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INTERIM FINAL TECHNICAL MEMORANDUM

DEVELOPMENT OF TOXICITY REFERENCE VALUES FOR CONDUCTING ECOLOGICAL RISK ASSESSMENTS AT NAVAL FACILITIES IN CALIFORNIA

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F GLOSSARY OF TERMS

Missing?

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ABBREVIATIONS AND ACRONYMS

AC	Area of contamination
ALAD	D-aminolevulinic acid dehydrase
APE	Area of potential exposure
ATSDR	Agency for Toxic Substances and Disease Registry
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
Br MRBC	Bromelain-treated mouse red blood cells
BUN	Blood urea nitrogen
BTAG	Biological Technical Advisory Group
BW	Body weight
CLEAN	Comprehensive Long-term Environmental Action Navy
Con A	Concanavalin
DBT	Dibutylin
DDD	Dichlorodiphenyldichloroethane
DDE	Dichlorodiphenyldichloroethene
DDT	Dichlorodiphenyltrichloroethane
DFG	California Department of Fish and Game
DTSC	California Department of Toxic Substances Control
EFA WEST	Engineering Field Activity West
EL	Effect level
ERA	Ecological Risk Assessment
EPA	United States Environmental Protection Agency
FWS	United States Fish and Wildlife Service
HQ	Hazard quotient
LD_{50}	Fifty percent lethal dose
LOAEL	Lowest observed adverse effect level
mg/kg	Milligrams per kilogram
mg/kg-day	Milligrams per kilogram per day
MT	Methoxychlor technical grade
NEL	No effect level
NG	Not given

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ABBREVIATIONS AND ACRONYMS (Continued)

NOAEL	No observed adverse effect level
PAH	Polycyclic aromatic hydrocarbon
PCB	Polychlorinated biphenyl
PPD	Purified protein derivative
ppm	Parts per million
PRC	PRC Environmental Management, Inc.
RWQCB	San Franciso Bay Regional Water Quality Control Board
SUF	Site use factor
TBT	Tributylin
TRV	Toxicity reference value
UF	Uncertainty factor

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EXECUTIVE SUMMARY

Tetra Tech EM Inc., formerly known as PRC Environmental Management, Inc., was contracted by the Naval Facilities Engineering Command, Engineering Field Activity West (EFA WEST) to prepare this technical memorandum to aid in evaluating ecological risks to birds and mammals at naval installations in the San Francisco Bay area. The approach for modeling chemical exposure and effects for higher trophic level aquatic and terrestrial receptors relies upon the derivation of chemical- and receptor-specific toxicity reference values (TRV).

A TRV is a daily dose level at which a particular biological effect may occur in an organism, based on laboratory toxicological investigations. For animal receptors, TRVs are compared to estimates of site-specific daily chemical doses ingested via food and media using the hazard quotient (HQ) approach to model potential risk. HQs for each critical ecological receptor and chemical are calculated by dividing site-specific doses by TRVs.

TRVs were derived based on evaluation of published toxicological data on 20 chemicals found at San Francisco Bay area naval installations. The chemicals include 12 metals and metalloids (arsenic, butyltins, cadmium, cobalt, copper, mercury, lead, manganese, nickel, selenium, thallium, and zinc), five pesticides (aldrin, DDT, heptachlor, lindane, and methoxychlor) and three other organic compounds (benzo(a)pyrene, naphthalene, and total polychlorinated biphenyls). High and low TRVs were derived for each chemical to reflect the variability of parameters within an ecological risk context. Specifically, a low TRV is a conservative value consistent with a chronic no effect level. A no effect level is a dose within a laboratory study at which no effect to the test organism is observed. A high TRV is a less conservative value consistent with an effect level. An effect level is a dose at which a specific biological effect was seen in the laboratory test organism. Hence, the high TRV is a value at which adverse effects have been demonstrated. When compared to site-specific doses to receptors of concern, the high TRV can be used to identify sites posing potential risk to birds or mammals. Conversely, the low TRV is a dose level below which no adverse effects are expected.

TRVs were selected from empirical studies published in the toxicological literature. To compile the core data set, electronic searches of various bibliographic databases were performed. More than a thousand papers were reviewed during the project. All TRVs were based upon peer-reviewed published-work, although unpublished literature such as government reports and technical conference proceedings were

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occasionally cited to support the derivation of TRVs. The TRVs were developed by the Navy in consultation with the EPA Region 9 Biological Technical Advisory Group (BTAG). As a consensus-building technical panel, the group reviewed and discussed literature and agreed upon high and low TRVs for each of the chemicals. Additional data are continually being published by empirical researchers and reviewers. The TRVs presented in the technical memorandum are based on data available at the time of the derivation.

Bird and rodent TRVs for each chemical were selected based on the quality and quantity of studies available in the ecotoxicological literature. The rationale for selection of these TRVs is detailed in the TRV technical memorandum. The papers discussed in the rationale sections are a subset of all the papers considered in deriving the various TRVs. Information on the derivation of TRVs for each chemical is presented in five parts: (1) overview of the chemical, (2) effects on mammals, (3) mammalian TRV, (4) effects on birds, and (5) avian TRV. Subsections on each chemical were written to be used independently, so that the reader need only review the data on the chemicals of interest.

In addition to the technical rationale supporting each TRV, this technical memorandum includes toxicological profiles for more than 20 chemicals, a discussion of the use of food-chain modeling and TRVs in risk assessment, a list of databases and search results, a complete set of minutes from the TRV work group meetings, and a table of test organism body weights. Searches were also performed on chemicals for which no TRVs were derived due to inadequate data. The complete record of search results includes citations and abstracts comprising several thousand pages. All search results are available from the Navy for review upon request.

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1.0 INTRODUCTION

Tetra Tech EM Inc., formerly known as PRC Environmental Management, Inc., was contracted by the Department of the Navy, Naval Facilities Engineering Command, Engineering Field Activity West, under the Comprehensive Long-term Environmental Action Navy (CLEAN) contract to develop and implement a methodology for deriving toxicity reference values (TRV) for use in ecological risk assessments (ERA) conducted by the Navy in the San Francisco Bay area. To supplement screening tools available for evaluating chemicals in sediment and water, TRV derivation focused on birds and mammals common in terrestrial and wetland habitats.

Evaluation of ecological risk requires that conditions at the site be compared to a benchmark. In addition, toxicity of environmental media to organisms is often tested directly through laboratory bioassays, in which a test organism is exposed to a potentially contaminated material and monitored for adverse effects. In the case of water and, to some extent, sediment, chemical concentrations in samples from the site can be compared to published toxicological benchmarks in a screening level risk assessment. The ambient water quality criteria developed by the Unites States Environmental Protection Agency (EPA) are designed to be protective of most aquatic life. Although no analogous criteria exist for sediment, published effects ranges are widely used as surrogates for promulgated criteria. For water and sediments, bioassays using invertebrates and plants are in use.

Concentrations of chemicals in soil are ideally compared first to background, or naturally occurring, concentrations in the area. However, because appropriate background concentrations are often not available, and background concentrations of organic constituents are difficult to evaluate, other screening methods are needed. In addition, concentrations exceeding background are not necessarily toxic to organisms. Because no criteria or benchmarks are available for ecological screening of soils, the Navy has derived TRVs for birds and mammals for a variety of common chemicals. Appendix A contains toxicity profiles for each of these common chemicals.

For the evaluation of ecological risks at naval installations in the San Francisco Bay area, an approach for modeling chemical exposure and effects for higher trophic level aquatic and terrestrial receptors (that is, primary and secondary consumers) was developed that relies upon the development of chemical- and receptor-specific TRVs. The TRVs were developed by the Navy in consultation with the EPA Region 9 Biological Technical Advisory Group (BTAG). The TRVs may be re-evaluated as additional data become available and adjusted accordingly.

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A TRV is a dose level at which a particular biological effect may occur in an organism, based on laboratory toxicological investigations. For animal receptors, TRVs are compared to estimates of site-specific daily chemical doses ingested from food and media in the hazard quotient (HQ) approach to model potential risk. Appendix B contains general discussions on how site-specific doses and HQs are calculated using food chain modeling. HQs for each critical ecological receptor and chemical are calculated by dividing doses by TRVs. These HQs represent a range of possible exposure and effect scenarios; when evaluated with other data in a weight-of-evidence approach, the HQs help identify the potential for adverse impacts to receptors from chemical exposure under different conditions. The following sections describe the methodology used to derive high and low TRVs.

This technical memorandum is organized so that information on each chemical can be read independently of the others. Sections 2.0 and 3.0 pertain to all chemicals. Section 2.0 describes the methods used to derive the TRVs, including (1) literature search strategy, (2) criteria for selection of TRVs, (3) literature review and data extraction, and (4) data evaluation and derivation.

Section 3.0 addresses sources of uncertainty, such as (1) effect level conversions, (2) test duration conversions, (3) allometric conversions, and (4) nutritional requirements of trace metals. Characterization of the confidence associated with each TRV is also addressed in this section.

Section 4.0 discusses briefly the qualitative methods used to address several chemicals for which TRVs were not derived because data were insufficient.

Section 5.0 contains the TRVs; each chemical is presented in a separate subsection. Because the subsections are meant to be independent, the text in Section 5.0 includes some redundancy.

A comprehensive list of references reviewed during the project appears in Section 6.0. Several appendices are included in the technical memorandum, including toxicological profiles (Appendix A), a discussion of the use of food-chain modeling and TRVs in risk assessment (Appendix B), a list of databases and search results (Appendix C), a complete set of minutes from the TRV work group meetings (Appendix D), and others. The complete record of search results includes citations and abstracts comprising several thousand pages, and so is not included with this technical memorandum. Searches were also performed on chemicals for which no TRVs were derived due to inadequate data. All search results are available for review upon request.

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2.0 METHODOLOGY

TRVs for birds and mammals were derived from published toxicological data for 20 chemicals found at San Francisco Bay area naval installations. Rather than a single point estimate associated with adverse biological effects, high and low TRVs were derived for each chemical to reflect the variability of parameters within an ecological risk context. Specifically, a low TRV is consistent with a chronic no effect level. A no effect level is a dose within a study at which no effect to the test organism was observed. A high TRV is consistent with an effect level. An effect level is a dose at which a specific biological effect was seen in the laboratory test organism. High TRVs were selected from approximately the middle of the range of all sublethal effect levels for a particular chemical. Hence, the high TRV is a value at which adverse effects have been demonstrated in at least one laboratory study and are assumed likely to occur in the field.

In some cases, the high and low TRVs were derived using dose levels from the same study; in other cases, independent no-effect and effect levels were selected as the low and high TRVs, respectively. The low TRV represents a level at which no adverse effects are likely to occur, and, when compared to site-specific doses to receptors of concern, can be used to identify sites posing little or no risk. The high TRV represents a level at which ecologically significant adverse effects are likely to occur. When compared to site-specific doses to receptors of concern, the high TRV can be used to identify sites posing potential ecological risk. Appendix B presents the Navy's recommended methods for calculating site-specific receptor doses and hazard quotients.

