

ATTACHMENT U-7

DEVELOPMENT OF TISSUE-BASED TOXICITY REFERENCE VALUES

TABLE OF CONTENTS

1.0	INTRODUCTION	1-1
2.0	TRV DEVELOPMENT PROCESS	2-1
2.1	Mode of Action Review	2-1
2.1.1	Barium	2-1
2.1.2	Cadmium	2-1
2.1.3	Chromium	2-2
2.1.4	Copper	2-2
2.1.5	Lead	2-2
2.1.6	Zinc	2-2
2.2	Literature Search	2-2
2.3	Tissue TRV Selection	2-3
3.0	TISSUE TRV DEVELOPMENT RESULTS	3-1
3.1	Barium	3-1
3.2	Cadmium	3-1
3.2.1	Kidneys	3-1
3.2.2	Liver	3-2
3.3	Chromium	3-2
3.3.1	Kidneys	3-2
3.3.2	Liver	3-2
3.4	Copper	3-3
3.4.1	Kidneys	3-3
3.4.2	Liver	3-3
3.5	Lead	3-4
3.5.1	Kidneys	3-4
3.5.2	Liver	3-4
3.6	Zinc	3-4
3.6.1	Kidneys	3-5
3.6.2	Liver	3-5
4.0	SUMMARY AND CONCLUSIONS	4-1
5.0	REFERENCES	5-1
5.1	General References	5-1
5.2	References Reviewed During Cadmium TRV Development	5-2
5.3	References Reviewed During Chromium TRV Development	5-5
5.4	References Reviewed During Copper TRV Development	5-6
5.5	References Reviewed During Lead TRV Development	5-10
5.6	References Reviewed During Zinc TRV Development	5-14

LIST OF TABLES

Table #	Description
U.A7-1	Summary of Data Used to Develop Kidney Tissue TRVs for Cadmium
U.A7-2	Summary of Data Used to Develop Liver Tissue TRVs for Cadmium
U.A7-3	Summary of Data Used to Develop Kidney Tissue TRVs for Chromium
U.A7-4	Summary of Data Used to Develop Liver Tissue TRVs for Chromium
U.A7-5	Summary of Data Used to Develop Kidney Tissue TRVs for Copper
U.A7-6	Summary of Data Used to Develop Liver Tissue TRVs for Copper
U.A7-7	Summary of Data Used to Develop Kidney Tissue TRVs for Lead
U.A7-8	Summary of Data Used to Develop Liver Tissue TRVs for Lead
U.A7-9	Summary of Data Used to Develop Kidney Tissue TRVs for Zinc
U.A7-10	Summary of Data Used to Develop Liver Tissue TRVs for Zinc
U.A7-11	Summary of Selected Tissue TRVs for Kidney Tissue and Key Parameters used in the TRV Development Process
U.A7-12	Summary of Selected Tissue TRVs for Liver Tissue and Key Parameters used in the TRV Development Process

LIST OF FIGURES

<u>Figure #</u>	<u>Description</u>
U.A7-1	Toxicity Reference Value Development Procedure
U.A7-2	Data Plot of Data Used to Develop Kidney Tissue TRVs for Cadmium
U.A7-3	Data Plot of Data Used to Develop Liver Tissue TRVs for Cadmium
U.A7-4	Data Plot of Data Used to Develop Kidney Tissue TRVs for Chromium
U.A7-5	Data Plot of Data Used to Develop Liver Tissue TRVs for Chromium
U.A7-6	Data Plot of Data Used to Develop Liver Tissue TRVs for Copper
U.A7-7	Data Plot of Data Used to Develop Kidney Tissue TRVs for Copper
U.A7-8	Data Plot of Data Used to Develop Kidney Tissue TRVs for Lead
U.A7-9	Data Plot of Data Used to Develop Liver Tissue TRVs for Lead
U.A7-10	Data Plot of Data Used to Develop Kidney Tissue TRVs for Zinc
U.A7-11	Data Plot of Data Used to Develop Liver Tissue TRVs for Zinc

