The magnitude of potential effect reported here reflects values reported in the literature. They should not be interpreted as definitive, but rather as an approximate indication of the relative importance of environmental factors of children’s IQ.

** Sattler 2001.