High and low TRVs were selected from empirical studies published in the toxicological literature. To compile the core data set, electronic searches of various bibliographic databases were performed. The searches focused on each chemical and receptor group (such as birds or rodents) and resulted in a collection of published literature for each chemical. All TRVs were based upon peer-reviewed published work, although unpublished literature such as government reports and technical conference proceedings were occasionally cited to add support to the derivation of TRVs. Additionally, data cited in the Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles were used to supplement rodent data sets.

Because toxicological data on some receptors of concern were limited, the TRVs were frequently based on studies using other test species. Animals of various ages and sexes were examined for a variety of endpoints, biological effects, and exposure duration. The data necessary for deriving TRVs were

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extracted from each study and included in a spreadsheet comprising the core toxicological data set for each chemical. The quality of the original data, endpoints measured, test species, and exposure duration influenced the selection of doses on which to base TRVs. When appropriate, these doses were modified through the application of uncertainty factors and allometric conversion to arrive at receptor-specific chronic, no effect level (low TRV) and mid-range effect level (high TRV) equivalents.

The data used to derive TRVs were reviewed by the BTAG. As a consensus-building technical panel, the work group reviewed and discussed literature and agreed upon high and low TRVs for each chemical. Additional data are continually being published by empirical researchers and reviewers. The TRVs presented in this document are based on data available during the review period, and may change as new data are published.

The following sections detail the steps used to derive the TRVs.

2.1 LITERATURE SEARCH STRATEGY

Searching the toxicological literature was a tiered process. A decision tree illustrating this process is shown in Figure 1. The primary search strategy for obtaining toxicological data follows:

- First Tier - Bibliographic databases searched based on keywords establishing linkages between chemicals and receptor groups (for example, <birds AND zinc>)
- Second Tier - Literature compiled and reviewed by title for retrieval from library or placed in archive file for potential future review
- Third Tier - Titles gathered from library search and abstracts reviewed for preliminary evaluation of ecological relevance and usefulness for derivation of TRVs. Selection and complete review of peer-reviewed articles for compilation of core data set to support derivation of TRVs.

Sources of data on ecological effects potentially associated with each chemical included:

- Primary literature (that is, peer-reviewed scientific publications available in bibliographic databases)
- ATSDR Toxicological Profiles
- United States Fish and Wildlife Service Contaminant Hazard Reviews
- EPA Great Lake Water Quality Initiative

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- Integrated Risk Information System

Databases such as *Medline*, *Toxline*, Agricola, *Biosis*, and *Chemical Abstracts Services* were queried to acquire primary literature citations for each chemical. *Current Contents* was searched to include the most recent publications. Appendix C includes a list of databases searched (Table C-1), and a summary of the number of citations resulting from each search (Table C-2). More than 21,000 journal titles were included in the databases searched. In addition, articles discovered during the review and discussion process were reviewed for inclusion in the master data set.

2.2 CRITERIA FOR SELECTION OF TRVS

The selection of TRVs focused on receptor groups (rodents, birds, and larger mammals) and chemicals common at naval installations in the San Francisco Bay area. When possible, papers focusing on test conditions similar to field conditions at naval installations were preferentially selected. The following criteria were used in selecting toxicological data from the scientific literature:

- Experimental taxa should be as similar as possible to receptor species with respect to taxonomy, body size, feeding habits, and behavior
- Test exposure routes and media should be similar to those expected in the field
- Endpoints related to reproduction, growth, and development are preferred since they best reflect population effects; however, all ecologically relevant effects on individuals were included in the data set
- Chronic exposures and responses and no-effect or lowest observed levels data are preferred
- Study designs must be of high quality, with adequate sample size, explicit analysis of experimental uncertainty, and well-justified conclusions

In most cases, mortality was not considered an appropriate endpoint on which to base low TRVs, since detrimental effects on populations and ecosystems can occur at chemical concentrations much lower than those causing death. Also, the high degree of uncertainty involved in estimating a no-effect level from a lethal dose or concentration reduces the usability and certainty of the converted data. When data were very limited, the high TRV was occasionally based on a dose at which some mortality was observed.

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2.3 LITERATURE REVIEW AND DATA EXTRACTION

The studies obtained from the library were read and classified as high, medium, or low quality based on ecological relevance and whether the data were statistically analyzed. Studies were considered ecologically relevant if the test organisms were dosed orally and if the effects tested could reduce a wild population of those organisms. For example, studies in which mice were merely dosed and NO BIOACCUM. concentrations in tissues measured were not considered ecologically relevant if adverse effects were not measured also. Adequate statistical analysis required inclusion of a control group and sample sizes greater than one. See Appendix C for details regarding the search and retrieval strategy. High-quality studies were characterized as having ecological relevance and reporting adequate statistical analysis of the data. Medium-quality studies either did not perform statistics or were less ecologically relevant, while low-quality studies neither performed statistics nor were ecologically relevant. Some studies were not useful for deriving TRVs and were excluded from further consideration because they were qualitative or field studies that did not quantify measured effects or doses or address statistical significance or that only considered single-dose or acute exposures. In most cases, only high quality data were considered for TRV derivation. Occasionally, medium quality studies were included for consideration when few high quality studies were available.

Data from each study in the core data set (the high and medium quality studies only) for each critical receptor group and chemical were entered into a spreadsheet comprised of risk-relevant fields. The following information was recorded in the spreadsheet: chemical; species, age, and sex of test organism; endpoint measured; effect measured; concentration or dose administered; exposure (test) duration; reported body weights and food or water ingestion rates of test organism (when available); and any other information relevant to risk assessment.

Whether concentrations of chemicals administered in feed were based on wet or dry weight is not reported in many studies. If not specified by the authors, the concentration reported in a study was assumed to be in dry weight, unless the chemical was administered in fresh meat. When the chemical was administered in feed, ingestion rates for food were used; drinking water ingestion rates were used when the chemical was administered in water.

When not reported directly in a study, doses (in milligrams of chemical per kilogram body weight per day [mg/kg-day]) were calculated by dividing the concentration administered in feed by the body weight of

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the test organism and multiplying by the rate of ingestion. Doses reported by the authors in mg/kg-day were used directly in deriving TRVs whenever available. In this case, the authors used body weights and ingestion rates measured as part of the study to calculate doses. If the authors did not report a dose, but body weights and ingestion rates were reported in the study, doses were calculated using the reported body weights and ingestion rates. If the study did not report body weights or ingestion rates, estimates of these parameters were used to calculate a dose to the test organism. A decision tree depicting this process is shown in Figure 2. Species-specific, sex-specific, strain-specific, and age-specific estimated body weights and ingestion rates used in the spreadsheet were grand means of means presented in various body weight and ingestion rate reviews. Data on captive animals were preferred over data on wild animals for body weights and ingestion rates of test organisms, whereas data on wild animals were preferred over data on captive animals for body weights for critical receptors. If no appropriate measured rate of ingestion was available for a particular test organism, ingestion rates were calculated using equations in Nagy (1987). Appendix E presents a table of body weights used for test organisms.

2.4 DATA EVALUATION AND DERIVATION

The studies on which to base high and low TRVs were chosen in consultation with the regulatory agencies and natural resource trustees representing the EPA Region 9 BTAG. After the toxicological data were reviewed and compiled in the core data sets, high and low TRVs for each receptor group and chemical were selected.

The high and low TRVs selected were based upon studies available for review and were graphically presented using dose-vs.-effect scatter plots. Evaluation and discussion of the range and pattern of the data were central to the approach to selecting TRVs based on best professional judgment and interpretation of available data. Evaluation of the data included review of the scatter plots in which various categories of adverse effects, endpoints, test organisms, and dose levels were considered within the context of potentially significant ecological effects on receptors of concern. The categories of adverse effects used to classify dose levels among test species included reproductive, developmental, neurological, immunological, and other systemic effects. Throughout the text, "other systemic effects" are referred to simply as "systemic." Often times, multiple effects at a single or several doses were reported in a single study; hence, multiple endpoints and ecological effects were recorded for each study during the data evaluation process.

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The dose-vs.-effect scatter plots for each chemical reflected the range of adverse effects potentially caused by the chemicals within and among species, sexes, and age groups of test organisms. The range of these plotted doses varied across chemicals, but the TRVs derived for each chemical captured the variability between the no effect levels consistent with the low TRV and the effect levels indicated by a high TRV.

In evaluating the dose-vs.-effect scatter plots for each chemical, the overall strength of the core data set was considered. Many studies in each core data set were reviewed by several toxicologists and biologists. Studies upon which TRVs were derived or that provided special insight into the toxicological data on a chemical were more thoroughly reviewed by additional members of the work group.

No single set of parameters held primacy in the decision process because the core data sets varied with respect to quality, intensity, and focus of reported findings. However, nearly all of the decisions were made with consideration of test species, sensitive life stages, test duration, measured effects and their ecological significance, and the relationship of any one particular study's results to the supporting core data set. The relationship among all points in the scatter plot was critical to the TRV derivation process; for example, the location of an individual data point within the overall distribution of the core data set was considered relevant to its interpretation. Ideally, the thresholds for lower effects were distinct, and the upper range toxicity values were consistent in their expression of chronic effects. Also, the upper range chronic toxicity values were generally widely separated from acute toxicity doses.

After review of the data, doses on which to base low and high TRVs were selected. The TRVs were then allometrically converted to receptor-specific TRVs as described in Section 3.3. Data sets for rodents were originally compiled under the assumption that separate TRVs would be derived for larger mammals. When literature searches for studies using larger mammals were conducted, toxicological data on larger mammals were, in most cases, extremely limited in quantity or inappropriate for TRV derivation. For example, many veterinary studies reported effects when a single animal had ingested an unknown quantity of a chemical and was brought in for treatment. The problem of sufficient data being unavailable to develop separate TRVs for larger mammals was unforeseen. For this reason, the rodent data set was used to derive mammalian TRVs, except in cases where data were sufficient to support a separate TRV for larger mammals (for example, mercury). The high and low TRVs derived for each chemical and receptor are summarized in the attachment to this document. Please see the minutes from the work group meeting on October 3, 1996 (Appendix D) for more detail on this method.

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3.0 SOURCES OF UNCERTAINTY

Published methods for conducting ecological assessments differ in the way in which uncertainty is addressed, including the magnitude and type of uncertainty factors recommended (Opresko and others 1993; Suter 1993; Calabrese and Baldwin 1993). DTSC is preparing a document to provide guidance on uncertainly analysis, but it is not yet available to the public.

One method of accounting for the uncertainty inherent in the derivation of TRVs is to use uncertainty factors (UF). Uncertainty factors are values by which the TRV is divided to overlay a level of conservatism to data that are, for one reason or another, incomplete. For example, uncertainty resulting from the lack of data on chronic exposure has been addressed traditionally by dividing the proposed TRV by a number, usually 10. The appropriateness of applying UFs has been questioned because of the difficulty in scientifically and quantitatively justifying the numerical value of the UF. Also, the multiplication of UFs in cases where more than one UF is applied can lead to an artificially low TRV and may misrepresent real effect levels. Because of these confounding factors and because the availability and type of toxicological data on chemicals and receptors of concern varied widely, the application of UFs was considered on an individual basis.