LIST OF SUB-ATTACHMENTS

SUB-ATTACHMENT 1 TARGET TISSUE TOXICITY DATA EXTRACTED FOR TISSUE
TRV DEVELOPMENT

LIST OF ACRONYMS AND ABBREVIATIONS

ALA	delta-aminolevulinic acid
ATSDR	Agency for Toxic Substances and Disease Registry
COI	chemical of interest
CSC	Casmalia Steering Committee
DNA	deoxyribonucleic acid
EcoSSL	Ecological Soil Screening Level
ERA	ecological risk assessment
LOAEL	lowest-observed adverse effects level
NOAEL	no-observed adverse effects level
site	former Casmalia Hazardous Waste Facility
TRV	toxicity reference value
µg/g	micrograms per gram
USEPA	U.S. Environmental Protection Agency
WHO	World Health Organization

1.0 INTRODUCTION

This attachment was prepared by ARCADIS for the Casmalia Steering Committee (CSC) for the former Casmalia Hazardous Waste Management Facility (the site), located in Casmalia, California. The purpose of this attachment is to develop and select appropriate mammalian tissue toxicity reference values (TRVs) for liver and kidney tissues for use in refining the Ecological Risk Assessment (ERA) conducted for the site. As we noted in the *Revised Next Steps for Ecological Risk Assessment* memorandum (Revised Next Steps Memo) dated November 26, 2008 (CSC, 2008a) and in U.S. Environmental Protection Agency's (USEPA) response letter, dated December 23, 2008, mammalian liver and kidney tissue TRV development were requested by USEPA as part of the ongoing remediation work at the site.

The CSC agreed to collect site-specific biota tissue data to further refine the ERA. As part of this effort, small mammals were collected onsite and whole body, liver, and kidney concentrations of chemicals of interest (COIs) were measured. Tissue TRVs developed in the attachment are intended for use in interpreting liver and kidney tissue COI concentrations. The whole body data is being used to develop site-specific uptake relationships. The results of this evaluation will be summarized in the forthcoming revised ERA. The COIs identified in the Revised Next Steps Memo included barium, cadmium, chromium, copper, lead and zinc. These metals were identified as potential risk drivers for terrestrial mammals in areas where remedial activities are yet to be determined. Dioxin toxicity equivalent (TEQ) and Total TEQ (i.e., sum of polychlorinated biphenyl [PCB] TEQ and dioxin TEQ) were identified as potential risk-drivers in the Revised Next Steps Memo. However, as reported in the Sampling and Analysis Plan dated April 2009 (CSC, 2009), upon re-evaluation and based on best professional judgment, the CSC are no longer considering dioxin TEQ and Total TEQ as COIs. In the Draft RI report (CSC, 2008), dioxin TEQ and Total TEQ risks to terrestrial mammals were based on maximum concentrations, which may not be reflective of actual risks. Additionally, the Total TEQ concentrations (e.g. maximum detected concentration for total TEQ for mammals is 6.06 picogram per gram [pg/g]) are less than the ecological site-specific surface soil screening level (8.2 pg/g as shown in the bubble plots).

Applicable publications on the effects of COIs were reviewed to determine whether adequate data exist to develop liver and kidney TRVs for small mammals. Literature references cited in USEPA guidance documents were reviewed and only those studies considered of acceptable quality that also contain tissue residue data suitable for developing tissue TRVs were selected for further evaluation. The specific methodology used to develop tissue TRVs is further described in Section 2. Narratives describing the TRV development for each COI are provided in Section 3. Section 4 provides the summary and conclusions for the tissue TRV development. General references considered in TRV development as well as the specific studies evaluated in tissue TRV development are provided in Section 5.

2.0 TRV DEVELOPMENT PROCESS

Tissue TRVs were developed using methods similar to those presented in the Ecological Soil Screening Level (EcoSSL) Guidance (USEPA, 2003; Attachment 4-5). The notable difference between the methods described in this attachment and those used for EcoSSL derivation is that the EcoSSL calculations required a dietary-based TRV, which is based on an average daily dose expressed as milligrams per kilogram per day whereas the TRVs developed in this attachment are tissue-based concentrations expressed as micrograms per gram ($\mu\text{g/g}$), wet weight. The TRV development procedure consisted of three primary steps: (1) mode of action review; (2) a literature search; and (3) TRV selection. Each of these three primary steps is described below.