The method for deriving TRVs restricted the use of UFs to cases where they were needed to arrive at a chronic, no-effect level equivalent for the low TRV. Full protection of assessment receptors requires that a chronic, no-effect level be used as one decision point for risk assessment. When the toxicological literature on a chemical indicated that a UF other than 10 was more defensible in the derivation of the low TRV, the adjusted UF was used and is described in the rationale section of this memorandum. The application of UFs was minimized by performing an extensive primary literature search to gather the maximum amount of available data, by using peer-reviewed literature, by calculating low and high TRVs to account for the distribution of data in the TRV data set, and by calculating low and high site-specific doses.

Several studies guided development of the methods for deriving TRVs and analyzing sources of uncertainty (Calabrese and Baldwin 1993, Opresko and others 1993). Four methods were used to address uncertainty in the TRVs. The first three are quantitative methods consistent with EPA draft guidance (EPA 1995b) and typically used in ecological assessments. The fourth method expresses confidence in the data sets used to derive TRVs. The fourth method is qualitative, providing risk assessors with

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another tool for data interpretation and guiding risk managers in making decisions based on the most reliable and accurate data.

The quantitative methods for analysis of uncertainty in the derivation of TRVs are: (1) application of a UF of 10 to adjust lowest observed adverse effect levels (LOAEL) and effect levels to no observed adverse effect levels (NOAEL) and no effect level equivalents, (2) application of a UF of 10 to the low TRV if the exposure duration is sub-chronic, and (3) allometric conversion (body scaling) to convert doses given to laboratory test organisms to equivalent doses for receptors of concern. The fourth method designates relative levels of confidence based on the quality of the data set for each TRV. Each of these methods is discussed in the following subsections.

3.1 LOAEL TO NOAEL CONVERSION

A UF was applied to LOAEL and effect level (EL) data when appropriate NOAEL and no effect level (NEL) data were unavailable; the default UF for each of these conversions was 10 (EPA 1989, Calabrese and Baldwin 1993, EPA 1993a, Opresko and others 1993, EPA 1995b). A LOAEL is the lowest dose in a particular study at which a given effect is observed and is always bounded by a lower dose at which the effect was not observed. An EL is an unbounded effect level at which a biological effect was observed in a laboratory study. For the purposes of this memorandum, LOAEL and EL data are handled in the same manner. A NOAEL is the highest experimental dose in a particular study at which a given effect to the test organism is not observed. A NEL is any no effect dose observed in a study. NOAEL and NEL data are handled in the same manner.

An example of an application of a UF to convert LOAEL data to a NEL equivalent occurs in the cadmium and birds data set presented in Section 5.5.3. The low TRV was based on the study by Cain and others (1983), in which kidney degeneration occurred in mallard ducklings at a dose of 0.78 mg/kg-day. The reported dose of 0.78 mg/kg-day was divided by a UF of 10 to convert the effect dose to a NEL equivalent. The resulting avian low TRV is 0.08 mg/kg-day.

3.2 SUBCHRONIC TO CHRONIC CONVERSION

In some cases, a UF was used to adjust a sub-chronic exposure duration to chronic exposure equivalent; the default UF for this conversion was 10. Chronic exposure durations were considered to be those

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greater than 10 percent of the life span of the receptor of concern. Acute exposures were not considered appropriate for TRV derivation. NO ACUTE

3.3 ALLOMETRIC CONVERSIONS

General TRVs for mammals must be converted to TRVs specific to each site-specific receptor of concern. This extrapolation of data based on body scaling is called an allometric conversion. For example, when toxicological data and dose levels are available for laboratory rats, but are needed for the deer mouse, an allometric conversion estimates a similar dose level for the deer mouse. The underlying assumption of allometric conversions is that a given effect on a species of small mammal is similar to the effect on a species of larger mammal, per unit body weight, and vice versa. Recent work by Mineau and others (1996) suggests that no allometric conversion is necessary for birds; that is, a body scaling factor of 1.0 is appropriate. *

Allometric equations generally follow the form:

$$Y = aM^b$$

where Y is some variable of structure or function and is dependent (following a power law equation) on body mass. Although several allometric conversion equations are available in the literature, the Navy recommends following Sample and others (1998) for conversion of avian and mammalian TRVs.

For Mammals: $\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$ (Equation 1)

For Birds: $\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1}$ (Equation 2)

The allometric conversion for mammals proposed in Sample and others (1998) is consistent with the method used to derive the Oak Ridge National Laboratory wildlife benchmarks (Sample and others 1996). The avian scaling factor of 1.0 recommended by Sample and others (1998) is based on research by Mineau and others (1996) that focused on pesticides. *

Numerous sources of uncertainty result from variability in physiological parameters (Peters 1983); the Navy TRV search strategy incorporated as much interspecies variability as possible in order to minimize the uncertainty inherent in extrapolation. However, most high quality laboratory studies reviewed used

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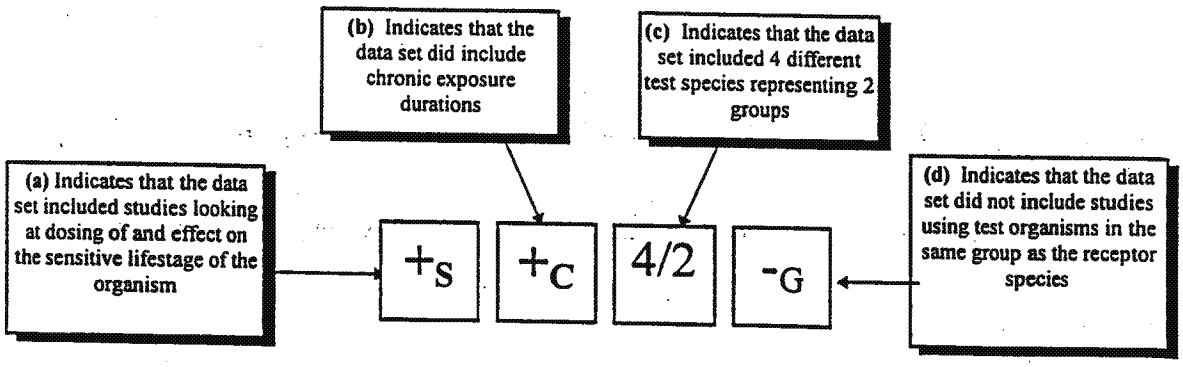
laboratory mice or rats as test organisms. The TRVs presented in Section 5 and summarized in Attachment 1 have not been allometrically adjusted. Adjustments should be made using Equation (1) to incorporate the body weight of the site-specific receptor of concern to which the TRV is applied.

3.4 CONFIDENCE CHARACTERIZATION

Derivation of TRVs was based on a comprehensive search of the toxicity literature for each chemical. In general, the greater the number and variety of toxicity studies, the less the uncertainty in the final TRVs; however, the available data for each chemical differ in quality and quantity. To incorporate the data quality issues pertinent to the development of TRVs, the derived values include a confidence characterization. This characterization conveys the level of confidence in the derived TRV based on criteria such as the quantity of data and the representation of animal groups of concern in the data set. For example, the available data sets for lead include a wide variety of species, test endpoints, and life stages, whereas data sets for some other chemicals are more limited.

The confidence rating system reflects four main sources of uncertainty, based on the: (a) availability of studies on sensitive life stages, (b) availability of data on chronic exposures, (c) variety of test organisms in the data set, and (d) similarity of test organisms to the receptor of concern. A confidence rating is illustrated below:



The use of the rating system for each of these sources of uncertainty is discussed below.

Sensitive Life Stage. For the TRV derivation, the sensitive life stage is defined as the time from conception to reproductive maturity. The data set is considered to include exposure in the most sensitive life stage (indicated by a "$+_S$" sign in the figure above) if it contains data on *multiple life stages* including at least one study in which effects on the sensitive life stage were measured *and* the test organism was

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actively dosed in its sensitive life stage by the researchers *or* was passively dosed in the sensitive life stage by receiving chemicals from a parent actively dosed during gestation or laying. For example, a study examining survival to day 21 of mouse pups dosed during gestation and lactation is considered to address the sensitive life stage of the mouse because the pups were dosed *in utero* and through nursing. Multigenerational studies were also considered to address the sensitive life stage. A study was given priority for TRV derivation based on the definition of sensitive life stages only if greater sensitivity was apparent compared with other studies.

Chronic Exposure Duration. Chronic data were sought for each chemical, but sometimes were not available. If the low TRV was based on a study of sub-chronic duration then an uncertainty factor was used to convert a low TRV to a chronic equivalent; however, the data set from which the low TRV was selected may include studies with chronic exposure durations. A data set used to derive a low and high TRV is considered to address chronic exposure (indicated by a "$+_C$" sign) if there is at least one study in which test organisms were exposed for at least 10 percent of the animal's natural life span.

Test Organism Diversity. The diversity of test organisms used in the data set is indicated by a ratio of the number of species in the data set over the number of groups represented in the data set. All breeds of chickens are considered one species; all strains of laboratory rats are considered one species; and all strains of laboratory mice are considered one species. A ratio of 4/2 means that the data set includes four test species representing two groups. For example, when deriving the TRVs for cadmium and birds, the four different avian species included black ducks, mallards, Japanese quail, and chickens. These species of birds belong in two different groups, ducks and gallinaceous birds. This ratio provides an indication of the variety of test organisms in the data set. Examples of the test species falling into each group are given below:

Avian Groups

- **Raptors:** falcons, hawks, owls, kestrels, harriers
- **Gallinaceous birds:** quail, pheasant, chickens, rails
- **Ducks:** mallards, black ducks, pekin ducks
- **Shorebirds:** sandpipers, plovers, herons
- **Passerines:** finches, blackbirds, starlings, sparrows, redstarts

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Mammalian Groups

- **Laboratory mice:** all strains of laboratory mice
- **Laboratory rats:** all strains of laboratory rats
- **Wild mice:** deer mice, white-footed mice, old-field mice

Correspondence to the Receptor of Concern. Because allometric conversion between a test organism and a receptor of concern may not account for differences in the sensitivity of the two organisms to contamination, the ranking system also includes information on the relative similarity of test organisms to the species of concern. If the data set includes a study using a test organism in the same group as the assessment receptor (as defined above), that TRV is given a higher confidence rating (indicated by a "$+_G$") than if no corresponding test organism were in the data set (indicated by a "$-_G$"). For example, for cadmium, if the receptor of concern were the black rail, the data set would receive a confidence rating of "$+_G$" because the data set included quail and chickens, which belong to the same group as the rail (gallinaceous birds). If the receptor of concern were the American kestrel, the confidence rating would be "$-_G$" because the data set did not include test organisms in the same group (raptors) as the kestrel.

3.5 OTHER SOURCES OF UNCERTAINTY – TRACE METAL NUTRITIONAL REQUIREMENTS

For various chemicals, the potential for confounding effects in the interpretation of toxicity is great, particularly for those metals and metalloids that also have nutritional value. Whether the component is considered essential or nonessential in an animal's diet, any mineral having a well established role in animal nutrition may confound the interpretation of toxicity, especially when nutritional requirements occur at concentrations in feed stocks that are close to concentrations that may be characterized as toxicity thresholds. Low TRVs may occur close to nutritionally required doses for some metals and metalloids. Frequently, the slope of the dose-response curve influences whether a given dose is associated with an adverse biological effect or a nutritionally beneficial effect. For example, for a required mineral presenting a linear dose-response curve with a steep slope, the margin between nutritional benefits and lower toxicity thresholds may be slight. In contrast, minerals characterized by a shallower sloped dose-response curves may have more clearly defined margins between nutritional requirements and incipient levels for toxicity. The distinctions between nutritionally beneficial effects and toxic effects, especially at mineral levels lying between required nutritional levels and lower estimates of toxicity thresholds, are most often a function of physicochemical form of the element (for

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example, inorganic or organic); duration of study addressing the nutritional versus toxicological effects; endpoints for evaluation of responses; and the test species. Also, clear distinctions between toxic and nutritional responses vary with age and sex of the animal, as well as the physical condition of the test species.

TRVs derived for the metals and metalloids were reviewed by the working group, recognizing that the potential for confounding effects caused by nutritional interactions existed. In some cases, the original value selected as a low TRV was at or close to values considered to be necessary for proper nutrition. These TRVs are indicated in the TRV summary table attached to this document. The application of uncertainty factors in toxicity evaluations must be exercised with caution in view of these often blurred lines between nutritional benefit and onset of toxicity.

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4.0 CHEMICALS OF CONCERN LACKING TOXICITY REFERENCE VALUES

TRVs could not be derived for some chemicals of concern at naval installations due to insufficient data. For some chemical-receptor pairs, like benzo(a)pyrene and birds, all available studies focused on mortality or other acute effects and acute exposure durations. Because the TRV process requires chronic exposures and sublethal effects manifested at the individual and population levels, data on mortality and other acute effects were considered inappropriate for deriving TRVs. Also, the high degree of uncertainty involved in estimating a no-effect level from a lethal dose or concentration reduces the usability and relevance of the converted data.

For receptors and chemicals for which no TRVs were derived, site-specific doses should be estimated, but no HQs calculated. Instead, the site-specific high and low doses should be plotted with available data to determine where the site-specific doses fall in comparison to the range of published effects. In the absence of calculating HQs for a particular chemical and receptor (those lacking TRVs), this qualitative comparison of doses and toxicological data can be used in the weight-of-evidence risk analysis for that chemical.

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5.0 RATIONALE FOR TOXICITY REFERENCE VALUE DERIVATION

Bird and rodent TRVs for each chemical were selected based on the quality and quantity of studies available in the ecotoxicological literature. The rationale for selection of these TRVs is detailed in the following subsections. TRVs are summarized in Attachment 1. The papers discussed in the rationale sections are a subset of all the papers considered in deriving the various TRVs. In all cases, rodent TRVs are based on data sets containing studies on rodents only. Section 2.4 explains the rationale for applying rodent TRVs to larger mammals. Appendix D contains the meeting minutes from the TRV work group meetings and includes discussions pertinent to selection of the TRVs.

Each of the following subsections presents the TRVs for a given chemical in five parts: (1) overview of the chemical, (2) effects on mammals, (3) mammalian TRV, (4) effects on birds, and (5) avian TRV. The subsections are written to be used independently, so that the reader need only review the chemicals of interest.

5.1 TOXICITY REFERENCE VALUES FOR ALDRIN

A review of the literature on the toxicity of aldrin to rodent test organisms yielded three studies relevant for deriving TRVs. Despite an exhaustive search of the primary literature, insufficient data were available to derive avian TRVs for aldrin. In deriving the mammalian TRVs, data from ATSDR toxicity profiles (ATSDR 1993a) were used to supplement available data. In both the Navy and ATSDR data set the range of effects extended from 0.125 mg/kg-day (Treon and others 1954) to 5 mg/kg-day (Fitzhugh and others 1964). In the rodent data set, most adverse effects were systemic and behavioral. Papers representing the effects presented in the studies reviewed are summarized below.

5.1.1 Effects of Aldrin on Rodents

Paul and others (1992) administered aldrin to male and female Wistar rats by gastric intubation for 90 days. At a dose of 1 mg/kg-day, motor coordination was adversely affected. Motor coordination was considered an important endpoint because it may limit an animal's ability to avoid predators. Moreover, the dose of 1 mg/kg-day was corroborated by similar doses reported in ATSDR (1993a). This dose was the basis for the low and high TRVs. Studies using gastric intubation are usually not used for TRV

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derivation; however, the only study that exposed the test organisms orally in the diet did not meet other data quality criteria.

Treon and others (1954 as cited in ATSDR 1993a) administered aldrin to laboratory rats for three generations. A dose of 0.125 mg/kg-day resulted in increased mortality of offspring. In the same study, a decrease in the number of litters was observed in rats exposed to 0.625 mg/kg-day. In another study by Treon and others (1953 as cited in ATSDR 1993a), aldrin was administered to laboratory rats for 27 weeks. At a dose of 1.25 mg/kg-day, no effects were reported on the hepatic or renal systems. The doses in the Treon papers cited by ATSDR were taken from end-of-the-year reports from the Treon laboratory. The studies were rejected as the bases for TRV derivation because very little information was provided in ATSDR (1993a) to support the means by which the doses were calculated, and the actual studies that are cited could not be found.

Fitzhugh and others (1964 as cited in ATSDR 1993a) administered aldrin to laboratory rats for 2 years. An increase in mortality was reported at a dose of 2.5 mg/kg-day. This study established a chronic mortality dose and provided a reference dose below which the high and low TRVs must occur. In the same study, at a dose of 0.025 mg/kg-day, effects were reported on the hepatic system.

ALDRIN TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Wistar rats	NG	Inhibition of learning ability and conditioned avoidance response	EL	90 d	GI	1[1,2]	Paul and others 1992
Wistar rats	NG	Inhibition of learning ability and conditioned avoidance response	EL	90 d	GI	1[1,2]	Paul and others 1992
Rat	*NG*	*No effects*	*NOAEL*	*27 wk*	*F*	*1.25*	*Treon and others 1953, in ATSDR 1993a*
Rat	*NG*	*Increase in mortality*	*LOAEL*	*2 yr*	*O*	*2.5*	*Fitzhugh and others 1964, in ATSDR 1993a*
Rat	*NG*	*Hepatocellular vacuolation; bile duct proliferation*	*LOAEL*	*2 yr*	*O*	*0.025*	*Fitzhugh and others 1964, in 1993a*

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Rat	*NG*	*Increase in mortality of offspring*	*LOAEL*	*3 gen*	*F*	*0.125*	*Treon and others 1954, as cited in ATSDR 1993a*
Rat	*NG*	*Decrease in number of litters*	*LOAEL*	*3 gen*	*F*	*0.625*	*Treon and others 1954, as cited in ATSDR 1993a*

Notes:

1 Selected low mammalian TRV; an uncertainty factor of 10 was applied for EL to NEL conversion giving a TRV = 0.1 mg/kg-day

2 Selected high mammalian TRV = 1 mg/kg-day

Italicized Text	Information cited in ATSDR 1993a
Highlighted rows	The bases for high and low TRVs
NEL	No effect level
NOAEL	No observed adverse effect level
LOAEL	Lowest observed adverse effect level
EL	Adverse effect level
NG	Not given
Exposure route:	GI = gastric intubation
	F = food, O = oral

5.1.2 Mammalian TRVs for Aldrin

The low mammalian TRV was based on the study by Paul and others (1992). At a dose of 1 mg/kg-day effects on motor coordination were reported. The dose was divided by an uncertainty factor of 10 to convert the effect level to a no effect level equivalent. The resulting low TRV was 0.1 mg/kg-day.

The high TRV of 1 mg/kg-day was also based on Paul and others (1992). The dose of 1 mg/kg-day was in the mid-range of effects in the data set and was less than an increase in mortality (2.5 mg/kg-day) reported by Fitzhugh and others (1964 as cited in ATSDR 1993a).

TRVs must be allometrically converted to account for differences in body size between the test organism (Wistar rats) and the mammalian receptor species of concern. The following allometric equation as outlined in Section 3.3 will yield a TRV for a specific receptor species when the receptor body weight in grams is substituted:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.1 \text{ mg/kg-day } (65 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

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$$\text{High TRV: Dose}_{receptor} = 1 \text{ mg/kg-day } (65 \text{ g/Body Weight}_{receptor})^{1/4}$$

Confidence ratings were applied to all TRVs. The method for determining confidence ratings is described in Section 3.4. The following information may by used in determining confidence ratings. The data set of aldrin effects on rodents included: (a) studies on the sensitive life stage of the test organism (+S); (b) chronic exposure durations (+C); and (c) 2 test species representing 2 different mammalian groups (2/2). The low and high TRV test organism are in the mammalian group of laboratory rats. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.2 TOXICITY REFERENCE VALUES FOR ARSENIC

In a review of the literature on the toxicity of arsenic to rodent and avian test organisms, 7 studies on rodents and 5 studies on birds were considered relevant for deriving TRVs. In deriving the mammalian TRVs, data from ATSDR toxicity profiles (ATSDR 1993b) were used to supplement available data. The levels at which adverse effects occur in rodents ranged from 0.24 mg/kg-day (Schroeder and others 1968) to 10.9 mg/kg-day (Brown and others 1976) and in birds from 1.9 mg/kg-day (Whitworth and others 1991) to 45.11 mg/kg-day (Camardese and others 1990). In the rodent data set, most adverse effects were systemic and hematological, including decreases in body and kidney weight, and decreases in hemoglobin. For birds, the adverse effects included glycogen depletion and decreases in body weight and liver protein.

5.2.1 Effects of Arsenic on Rodents

In Schroeder and others (1968), sodium arsenate was administered to Long-Evans rats in drinking water from weaning until natural death. At a dose of 0.32 mg/kg-day, no effects were reported on growth rates, survival, blood pressure, tumors or metabolic breakdown products in the blood. This dose was selected as the rodent low TRV. At doses of 0.28 mg/kg-day and 0.24 mg/kg-day, increased cholesterol and decreased glucose levels in the blood were reported. These effects were not considered ecologically relevant because there is no indication that these types of effects alter the life span or reproductive success of wild rodents.

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Schroeder and Mitchener (1971) administered arsenic salts in drinking water to CD mice for three generations. At a dose of 0.01 mg/kg-day, no effects were reported on litter size, pup survival, number of litters, or maternal survival. This was considered for the low TRV, but rejected because reproduction does not appear to be the most sensitive endpoint for rodents exposed to arsenic. The data suggest that reproductive endpoints may be less sensitive than other systemic endpoints for arsenic.

In Schroeder and Balassa (1967), 0.35 mg/kg-day resulted in decreased longevity in laboratory mice administered sodium arsenite in drinking water for three years. This study was not considered appropriate for TRV consideration because it was not applicable to field conditions. The typical life span of most wildlife species of mice is approximately one year. This study showed decreased longevity at three years. For this reason, this study was not considered relevant.

Brown and others (1976) administered sodium arsenate to Sprague-Dawley rats in drinking water for 64 days. A decrease in weight gain and cell respiratory parameters were reported at a dose of 10.9 mg/kg-day. This was the highest adverse effect reported in the data set. In the same study, a dose of 4.7 mg/kg-day resulted in decreased water intake, changes in cellular respiratory parameters, and decreased kidney to body weight ratio. This dose was in the mid-range of systemic effects and was selected as the high TRV.