2.1 Mode of Action Review

The first step in developing tissue TRVs was to review the modes of action of each COI so that tissue TRVs were only developed for those COIs that exhibit toxic effects in either kidney and/or liver tissue. Standard toxicology databases such as TOXNET (<http://toxnet.nlm.nih.gov/>) were reviewed to identify COIs that have modes of action relevant to kidney and/or liver tissue. The modes of action for each COI are summarized in the following sections.

2.1.1 Barium

Barium replaces or competes with calcium in processes normally mediated by calcium, particularly those relating to the release of adrenal catecholamines and neurotransmitters, such as acetylcholine and noradrenaline (World Health Organization [WHO], 1990). Barium's primary targets include nerves, skeletal muscles, smooth muscles, and the heart. Barium is incorporated into the bone matrix in much the same way as calcium, especially in young animals that are still growing. This results in the major part of the body burden being in the skeleton. Soft tissues generally have low concentrations of barium (WHO, 1990). Because TRVs are only being developed for target tissues (liver and kidney tissue), and barium does not exhibit toxic effects on these tissues, tissue TRVs were not developed for barium for the purposes of this attachment.

2.1.2 Cadmium

Recent studies have shown that cadmium depletes glutathione and protein-bound sulfhydryl groups, resulting in the production of reactive oxygen species. As a consequence, enhanced lipid peroxidation, deoxyribonucleic acid (DNA) damage and altered calcium and sulfhydryl homeostasis can occur. Lipid peroxidation is often discussed as a cause of metal-induced toxicity, although many other authors suggest a pivotal role of interaction with sensitive sulfhydryl groups in determining cadmium and lead toxicity. Cadmium's primary targets include liver and kidneys (Agency for Toxic Substances and Disease Registry [ATSDR], 1989), and cadmium primarily accumulates in these tissues, perhaps because these organs contain metallothioneins (a family of cysteine-rich proteins which have the capacity to bind to metals). Because cadmium exhibits toxic effects on target tissues (liver and kidney tissue), tissue TRVs were developed for cadmium in this attachment.

2.1.3 Chromium

Most of the effects of chromium are mediated by direct binding to macromolecules, although there is a slight possibility that it may also contribute to free radical formation. The radical intermediates and the direct binding to macromolecules can then result in DNA-protein crosslinks, DNA-DNA crosslinks, DNA strand breaks, lipid peroxidation, and alterations in cellular signaling pathways (ATSDR, 2000). All of these may contribute to toxicity and carcinogenicity of chromium compounds. Whole body distribution studies indicate that the liver, spleen, kidney, and testes accumulate the majority of chromium after exposure. Because chromium exhibits toxic effects on target tissues (liver and kidney tissue), tissue TRVs were developed for chromium in this attachment.

2.1.4 Copper

Copper is readily absorbed through the gastrointestinal system and accumulates primarily in the liver and bone marrow, where it may be bound to metallothionein. Ingestion of copper salts such as copper sulfate may produce hepatic necrosis and death (Goyer and Clarkson, 2001). Kidney tissue has been reported to fail during hemolytic crisis as a result of clogging renal tubules with hemoglobin. Excessive amounts of copper in kidney tissue may also result in renal tubular and glomerular necrosis (Booth and McDonald, 1982). Because copper exhibits toxic effects on target tissues (liver and kidney tissue), tissue TRVs were developed for copper in this.

2.1.5 Lead

Lead can interfere with the synthesis of heme, consequently altering the urinary or blood concentration of enzymes and their intermediates, in heme synthesis or their derivatives. Lead poisoning can result in accumulation of non-heme iron and protoporphyrin-IX in red cells, an increase in delta-aminolevulinic acid (ALA) in blood and urine; an increase in urinary coproporphyrin, protoporphyrin, and porphobilinogen; inhibition of blood ALA-dehydratase (ALA-D); and an increase proportion of immature red cells in blood (reticulocytes and basophilic stippled cells (Hardman et al., 1996). Lead's primary targets include kidneys, liver, bone, and central and peripheral nervous systems. Lead initially adsorbs to kidney and liver tissues but is ultimately redistributed and deposited into bone. Because lead exhibits toxic effects on target tissues (liver and kidney tissue), tissue TRVs were developed for lead in this attachment.