ARSENIC TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Long-Evan rat	weanling	No effect on growth rates, survival, glycosuria, proteinuria, blood pressure, tumors, heart weight; no effect on serum glucose in females	NEL	weaning-natural death	DW	0.32[1]	Schroeder and others 1968
Long-Evan rat	weanling	Increase in cholesterol levels	EL	weaning-natural death	DW	0.28	Schroeder and others 1968
Long-Evan rat	weanling	Decrease in serum glucose levels	EL	weaning-natural death	DW	0.24	Schroeder and others 1968

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Charles River CD mice	weanling	No effect on maternal deaths, dead litters, young deaths, failures to breed, runts, number of litters, pair age at first litter, interval between litters, male/female pup ratio, or average litter size	NEL	3 generations	DW	0.01	Schroeder and Mitchener 1971
Charles River CD mice	weanling	Decrease in longevity of mice	EL	540 d	DW	0.35	Schroeder and Balassa 1967
Sprague-Dawley rat	adult	Decrease in water intake, kidney weight/body weight ratio, state 3 respiration parameter	EL	6 wk	DW	4.7[2]	Brown and others 1976
Sprague-Dawley rat	adult	Decrease in weight gain, and ADP:O_2 ratio respiratory parameters	LOAEL	6 wk	DW	10.9	Brown and others 1976

Notes:
1 Selected low mammalian TRV = 0.32 mg/kg-day
2 Selected high mammalian TRV = 4.7 mg/kg-day

Highlighted rows	The bases for high and low TRVs
NEL	No effect level
LOAEL	Lowest observed adverse effect level
EL	Effect level
Exposure route	DW = drinking water

5.2.2 Mammalian TRVs for Arsenic

The mammalian low TRV was based on Schroeder and others (1968), who reported no effects on systemic endpoints at a dose of 0.32 mg/kg-day. The doses of 0.28 mg/kg-day and 0.24 mg/kg-day (Schroeder and others 1968) were not considered appropriate for TRVs because the endpoints have limited ecological relevance. The no effect level reported in Schroeder and Mitchener (1971) was rejected because reproduction does not appear to be the most sensitive endpoint for rodents exposed to arsenic. Therefore, 0.32 mg/kg-day was selected as the low TRV.

The high TRV was based on Brown and others (1976). The dose of 4.7 mg/kg-day was in the mid-range of effects in the data set and was below LD_{50}s reported at 8-10 mg/kg-day in ATSDR toxicity profiles (ATSDR 1993b). The effects were systemic and representative of the majority of effects reported in the data set. A dose of 4.7 mg/kg-day was chosen as the high TRV.

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The low TRV should be allometrically converted to account for differences in body size between the test organism (Long-Evans rats) and the receptors species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.32\text{mg/kg-day} (332 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The dose of 4.7 mg/kg-day should be allometrically converted to account for differences in body sizes between the test organism and receptor species. The following allometric equation can be used to arrive at the high TRV for a specific receptor species with the addition of the receptors body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 4.7 \text{ mg/kg-day} (110 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The data set of effects of arsenic on rodents (a) included studies looking at the sensitive life stage of the test organism (1/1); (b) included chronic exposure durations (+c); and (c) included 2 different test species representing 2 different mammalian groups (2/2). The high and low TRV test organisms are in the mammalian group of laboratory rats. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.2.3 Effects of Arsenic on Birds

In Stanley, Jr. and others (1994), 1-year-old mallards were administered sodium arsenate in feed from 4 weeks prior to pairing through multiple hatching cycles. At a dose of 5.5 mg/kg-day no effects were reported on liver, egg, or body weight of ducklings, or on duckling production. In the same study, a dose of 22.01 mg/kg-day caused decreases in liver weight, duckling weight, duckling liver weights, duckling production, and whole egg weight. This dose also caused increased glycogen depletion and an increase in the number of days between pairing and first egg. This was the highest dose causing reproductive effects in the data set, but was in the mid-range of all effects. Stanley, Jr. and others (1994) was the only study in the data set that tested reproductive, systemic, and developmental endpoints, and was of exceptionally high quality. Based on this paper, the dose of 5.5 mg/kg-day was chosen for the low TRV and the dose of 22.01 mg/kg-day was chosen for the high TRV.

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In Camardese and others (1990), mallards ducklings were administered sodium arsenate in feed for 19 weeks. At a dose of 4.02 mg/kg-day, the authors reported changes in specific enzyme activities, and in hepatic, hematological, and neurological molecular parameters. The hematological and enzyme effects were of questionable ecological significance. Enzymatic effects are frequently considered biomarkers of exposure, and may simply indicate healthy responses to chemical exposure. In any case, the parameters measured in this study were not associated with adverse effects or toxicity, and so were not appropriate for deriving TRVs. Also in this study, a dose of 45.11 mg/kg-day resulted in a decrease in growth rate and brain ATP, and increases in SDH activity and plasma glucose. This was the highest dose in the data set.

In Whitworth and others (1991), mallard ducklings were given sodium arsenate in feed for 9 weeks. A dose of 1.9 mg/kg-day resulted in a decrease in time spent bathing. This behavioral study reported effects at the lowest dose in the data set. Because bathing time was not considered ecologically relevant, this paper was not critical for deriving TRVs.

ARSENIC TOXICITY DATA (AVIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Mallard	1 yr	Decrease in liver weight; increase in glycogen depletion, number of days between pairing and first egg; decrease in whole egg weight, duckling body and liver weights at post-hatching, duckling growth rate, and duckling production	LOAEL	4 wk prior to pairing and through multiple hatching cycles	F	22.01[2]	Stanley, Jr. and others 1994
Mallard	1 yr	No effect on liver weight, glycogen depletion, number of days between pairing and first egg, whole egg weight, duckling body and liver weights post-hatching, duckling growth rate, and duckling production	NOAEL	4 wk prior to pairing and through multiple hatching cycles	F	5.5[1]	Stanley, Jr. and others 1994
Mallard	duckling	Decrease in time spent bathing	EL	9 wk	F	1.9	Whitworth and others 1991
Mallard	duckling	Decrease in growth rate, brain ATP, increase in SDH activity, plasma glucose	LOAEL	10 wk	F	45.11	Camardese and others 1990

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Mallard	duckling	Decrease in CK activity; Increase in brain ache	EL	10 wk	F	4.02	Camardese and others 1990
Mallard	duckling	Increase in plasma triglycerides, brain Na+, K+, ATPase, and total ATPase, liver NPSH levels; Decrease in hepatic DRA:RNA ratio levels	EL	10 wk	F	4.02	Camardese and others 1990

Notes:
1 Selected low avian TRV = 5.5 mg/kg-day
2 Selected high avian TRV = 22.01 mg/kg-day
Highlighted rows The bases for high and low TRVs
NOAEL No observed adverse effect level
LOAEL Lowest observed adverse effect level
EL Effect level
Exposure route F = food

5.2.4 Avian TRVs for Arsenic

The low TRV was based on Stanley, Jr. and others (1994), in which a dose of 5.5 mg/kg-day had no effect on reproductive endpoints. This was the only reproductive study in the data set. It was also considered to have greater ecological relevance than the enzymatic and hematological effects reported at 4.02 mg/kg-day and no effect on behavioral endpoints reported at a dose of 1.9 mg/kg-day. The dose of 5.5 mg/kg-day was chosen for the low TRV.

The high TRV was also based on Stanley, Jr. and others (1994). At a dose of 22.01 mg/kg-day reproductive, developmental, and systemic effects were reported. This dose was in the mid-range of effects, looked at several types of endpoints, and was ecologically relevant. Therefore, the dose of 22.01 mg/kg-day was chosen as the high TRV.

The data set of effects of arsenic on birds (a) included studies in which the test organisms were dosed in their sensitive life stage (+S); (b) included chronic exposure durations (+C); and (c) included one test species representing one avian group (1/1). The low and high TRV test organisms are both in the duck avian group. This information should be included in the confidence rating for each of the TRVs as outlined in Section 3.4.

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5.3 TOXICITY REFERENCE VALUES FOR BENZO(A)PYRENE

In a review of the literature on the toxicity of benzo(a)pyrene to rodent and avian test organisms, 6 studies on rodents, but no studies on birds, were considered relevant for deriving TRVs. Because data on the toxicity of benzo(a)pyrene to birds were insufficient, no avian TRVs were derived. The range of adverse effects for rodents extended from 0.11 mg/kg-day (Brune and others 1981) to 160 mg/kg-day (Mackenzie and Angevine 1981). The majority of these effects were reproductive and carcinogenic, including increase in frequency of tumors and decrease in fertility and pup weight.

5.3.1 Effects of Benzo(a)pyrene on Rodents

In Brune and others (1981), laboratory rats were administered benzo(a)pyrene in food throughout their lifetime. At a dose of 0.11 mg/kg-day, no effects were reported on mean survival time or on malignant tumor development. At the same dose, an increase in benign tumors was reported. No increase in benign tumors was observed at a dose of 0.016 mg/kg-day. The dose of 0.016 mg/kg-day was the lowest dose in the data set at which no effects were observed.

In Neal and Rigdon (1967), benzo(a)pyrene was administered in feed to laboratory mice for 110 days. A dose of 1.31 mg/kg-day resulted in no effects on gastric neoplasms (i.e. new and abnormal tissue in or on the stomach) or life span. This dose was chosen as the low TRV.

Rigdon and Neal (1969) administered benzo(a)pyrene in feed to laboratory mice for 80 to 140 days. At a dose of 32.79 mg/kg-day, male and female mice displayed increased pulmonary adenomas (lung tumors). This was the highest dose reflecting carcinogenicity and was in the mid-range of adverse effects in the data set. For these reasons, it was chosen as the high TRV.

In Mackenzie and Angevine (1981), benzo(a)pyrene was administered to laboratory mice by oral gavage on days 7 through 16 of gestation. This study reported the lowest and highest reproductive effect levels, at 10 mg/kg-day and 160 mg/kg-day, respectively. This study was not considered for TRV development because other studies using more ecologically relevant exposure routes than oral gavage were found in the data set.

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BENZO(A)PYRENE TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
CD-1 mice	adult	Decrease in fertility male:female offspring (52 & 65.7), mean litter size of female offspring, testes weight in male offspring, mean pup weight at day 42. Increase atrophic seminiferous tubules, no ovaries or only remnants-hypoplastic with very follicles per corpora lutea	EL	d 7 - 16 of gestation	G	10	Mackenzie and Angevine 1981
CD-1 mice	adult	Decrease % pregnancy maintenance, decrease % viable litters	LOAEL	d 7-16 of gestation	G	160	Mackenzie and Angevine 1981
CFW mice	17-180 d	No occurrences of gastric neoplasms, no change in life span	NOAEL	110 d	F	1.31[1]	Neal and Rigdon 1967
CFW mice	17-180 d	Increase in pulmonary adenoma	EL	80-140 d	F	32.79[2]	Rigdon and Neal 1969
Sprague-Dawley rats	10 wk	No effect in the frequency of malignant tumors or on mean survival time	NEL	lifetime	F	0.11	Brune and others 1981
Sprague-Dawley rats	10 wk	Increase in the frequency of benign tumors	LOAEL	lifetime	F	0.11	Brune and others 1981
Sprague-Dawley rats	10 wk	No effect in frequency of benign tumors	NOAEL	lifetime	F	0.016	Brune and others 1981

Notes:

1 Selected low mammalian TRV = 1.31 mg/kg-day

2 Selected high mammalian TRV = 32.79 mg/kg-day

Highlighted rows	The bases for high and low TRVs
NOAEL	No observed adverse effect level
NEL	No effect level
LOAEL	Lowest observed adverse effect level
EL	Effect level
Exposure route	F = food
	G = gavage

5.3.2 Mammalian TRVs for Benzo(a)pyrene

The low TRV was based on Neal and Rigdon (1967). At a dose of 1.31 mg/kg-day no effects were reported on life span or gastric neoplasms. This study had a chronic duration of up to 180 days.