2.1.6 Zinc

Zinc salts adversely affect tissues; interferes with the metabolism of other ions such as copper, calcium, and iron; and inhibits erythrocyte production and function. Following absorption by the intestine, zinc is rapidly distributed to the liver, kidneys, prostate, muscles, bones, and pancreas (ATSDR, 2005). Because zinc exhibits toxic effects on target tissues (liver and kidney tissue), a TRV was developed for zinc in this attachment.

2.2 Literature Search

A literature search was performed to identify studies that were appropriate for consideration during tissue TRV development. Appropriate studies were defined as those that met the following two primary criteria:

1. Toxic effects that have been shown to produce population-level effects such as reproduction, growth, and survival were measured
2. Target tissue residues were quantified.

For the purposes of this evaluation, literature identified as suitable for population-level effects during TRV development in the EcoSSL guidance (USEPA, 2003) was used as a starting point of the literature search. Because the literature search for developing EcoSSLs was comprehensive, relatively recent, and evaluated key attributes of studies available in the primary literature, only those studies that were determined to be suitable for TRV development for EcoSSL derivation were evaluated in this attachment. Those studies included in the EcoSSL guidance (USEPA, 2003) that reported results that are relative to population-level effects (reproduction, growth, and survival) were queried in USEPA's ECOTOX database (<http://cfpub.epa.gov/ecotox>; USEPA, 2009) to determine which relevant studies reported kidney and/or liver tissue residues. Those studies that met both criteria listed above were selected for further evaluation for the purposes of developing tissue TRVs. Additionally, studies that were used for EcoSSL TRV development but were not included in the ECOTOX database (USEPA, 2009) were obtained for further evaluation to reduce the possibility that suitable studies were omitted from the literature search.

An additional literature search was performed for chromium studies because the procedure described above did not produce a sufficient number of results to develop TRVs as specified in the EcoSSL guidance (USEPA, 2003; Attachment 4-5). The results of this literature search are further discussed in Section 3.3. This additional literature search was not conducted for any other COIs because the procedure described above yielded sufficient results for TRV development.

All relevant studies identified above were reviewed and relevant toxicity data were compiled into a data summary table for each COI. The table included relevant study information (e.g., test compounds, doses, test organism, etc.), no-observed adverse effects level (NOAEL) and lowest-observed adverse effects level (LOAEL) doses/concentrations, and target tissue residues that correspond with NOAEL and LOAEL doses/concentrations. The results are presented in Sub-Attachment 1.

2.3 Tissue TRV Selection

All studies that reported target tissue residues that could be clearly and accurately associated with NOAEL and LOAEL doses/concentrations were included in the tissue TRV selection process for the purposes of this attachment. Examples of studies that were reviewed but not included in the tissue TRV selection process include studies in which the exact residue concentrations could not be determined because target tissue residues were presented on graphs or other figures, studies in which target tissue concentrations were measured in offspring of dosed organisms (i.e., tissue residues were not directly comparable to NOAEL and LOAEL doses/concentrations), or studies in which tissue residues were not quantified.

Studies that reported target tissue residues and toxic responses shown to produce population-level effects were summarized in a data table (Table 1 through 10) and the NOAEL and LOAEL tissue residues were plotted (Figures 2 through 11). NOAEL-based tissue TRVs were

developed using information in these tables and figures according to procedures described in EcoSSL guidance (USEPA, 2003; Attachment 4-5). This procedure is summarized in Figure 1. Once the approach for the NOAEL TRV was selected, LOAEL TRVs were developed using the following approach. If the NOAEL TRV was selected based on a specific study, the bounded LOAEL endpoint from the same study was selected as the LOAEL TRV. Or if the NOAEL-based TRV was selected based on the geometric mean of reproduction and growth NOAEL endpoints, then the LOAEL TRV was based on the geometric mean of reproduction and growth LOAEL endpoints. However, based on recent discussions with USEPA (June, 2009) on the LOAEL TRVs for the ERA, this approach was modified and the LOAEL TRV was selected based on the lower of the (1) geometric mean of reproduction and growth LOAEL endpoints and (2) the lowest bounded survival LOAEL endpoint. Lastly, if no LOAELs were obtained during the literature search described in Section 2.2, additional references were reviewed to select an appropriate LOAEL.

3.0 TISSUE TRV DEVELOPMENT RESULTS

This section describes the tissue TRV development process for those COIs identified as exhibiting toxic effects on either kidney or liver tissue. NOAEL-based tissue TRVs were developed following the procedure described above consistent with EcoSSL guidance (USEPA, 2003; Attachment 4-5). LOAEL tissue TRVs were developed following the approach described in Section 2. The tissue TRV development results for each COI and target tissue are provided in the following sections.

3.1 Barium

As described in Section 2.1.1, barium is a calcium competitor and the primary mode of action is disruption of ion potential in muscles. Since the mode of action is not relevant to kidney or liver tissue, a TRV was not developed for barium.

3.2 Cadmium

A total of 72 results from 46 studies were reviewed in the tissue TRV development for cadmium. Ten of the 72 results were not included in TRV development because tissue residues were presented on graphs and exact concentrations could not be accurately estimated. An additional five results were not considered further because tissue residues were not quantified. Therefore, a total of 57 of the available 72 results were used to develop TRVs for the kidney and/or liver tissues as described in the following sections.

Please note for the purposes of this attachment, the term “result” corresponds to either a sublethal (reproduction and growth) or lethal (mortality) toxic endpoint. A single result may correspond to either liver and/or kidney tissue concentrations and may be used in TRV development for both tissue types. For example, both kidney and liver tissue concentrations may be reported in a study for an individual endpoint. Since this endpoint can be related to both kidney and liver tissue concentrations, it was evaluated separately for both tissue types. Thus, the number of results used for kidney and liver TRV development should not be considered mutually exclusive.

3.2.1 Kidneys

A total of 51 results were used to develop tissue TRVs for cadmium in kidney tissue. Of these 51 results, 6 results were for reproductive endpoints, 38 results were for growth endpoints, and 7 results were for survival endpoints. These data are plotted on Figure 2 and correspond with data presented in Table 1.

The geometric mean of the NOAEL values for reproduction and growth was 12.4 µg/g. However, this value is higher than the lowest bounded LOAEL for reproduction, growth, or survival results. Therefore, the NOAEL TRV is equal to the highest bounded NOAEL below the lowest bounded LOAEL for reproduction, growth, or survival of 8.35 µg/g. The LOAEL TRV

corresponds to the bounded LOAEL result reported in the same study (Koller and Roan, 1977) as the selected NOAEL TRV and is equal to 44.8 µg/g.

3.2.2 Liver

A total of 48 results were used to develop tissue TRVs for cadmium in liver tissue. Of these 48 results, 6 results were for reproductive endpoints, 36 results were for growth endpoints, and 6 results were for survival endpoints. These data are plotted on Figure 3 and correspond with data presented in Table 2.

The geometric mean of the NOAEL values for reproduction and growth was 5.40 µg/g. However, this value is higher than the lowest bounded LOAEL for reproduction, growth, or survival results. Therefore, the NOAEL TRV is equal to the highest bounded NOAEL below the lowest bounded LOAEL for reproduction, growth, or survival of 3.63 µg/g. The LOAEL TRV corresponds to the bounded LOAEL result reported in the same study (Yuhás et al., 1979) as the selected NOAEL TRV and is equal to 24.6 µg/g.

3.3 Chromium

A total of 5 results from 5 studies were initially reviewed to develop TRVs for chromium in kidney and/or liver tissues. Tissue residue data were presented for only 1 of the 5 results. Consistent with EcoSSL guidance (USEPA, 2003; Attachment 4-5), tissue TRVs could not be developed from literature provided in EcoSSL guidance for chromium because the minimum requirement of at least three toxicity results for two species for reproduction, growth, and survival were not available. In an effort to develop tissue TRVs for chromium, an additional literature search was conducted to identify recent studies that may be acceptable for tissue TRV development. Four results from one study were identified in this secondary literature which met the minimum requirements for TRV development. Chromium TRV development for kidney and liver tissue are described below.

3.3.1 Kidneys

A total of 5 results were used to develop tissue TRVs for chromium in kidney tissue. Of these 5 results, 3 results were for growth endpoints and 2 results were for survival endpoints. These data are plotted on Figure 4 and correspond with data presented in Table 3.

The geometric mean of the NOAEL values for reproduction and growth was 2.77 µg/g. Bounded LOAELs for reproduction, growth, or survival results were not available from the literature. Therefore, the NOAEL TRV is equal to the geometric mean of NOAEL values for reproduction and growth of 2.77 µg/g. An appropriate LOAEL TRV could not be estimated from the available NOAELs; therefore, additional literature was reviewed and a LOAEL of >15.0 µg/g was selected based on the review of tissue data provided in Eisler (2000).