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The high TRV was based on Rigdon and Neal (1969). At a dose of 32.79 mg/kg-day there was a reported increase in pulmonary adenomas. This was a carcinogenic effect in the mid-range of adverse effects in the data set. This study was chosen over reproductive studies because a more appropriate exposure route was used. Additionally, pulmonary adenomas reduce the efficacy of the lungs, which is considered an ecologically relevant effect.

This dose should be allometrically converted to account for differences in body size between the test organism and the receptor species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 1.31 \text{ mg/kg-day } (30.5 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

This high TRV of 32.79 mg/kg-day should be allometrically converted to account for differences in body sizes between the test organisms and the receptor species. The following allometric equation can be used to arrive at the high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 32.79 \text{ mg/kg-day } (30.5 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The data set of benzo(a)pyrene effects on rodents (a) included exposure to the most sensitive life stage (+S); (b) included chronic exposure durations (+C); and (c) contained 2 different test species representing 2 different mammalian groups (2/2). The low and high TRV test organisms are both in the mammalian group (laboratory mice). This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.4 TOXICITY REFERENCE VALUES FOR BUTYLTINS

In review of the literature on the toxicity of dibutyltin and tributyltin to rodent test organisms, the dibutyltin data set contained only 2 studies, and the tributyltin data set 6 studies, that were considered relevant for deriving TRVs. Therefore, the dibutyltin and tributyltin data sets were combined to derive mammalian butyltin TRVs because the compounds are closely related and have similar modes of action.

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In a review of the literature on the toxicity of tributyltin and dibutyltin to avian test organisms, no studies on dibutyltin contained the kind or quality of information needed to derive TRVs specific to dibutyltin. One high quality study on the reproductive effects of tributyltin to Japanese quail was used to derive avian TRVs for both tributyltin and dibutyltin. Normally, a single study was not considered sufficient to derive TRVs since most TRVs are based on a data set consisting of many studies on a range of toxicological endpoints. In this case, the study was of high quality, tested several doses, and measured ecologically important endpoints on the sensitive life stage of the test organism. The study provided sufficient data to develop TRVs.

5.4.1 Effects of Butyltin on Rodents (Dibutyltin and Tributyltin)

Ema and others (1995) reported that a dose of 10 mg/kg-day of dibutyltin dichloride, administered to Wistar rats by gastric intubation for 2 days, caused a series of adverse reproductive effects. Specifically, decreases in maternal weight gain, live fetuses per litter, and fetal weight, and increases in fetal malformations were reported. This was the lowest adverse effect reported in the dibutyltin (DBT) data set. Also in this study, at a dose of 15 mg/kg-day, increases in litters totally resorbed and fetuses with malformations were reported. This was considered to be in the mid-range of adverse effects below mortality doses and was chosen for the high TRV.

Smialowicz and others (1989) administered bis(tri-n-butyltin)oxide by gavage to Fischer rats for 21 days. At a dose of 2.5 mg/kg-day no effects were reported on thymus to body weight ratio or lymphatic responses. This study, which was used to derive the low TRV, was the lowest no effect dose in the data set and was lower than the reproductive effect dose. At a dose of 20 mg/kg-day a reduction in mixed lymphocyte reaction was reported. A mixed lymphocyte reaction causes a decrease in the activity of a given quantity of a variety of lymphocytes (specialized white blood cells) which may compromise immune response. This dose was in the mid-range of effects for the tributyltin (TBT) data set, and was considered for the high TRV for butyltin, but was rejected because it was too close to a mortality dose. Also in this study, at a dose of 10 mg/kg-day, decreases in spleen to body weight ratio, lympho-proliferative response and lymphocyte activity were reported. This dose was chosen for the high TRV.

Both the low and the high TRVs for butyltin were based on studies using exposure routes not generally considered appropriate for TRV derivation. The combined dibutyltin and tributyltin data sets contained 11 studies. Only three of the studies used oral exposure, and the measured effects in those studies

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(enzyme activity and organ weights) were less ecologically relevant than the endpoints in the gavage studies. Additionally, it was considered preferable to base the TRVs on gavage studies than to derive no TRVs at all.

In Itami and others (1990), Wistar rats were administered tri-n-butyltin chloride by gavage for 9 days. At a dose of 25 mg/kg-day all the fetuses of the test organisms died. This represented the high end of the effects doses, so the high TRV to protect against mortality had to be below this dose. Also in this study, a dose of 15 mg/kg-day caused no increase in mortality.

BUTLYTIN TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Wistar rats	14 wk	Decreased maternal weight gain, increased % postimplantation loss per litter, decreased live fetuses per litter, decreased fetal weight, increased fetal malformations	LOAEL	2 d	GI	10	Ema and others 1995
Wistar rats	14 wk	Increase in litters totally resorbed, fetuses with encephalocele, cleft tongue, omphalocele, defect of mandible, fusion of sternbrae)	LOAEL	2 d	GI	15[1]	Ema and others 1995
Fischer rats	adult	No effect on thymus to body weight ratio, natural killer cell activity, lymphoproliferative response	NOAEL	21 d	G	2.5[2]	Smialowicz and others 1989
Fischer rats	adult	Reduced mixed lymphocyte reaction	LOAEL	21 d	G	20	Smialowicz and others 1989
Fischer rats	adult	Decreased spleen to body weight ratio, decreased lymphoproliferative response	LOAEL	21 d	G	10	Smialowicz and others 1989
Wistar rats	adult	Fetal mortality	LOAEL	9 d	G	25	Itami and others 1990
Wistar rats	adult	No increase in mortality	NOAEL	9 d	G	15	Itami and others 1990

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Notes:

1 Selected high mammalian TRV = 15 mg/kg-day

2 Selected low mammalian TRV; an uncertainty factor of 10 was applied for sub-chronic to chronic conversion resulting in TRV = 0.25 mg/kg-day

Highlighted rows	The bases for high and low TRVs
NOAEL	No observed adverse effect level
LOAEL	Lowest observed adverse effect level
Exposure Route	GI = gastric intubation G = gavage

5.4.2 Mammalian TRVs for Butyltin

The mammalian low TRV for butyltin was based on Smialowicz and others (1989). At a dose of 2.5 mg/kg-day no effects were reported on systemic endpoints. This dose was divided by an uncertainty factor of 10 for a sub-chronic to chronic conversion resulting in a dose of 0.25 mg/kg-day. This was the lowest no effect in the data set for tributyltin (TBT) that was also below the reproductive effects reported in the data set. It was used to derive the low TRV.

The high TRV was based on Ema and others (1995). The dose of 15 mg/kg-day was considered to be in the mid-range of adverse effects below mortality doses at 25 mg/kg-day as reported by Itami and other (1990). This dose had reproductive endpoints.

The low TRV should be allometrically converted to account for differences in body size between the test organism (Fischer rats) and the receptors species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.25 \text{ mg/kg-day } (188 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The dose of 15 mg/kg-day should be allometrically converted to account for differences in body sizes between the test organism (Wistar rats) and receptor species. The following allometric equation can be used to arrive at the high TRV for a specific receptor species with the addition of the receptors body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 15 \text{ mg/kg-day } (241 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

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The data set on the effects of butyltin on rodents (a) included studies on the sensitive life stage of the test organism (+S); (b) did not include chronic exposure durations (−C); and (c) included 5 different test species representing 2 different mammalian groups (5/2). The low and high TRV test organisms were in the mammalian group of laboratory rats. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.4.3 Effects of Butyltin on Birds

In Schlatterer and others (1993), five different laboratories conducted identical studies on Japanese quail. Adult males and females were given bis(tri-n-butyltin)oxide at four dose concentrations in feed for six weeks. Several reproductive parameters of eggs and offspring of the dosed adults were measured. At a dose of 7.34 mg/kg-day, no effects were observed on number of eggs laid per week, eggshell thickness, egg fertility, dead chicks in fertile eggs, or hatched chicks. This was the lowest dose in the study and was the basis for the low TRV. The next dose (18.34 mg/kg-day) resulted in effects on all of these parameters in at least one laboratory. The number of eggs laid per week was reduced; eggshell thickness decreased; egg fertility decreased; the number of dead chicks in fertile eggs increased; and the number of hatched chicks decreased. The next dose (45.85 mg/kg-day) resulted in reduced number of eggs laid per week, reduced egg mass, reduced hatchability, and a reduction in chicks surviving to 14-days. This dose was selected as the high TRV. The highest dose given in the study was 114.64 mg/kg-day. This dose resulted in decreased eggshell strength, reduced hatchling body weights (of those that hatched), and reduced weight of 14 day-old survivors.

BUTLYTIN TOXICITY DATA (AVIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Japanese quail	8-12 wk	No effect on the number of eggs laid per week, eggshell thickness, egg fertility, dead chicks in fertile eggs, hatched chicks	NOAEL	6 wk	F	7.34[1]	Schlatterer and others 1993
Japanese quail	8-12 wk	Decrease in the number of eggs laid per week, egg mass, hatchability, 14 day-old survivors	LOAEL	6 wk	F	45.85[2]	Schlatterer and others 1993
Japanese quail	8-12 wk	Decrease in egg shell strength, hatchling body weight (of hatched groups), weight of 14 day-old survivors	LOAEL	6 wk	F	114.64	Schlatterer and others 1993

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Japanese quail	8-12 wk	Decrease in number of eggs laid per week, eggshell thickness, egg fertility, and hatched chicks; increase in dead chicks in fertile eggs	LOAEL	6 wk	F	18.34	Schlatterer and others 1993

Notes:

1 Selected low avian TRV; an uncertainty factor of 10 was applied for sub-chronic to chronic conversion resulting in TRV = 0.73 mg/kg-day

2 Selected high avian TRV = 45.85 mg/kg-day

Highlighted rows The bases for high and low TRVs

NOAEL No observed adverse effect level

LOAEL Lowest observed adverse effect level

Exposure route F = food

5.4.4 Avian TRVs for Butyltin

The high and low TRVs for both tributyltin and dibutyltin were selected from the single study on tributyltin by Schlatterer and others (1993). The lowest dose given in the study was 7.34 mg/kg-day; this dose was the basis for the low TRV. The dose was divided by an UF of 10 because the exposure duration was sub-chronic. This conversion resulted in a low TRV of 0.73 mg/kg-day.

The high TRV was based on a dose of 45.85 mg/kg-day from the same study (Schlatterer and others 1993). This dose caused adverse reproductive effects and was considered to have an ecologically relevant endpoint that would effect wild avian species population-levels.