3.3.2 Liver

A total of 4 results were used to develop tissue TRVs for chromium in liver tissue. Of these 4 results, 2 results were for growth endpoints and 2 results were for survival endpoints. These data are plotted on Figure 5 and correspond with data presented in Table 4.

A geometric mean of the NOAEL values for reproduction and growth was could not be calculated because only two results were available from the literature. Therefore, the NOAEL TRV is equal to the lowest NOAEL values for reproduction, growth, or survival and is equal to 1.28 µg/g. An appropriate LOAEL TRV could not be estimated from the available NOAELs; therefore, additional literature was reviewed and a LOAEL of >15.0 ug/g was selected based on the review of tissue data provided in Eisler (2000).

3.4 Copper

A total of 116 results from 61 studies were reviewed in the tissue TRV development for copper. Three of the 116 results were not included in TRV development because tissue residues were presented on graphs and exact concentrations could not be accurately estimated. An additional 40 results were not considered further because tissue residues were not quantified. Four results were not used because the results were duplicates of results presented elsewhere or reported tissue residues were not related to the reported results (i.e., reported tissue concentrations were associated with offspring of dosed organisms and are not a direct measure of tissue accumulation). Therefore, a total of 69 of the available 116 results were used to develop TRVs for the kidney and/or liver tissues as described in the following sections.

3.4.1 Kidneys

A total of 24 results were used to develop tissue TRVs for copper in kidney tissue. Of these 24 results, 2 results were for reproductive endpoints, 14 results were for growth endpoints, and 8 results were for survival endpoints. These data are plotted on Figure 6 and correspond with data presented in Table 5.

The geometric mean of the NOAEL values for reproduction and growth was 18.7 µg/g. However, this value is higher than the lowest bounded LOAEL for reproduction, growth, or survival results. Therefore, the NOAEL TRV is equal to the highest bounded NOAEL below the lowest bounded LOAEL for reproduction, growth, or survival of 3.65 µg/g. The LOAEL TRV corresponds to the bounded LOAEL result reported in the same study (Grobner et al., 1986) as the selected NOAEL TRV and is equal to 9.28 µg/g.

3.4.2 Liver

A total of 66 results were used to develop tissue TRVs for copper in liver tissue. Of these 66 results, 2 results were for reproductive endpoints, 49 results were for growth endpoints, and 15 results were for survival endpoints. These data are plotted on Figure 7 and correspond with data presented in Table 6.

The geometric mean of the NOAEL values for reproduction and growth was 83.9 µg/g. This value is lower than the lowest bounded LOAEL for reproduction, growth, or survival results. Therefore, the NOAEL TRV is equal to the geometric mean of NOAEL values for reproduction and growth and is equal to 83.9 mg/g. The LOAEL TRV is equal to the geometric mean of LOAEL values for reproduction and growth and is equal to 342 mg/g. The geometric mean is less than the lowest bounded survival LOAEL of 602.6 µg/g and therefore, the LOAEL TRV is equal to 342 µg/g.

3.5 Lead

A total of 77 results from 56 studies were reviewed in the tissue TRV development for lead. Eight of the 77 results were not included in TRV development because tissue residues were presented on graphs and exact concentrations could not be accurately estimated. An additional 23 results were not considered further because tissue residues were not quantified. One result (Jessup, 1967) was not used because the original study could not be located from standard literature sources. Six results could not be used because tissue residues could not be associated with the dosed organism. Therefore, a total of 39 of the available 77 results were used to develop TRVs for the kidney and/or liver tissues as described in the following sections.

3.5.1 Kidneys

A total of 34 results were used to develop tissue TRVs for lead in kidney tissue. Of these 34 results, 6 results were for reproductive endpoints, 20 results were for growth endpoints, and 8 results were for survival endpoints. These data are plotted on Figure 8 and correspond with data presented in Table 7.