The data set on the effects of butyltin on birds (a) contained studies looking at a sensitive life stage of the test organism ($+_S$); (b) did not include chronic exposure durations ($-_C$); and (c) contained one test species representing one avian group (1/1). The low and the high TRV test organisms are both in the avian group of gallinaceous birds. This information should be included in the confidence rating for each of the TRVs as outlined in Section 3.4.

5.5 TOXICITY REFERENCE VALUES FOR CADMIUM

In a review of the literature on the toxicity of cadmium to rodent and avian test organisms, 11 studies on rodents and 12 studies on birds were considered relevant for deriving TRVs. The range of adverse effects for rodents extended from 0.19 mg/kg-day (Valois and Webster 1989) to 110 mg/kg-day (Koller

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and Roan 1977) and for birds from 0.15 mg/kg-day (White and others 1978) to 51.92 mg/kg-day (Di Giulio and Scanlon 1984). For both rodents and birds the majority of adverse effects reported were systemic and reproductive, such as kidney effects, and decreases in body weights and fertility.

5.5.1 Effects of Cadmium on Rodents

Webster (1988) administered cadmium chloride to laboratory mice in drinking water for 8 weeks. No effects were reported on mean fetal weight at a dose of 0.06 mg/kg-day. Decreased mean fetal weight was observed at a dose of 10.31 mg/kg-day. The no effect dose of 0.06 mg/kg-day was chosen for the low TRV because it measured reproductive endpoints that may have population-level effects.

In Valois and Webster (1989), cadmium chloride was administered to laboratory mice in drinking water for 22 weeks. At a dose of 0.19 mg/kg-day, decreases in fluid consumption and body weight were observed. The same dose had no effect on the percentage of choroid epithelial cells with blebs or bald patches. (Choroid epithelial cells are cells that line the spinal column and secrete cerebrospinal fluid.) This dose (0.19 mg/kg-day) was considered for the low TRV, but was rejected because there were lower reproductive no effect levels. In the same study, an increase of blebs and bald patches on the choroid epithelial cells was reported at a dose of 1.90 mg/kg-day.

In Schroeder and Mitchener (1971), cadmium salts were administered to laboratory mice in drinking water for three generations. At a dose of 2.64 mg/kg-day, there was an increase in young deaths and runts in the second and third generations. This dose was chosen for the high TRV because it was a multigenerational study with significant reproductive effects. Additionally, the dose was in the mid-range of other reproductive effects.

In Koller and Roan (1977), a decrease in body weight was reported at a dose of 110 mg/kg-day. This was a 70 day study in which cadmium chloride was administered to Swiss Webster mice in drinking water. This was the highest reported effect in the data set.

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CADMIUM TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
QS mice	8 wk	No effect on mean fetal weight	NOAEL	6 wk + 18 d gestation	DW	0.06[1]	Webster 1988
QS mice	8 wk	Decrease in mean fetal weight	LOAEL	6 wk + 18 d gestation	DW	10.31	Webster 1988
QS mice	6 wk	Decrease in fluid consumption; decrease in body weight	EL	22 wk	DW	0.19	Valois and Webster 1989
QS mice	6 wk	No effect on % of choroid epithelial cells with blebs or bald patches	NOAEL	22 wk	DW	0.19	Valois and Webster 1989
QS mice	6 wk	Increase in % of choroid epithelial cells with blebs and bald patches	LOAEL	22 wk	DW	1.90	Valois and Webster 1989
CD mice	weanling	Increase in young deaths and runts in F_1 and F_2 generations; failure to breed in F_2B generation	EL	multi-generational	DW	2.64[2]	Schroeder and Mitchener 1971
Swiss Webster mice	28 d	Decrease in body weight	LOAEL	70 d	DW	110.00	Koller and Roan 1977

Notes:
1 Selected low mammalian TRV = 0.06 mg/kg-day
2 Selected high mammalian TRV = 2.64 mg/kg-day

Highlighted rows	The bases for high and low TRVs
NOAEL	No observed adverse effect level
NEL	No effect level
LOAEL	Lowest observed adverse effect level
EL	Effect level
Exposure route	DW = drinking water

5.5.2 Mammalian TRVs for Cadmium

The mammalian low TRV was based on Webster (1988) in which 0.06 mg/kg-day had no effect on reproductive parameters. This dose was chosen because the endpoints of the study were reproductive and may have population-level effects.

The high TRV was based on Schroeder and Mitchener (1971), in which a dose of 2.64 mg/kg-day resulted in reduced reproductive capacity. The highest reproductive effect was at a dose of 10.31 mg/kg-day in Webster (1988). Since the lowest effect was reported at 0.19 mg/kg-day, the chosen TRV was in the mid-range of effects.

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The low TRV should be allometrically converted to account for differences in body size between the test organism (QS mice) and the receptor species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.06 \text{ mg/kg-day } (32.2 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The high TRV (2.64 mg/kg-day) should be allometrically converted to account for differences in body size between the test organism and the receptor species. The following allometric equation can be used to arrive at the high TRV for a specific receptor species:

$$\text{High TRV: Dose}_{\text{receptor}} = 2.64 \text{ mg/kg-day } (31.41 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The data set of the effects of cadmium on rodents (a) included studies on the sensitive life stage of the test organism (+s) (b) included chronic exposure durations (+c) and (c) included 2 different test species representing 2 different mammalian groups (2/2) The low and high TRV test organisms are both in the mammalian group of laboratory mice. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.5.3 Effects of Cadmium on Birds

In White and others (1978), cadmium chloride was administered in feed to mallard ducks for 90 days. At a dose of 20.03 mg/kg-day an increase in kidney weight and kidney lesions and a decrease in testes weight were reported. This was the highest reported adverse reproductive effect in the data set.

Cain and others (1983) administered cadmium chloride to mallards in feed for 12 weeks. At a dose of 0.78 mg/kg-day, no effects were observed on hematological or systemic endpoints. At the same dose, kidney degeneration was observed in 4 out of 12 ducklings. This dose was used to derive the low TRV. It was chosen over other doses because the test organism was the mallard, which, based on the cadmium data set, appears to be more sensitive to cadmium toxicity than are other test organisms. Additionally, the endpoint tested in the study was the kidney, which is the target organ of cadmium.

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In Leach and others (1979), a decrease in egg production was reported at a dose of 1.06 mg/kg-day. This study was on white leghorn chickens that had been administered cadmium sulfate in feed for 12 weeks. This study was considered for the low TRV but was not used because chickens appear to be less sensitive than the mallard to the effects of cadmium.

In Richardson and others (1974), cadmium chloride was given to Japanese quail hatchlings in feed for 6 weeks. A dose of 10.43 mg/kg-day resulted in decreases in body weight and testis weight, and altered hematological functions. This dose was chosen for the high TRV because the study tested ecologically significant endpoints and was in the mid-range of reproductive effects.

CADMIUM TOXICITY DATA (AVIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Mallard	1 yr	Increase in kidney weight and kidney lesions; decrease in testes weight	LOAEL	90 d	F	20.03	White and others 1978
Mallard	1 yr	Decrease in testes weight	EL	90 d + 30 d no dose	F	0.15	White and others 1978
Mallard ducklings	1 d	No effect on blood chemistry (packed cell volume, hb, rbc, mean corpuscular hemoglobin count and volume), serum chemistry (total protein, GPT, GOT, LDH, UA, Ca, P); body and liver weight, femur density	NEL	12 wk	F	0.78	Cain and others 1983
Mallard ducklings	1 d	Mild to moderately severe kidney degeneration in four out of 12 ducklings	EL	12 wk	F	0.78	Cain and others 1983
Mallard ducklings	1 d	No degenerative effects in gizzard, proventriculus, intestine, liver, heart, thymus, lung, spleen	NEL	12 wk	F	0.78	Cain and others 1983

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Mallard	11 mos	Decrease in body, liver weights, liver aldolase activity, and plasma T3 concentration; increase in plasma uric acid and adrenal corticosterone	LOAEL	42 d	F	51.92	Di Giulio and Scanlon 1984
Japanese quail	hatchling	Decrease in body and testis weight, hematocrit and hemoglobin; changes in liver trace element stores; histological effects to duodenum, bone marrow, and adrenal; increase in heart weight	EL	6 wk	F	10.43[2]	Richardson and others 1974
White leghorn	8 mos	Decrease in egg production	LOAEL	12 wk	F	1.06	Leach and others 1979
White leghorn	8 mos	No adverse effect on egg production	NOAEL	12 wk	F	0.26	Leach and others 1979

Notes:

1 Selected low avian TRV; an uncertainty factor of 10 was applied for EL to NEL conversion giving a TRV = 0.08 mg/kg-day

2 Selected high avian TRV = 10.43 mg/kg-day

Highlighted row The bases for high and low TRVs

NOAEL No observed adverse effect level

NEL No effect level

LOAEL Lowest observed adverse effect level

EL Effect level

Exposure route F = food

TRV low = 0.7

5.5.4 Avian TRVs for Cadmium

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The low TRV was based on Cain and others (1983) in which kidney degeneration occurred in mallard ducklings at a dose of 0.78 mg/kg-day. The reported dose of 0.78 mg/kg-day was divided by an uncertainty factor of 10 to convert the effect dose to a no effect level equivalent. The resulting avian low TRV is 0.08 mg/kg-day.

The data set of the effects of cadmium on birds (a) included exposure to the most sensitive life stage (+S) (b) addressed chronic exposures (+C) and (c) contained 4 different test species representing 2 different avian groups (4/2). The low TRV test organism is in the Duck avian group and the high TRV

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test organism is in the avian group of gallinaceous birds. This information should be included in the confidence rating for each of the TRVs as outlined in Section 3.4.

5.6 TOXICITY REFERENCE VALUES FOR COBALT

In a review of the literature on the toxicity of cobalt to rodent and avian test organisms, 6 studies of rodents but no studies of birds were considered relevant for deriving TRVs. The rodent data were supplemented by 17 studies from ATSDR toxicity profiles (ATSDR 1992). The range of adverse effects for rodents extended from doses of 12 mg/kg-day (Domingo and others 1985) to 60 mg/kg-day (Anderson and others 1992). The majority of adverse effects for rodents were reproductive, including effects on fertilization and sperm development.

5.6.1 Effects of Cobalt on Rodents

Pedigo and Vernon (1993) exposed mice (strain $B_6C_3F_1$) to cobaltous chloride hexahydrate in drinking water for 10 weeks. At a dose of 59.77 mg/kg-day several effects were reported on reproduction, including decreased number of total and live births, reduced implantation, and reduced fertilization rate. These were considered important reproductive effects, but the doses were at the high end of the range of effects.

In Paternain and Domingo (1988), several doses of cobalt (II) chloride hexahydrate were administered to Sprague-Dawley rats by gavage during gestation days 6-15. At all concentrations, adverse systemic and hematological effects were reported. At a dose of 100 mg/kg-day no effects were observed on either reproductive or other systemic endpoints. This was the highest no effect dose with a reproductive endpoint. This study was not considered in deriving TRVs because gavage was not considered an ecologically relevant exposure route. In general, gavage studies were only considered for TRV derivation if studies in which the test organism was given the chemical in the diet were not available.

Anderson and others (1992) reported decreased testicular size at a dose of 60 mg/kg-day cobaltous chloride hexahydrate. The dose was administered in drinking water to CD-1 mice for 13 weeks. This study reported the highest adverse reproductive effect dose in the data set.