The geometric mean of the NOAEL values for reproduction and growth was 6.89 $\mu\text{g/g}$. However, this value is higher than the lowest bounded LOAEL for reproduction, growth, or survival results. Therefore, the NOAEL TRV is equal to the highest bounded NOAEL below the lowest bounded LOAEL for reproduction, growth, or survival of 5.65 $\mu\text{g/g}$. The LOAEL TRV corresponds to the bounded LOAEL result reported in the same study (Miller et al., 1982) as the selected NOAEL TRV and is equal to 6.55 $\mu\text{g/g}$. It must be noted that the NOAEL TRV and the LOAEL TRV are similar and therefore, may not provide a range of potential risks for lead.

3.5.2 Liver

A total of 26 results were used to develop tissue TRVs for lead in liver tissue. Of these 26 results, 5 results were for reproductive endpoints, 12 results were for growth endpoints, and 9 results were for survival endpoints. These data are plotted on Figure 9 and correspond with data presented in Table 8.

The geometric mean of the NOAEL values for reproduction and growth was 3.21 $\mu\text{g/g}$. However, this value is higher than the lowest bounded LOAEL for reproduction, growth, or survival results. Therefore, the NOAEL TRV is equal to the highest bounded NOAEL below the lowest bounded LOAEL for reproduction, growth, or survival of 0.643 $\mu\text{g/g}$. The LOAEL TRV corresponds to the bounded LOAEL result reported in the same study (Miller et al., 1982) as the selected NOAEL TRV and is equal to 0.908 $\mu\text{g/g}$. It must be noted that the NOAEL TRV and the LOAEL TRV are similar and therefore, may not provide a range of potential risks for lead.

3.6 Zinc

A total of 74 results from 43 studies were reviewed in the tissue TRV development for lead. Six of the 74 results were not included in TRV development because tissue residues were presented on graphs and exact concentrations could not be accurately estimated. An additional 32 results were not considered further because tissue residues were not quantified. Therefore,

a total of 36 of the available 74 results were used to develop TRVs for the kidney and/or liver tissues as described in the following sections.

3.6.1 Kidneys

A total of 20 results were used to develop tissue TRVs for zinc in kidney tissue. Of these 20 results, 4 results were for reproductive endpoints, 10 results were for growth endpoints, and 6 results were for survival endpoints. These data are plotted on Figure 10 and correspond with data presented in Table 9.

The geometric mean of the NOAEL values for reproduction and growth was 58.8 $\mu\text{g/g}$. This value is lower than the lowest bounded LOAEL for reproduction, growth, or survival results. Therefore, the NOAEL TRV is equal to the geometric mean of NOAEL values for reproduction and growth of 58.8 $\mu\text{g/g}$. The geometric mean of LOAEL values for reproduction and growth was calculated and is equal to 209 $\mu\text{g/g}$. There are no bounded survival LOAEL endpoints and therefore, the LOAEL TRV is equal to 209 $\mu\text{g/g}$.

3.6.2 Liver

A total of 32 results were used to develop tissue TRVs for zinc in liver tissue. Of these 31 results, 9 results were for reproductive endpoints, 16 results were for growth endpoints, and 7 results were for survival endpoints. These data are plotted on Figure 11 and correspond with data presented in Table 10.

The geometric mean of the NOAEL values for reproduction and growth was 74.5 $\mu\text{g/g}$. This value is lower than the lowest bounded LOAEL for reproduction, growth, or survival results. Therefore, the NOAEL TRV is equal to the geometric mean of NOAEL values for reproduction and growth of 74.5 $\mu\text{g/g}$. The geometric mean of LOAEL values for reproduction and growth was calculated and is equal to 274 $\mu\text{g/g}$. There are no bounded survival LOAEL endpoints and therefore, the LOAEL TRV is equal to 274 $\mu\text{g/g}$.

4.0 SUMMARY AND CONCLUSIONS

A total of 348 results from 212 studies were reviewed during the tissue TRV development process. Target tissue TRVs were developed for kidney and liver tissue for cadmium, copper, lead, and zinc using methods similar to those presented in EcoSSL guidance (USEPA, 2003; Attachment 4-5). Tissue TRVs were not derived for barium because kidney and liver tissue are not target tissues for barium toxicity. Selected kidney tissue TRVs are summarized in Table 11 and selected liver tissue TRVs are summarized in Table 12.

After we have agreement with USEPA, CSC will use the target tissue TRVs as additional line-of-evidence in the revised ERA.

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