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In Domingo and others (1985), an effect on pup growth was reported at a dose of 12 mg/kg-day cobalt chloride. The receptors were rats and the test duration was from gestation day 14 to lactation day 21. This was the lowest reported effect on reproduction in all the considered data, and was used in deriving the low TRV, even though the dose was administered through gavage.

ATSDR record number 42 reported data from Krasovskii and Fridlyand (1971). In this study rats were exposed to cobalt chloride producing neurotropic effects at a dose of 2.5 mg/kg-day. At a dose of 0.05 mg/kg-day, no effects were observed. The rats were administered this dose by gavage for 7 months. This paper was not considered for deriving TRVs because studies using oral exposure in the diet are preferable to studies using gavage.

Mollenhauer and others (1985) conducted a study on rats administered cobalt chloride for 98 days. In this study testicular degeneration was reported in ATSDR (1992a) at 13.25 mg/kg-day. However, the authors reported the dose as 20 mg/kg-day. The doses reported in the original publication were was chosen for the high TRV because testicular degradation was considered a significant reproductive effect and was in the mid-range of effects.

Record number 46 in ATSDR, Nation and others (1983), reported testicular atrophy in rats exposed to cobalt chloride through feed for 69 days. This effect was at a dose of 20 mg/kg-day, which provided collaborative support for the high TRV.

Pedigo and others (1988) reported testicular degeneration in mice at a dose of 23 mg/kg-day. This reported effect supported the choice of a dose in the 20 mg/kg-day range for the high TRV.

COBALT TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
$B_6C_3F_1$ mice	8-10 wk (m) 6-7 wk (f)	Decrease in total and live births, increase in preimplantation losses, reduced implantations	EL	10 wk	DW	59.77	Pedigo and Vernon 1993
CD-1 mice	adult	Decrease in testicular size, degeneration of seminiferous tubules and vascular congestion	EL	13 wk	DW	60	Anderson and others 1992

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Sprague-Dawley rats	adult	No effect on corpora lutea, number of implantations, live or dead fetuses, resorptions, fetal sex ratio	NEL	gestation 6-15 d	G	100	Paternain and Domingo 1988
Laboratory mice	adult	Increase in testicular degeneration	EL	13 wk	DW	23	Pedigo and others 1988
Laboratory rats	adult	Increase in testicular degeneration	EL	98 d 7 d/wk	F	20[2,3]	Mollenhauer and others 1985
Laboratory rats	adult	Decrease in pup growth	EL	Gd 14 to lact d 21	G	12[1,3]	Domingo and others 1985
Laboratory rats	*adult*	*Increase in neurotrophic effects*	*EL*	*7 mos 6d/wk*	*G*	*2.5*	*Kraasovskii and Fridlyand 1971 (as cited in ATSDR 1992a)*
Laboratory rats	*adult*	*No effect on Neurology*	*NEL*	*7 mos 6 d/wk*	*G*	*0.05*	*Kraasovskii and Fridlyand 1971 (as cited in ATSDR 1992a)*
Laboratory rats	*adult*	*Increase in testicular atrophy*	*EL*	*69 d*	*F*	*20*	*Nation and others 1983 (as cited in ATSDR 1992a)*

Notes:

1 Selected low mammalian TRV; an uncertainty factor of 10 was applied for a EL to NEL conversion giving a TRV = 1.2 mg/kg-day

3 Selected high mammalian TRV = 20 mg/kg-day

Italic Text	Information associated with a study originally presented in ATSDR (1991)
Highlighted rows	The bases for high and low TRVs
NOAEL	No observed adverse effect level
NEL	No effect level
LOAEL	Lowest observed adverse effect level
Exposure route	DW = drinking water G = gavage F = food

5.6.2 Mammalian TRVs for Cobalt

The low TRV was based on Domingo and others (1985). The reported effect occurred at a dose of 12 mg/kg-day. An uncertainty factor of 10 was applied for an effect to no effect conversion. Therefore, the low TRV was 1.2 mg/kg-day. The study was considered important because exposure occurred at a sensitive life stage and it was the lowest reported reproductive effect.

The high TRV for rodents was 20 mg/kg-day based on Mollenhauer and others (1985). Pedigo and others (1988) and Nation and others (1983) also reported testicular damage at similar doses averaging

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around 20 mg/kg-day. This was considered to be in the mid-range of reported effects on ecologically relevant endpoints.

The dose for the low TRV should be allometrically converted to account for differences in body size between the test organism (laboratory rats) and the mammalian receptor species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 1.2 \text{ mg/kg-day } (275 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

This dose should also be allometrically converted to account for differences in body scaling between the test organism and the receptor of concern. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 20 \text{ mg/kg-day } (200 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The total data set of the effects of cobalt on rodents (a) included exposure to the most sensitive life stage (+s); (b) addressed chronic exposures (+c); and (c) contained 2 different test species representing 2 different mammalian groups (2/2). The low and high TRV test organisms are both in the mammalian group of laboratory rats. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.7 TOXICITY REFERENCE VALUES FOR COPPER

In a review of the literature on the toxicity of copper to rodent and avian test organisms, 3 studies on rodents and 7 studies on birds were considered relevant for deriving TRVs. In deriving the rodent TRVs, the data set was supplemented with studies from ATSDR toxicity profiles (ATSDR 1990b). The adverse effect doses for rodents ranged from 1.45 mg/kg-day (Massie and Aiello 1984) to 3,087.06 mg/kg-day (Hebert and others 1993) and for birds from 22.36 mg/kg-day (Bakalli and others 1995a) to 200 mg/kg-day (Shivanandappa and others 1983). In the rodent data set the majority of adverse effects were systemic, such as decreases in body weight, and food and water consumption. For birds, adverse effects included gizzard erosion and decreases in body weight.

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5.7.1 Effects of Copper on Rodents

Pocino and others (1991) administered copper sulfate to laboratory mice in drinking water for 10 weeks. The test organisms were 8 to 10 weeks old at the beginning of the study. A dose of 26.67 mg/kg-day had no effect on food consumption or body weight. In this study, several effects were reported from immune response experiments at doses below the no effect dose of 26.67 mg/kg-day. In the immune response studies the test organisms were injected with antigens and exposed to diseases. Such circumstances do not occur in the field and so were considered of questionable ecological importance. Therefore, the dose at 26.67 mg/kg-day was considered the most appropriate ecologically relevant no effect level in the data set, and was used to derive the low TRV.

In Massie and Aiello (1984), copper gluconate was administered in drinking water to laboratory mice for approximately 140 weeks. A dose of 1.45 mg/kg-day resulted in an increase in mortality. The authors of this study reported low confidence in this effect, stating that little or no change in the rate of senescence occurred below a dose of 36.23 mg/kg-day. Additionally, Massie and Aiello (1984) stated that all survival curves calculated from laboratory studies on mice should be regarded with suspicion. For these reasons, this effect was not considered appropriate for TRV derivation.

Hebert and others (1993) reported decreased water consumption, body weight and survival in six week old laboratory mice administered cupric sulfate in drinking water for 2 weeks. These effects occurred at a dose of 631.58 mg/kg-day. This dose was in the mid-range of effects, and, because the decrease in body weight was considered an ecologically relevant endpoint, was chosen for the high TRV. The corresponding no effect dose for these effects was 210.53 mg/kg-day. This study also reported an effect on feed consumption at a dose of 1,420.81 mg/kg-day. This effect was also considered ecologically relevant but was at the high end of the range of effects. Moreover, it exceeded a dose that caused an increase in mortality.

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COPPER TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
C57BL/6 mice	8-10 wk	No effect on food ingestion rate, body weight, number of cells in the thymus, or mortality	NEL	10 wk	DW	26.67[1]	Pocino and others 1991
C57BL/6	8-10 wk	Decrease in proliferative response to concanavalin (Con A) (in vitro)	LOAEL	8 wk	DW	13.56	Pocino and others 1991
C57BL/6	8-10 wk	Decrease in the PFC response to SRBC	LOAEL	8 wk	DW	13.56	Pocino and others 1991
C57BL/6	8-10 wk	Increase in number of anti-bromelain-treated mouse red blood cells (Br MRBC) PFC	EL	3 wk	DW	7.14	Pocino and others 1991
C57BL/6	8-10 wk	Decrease in magnitude of the DTH response	LOAEL	10 wk	DW	13.33	Pocino and others 1991
$B6C3F_1$ mice	6 wk	Decreased water consumption, body weight, and increased mortality	LOAEL	2 wk	DW	631.58[2]	Hebert and others 1993
$B6C3F_1$ mice	6 wk	No effect on water consumption, body weight, and mortality	NOAEL	2 wk	DW	210.53	Hebert and others 1993
$B6C3F_1$ mice	6 wk	Decrease in feed consumed	LOAEL	2 wk	DW	1,420.81	Hebert and others 1993
$B6C3F_1$ mice	6 wk	Decrease in body weight	LOAEL	2 wk	DW	3,087.06	Hebert and others 1993
C57BL/6J mice	58 d	Decrease in survival curve in mean life span	EL	986 d	DW	36.23	Massie and Aiello 1984
C57BL/6J mice	31 d	Decrease in survival curve in mean life span	EL	986 d	DW	1.45	Massie and Aiello 1984

Notes:

1 Selected mammalian low TRV; an uncertainty factor of 10 was applied for sub-chronic to chronic conversion giving a TRV = 2.67 mg/kg-day

2 Selected high mammalian TRV = 631.58 mg/kg-day

Highlighted rows	The bases for high and low TRVs
NOAEL	No observed adverse effect level
NEL	No effect level
LOAEL	Lowest observed adverse effect level
EL	Effect level
Exposure route	DW = drinking water

5.7.2 Mammalian TRVs for Copper

The low TRV was 2.67 mg/kg-day, based on Pocino and others (1991). This dose was divided by an uncertainty factor of 10 for a sub-chronic to chronic conversion. This study was considered to have the

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lowest ecologically relevant dose that resulted in no effects. The immune response effects occurring at doses below the 26.67 mg/kg-day were not considered for the low TRV because the ecological relevance of these effects was minimal.

The high TRV was 631.58 mg/kg-day from Hebert and others (1993). This was in the mid-range of effects and was an ecologically relevant study. Since there was also a reported increase in mortality at this same dose, any higher TRV was unacceptable.

The low TRV dose should be allometrically converted to account for difference in body size between the test organism (laboratory mice) and the receptor species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 2.67 \text{ mg/kg-day } (30 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The high TRV should be allometrically converted to account for size differences between the test organisms and the receptor species. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 631.58 \text{ mg/kg-day } (24.7 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The data set of the effects of copper on rodents (a) did not include exposure to the most sensitive life stage (–s); (b) included chronic exposures (+c); and (c) contained 2 different test species representing 2 different mammalian groups (2/2). The low and high TRV test organisms are both in the mammalian group of laboratory mice. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.7.3 Copper Effects on Birds

In Norvell and others (1975), copper sulfate was administered to broiler chicks for 8 weeks. The chickens were dosed in feed starting at the age of one day. At a dose of 22.99 mg/kg-day, no effects were observed on weight gain. A decrease in weight gain was reported at a dose of 45.97 mg/kg-day. The

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dose at 22.99 mg/kg-day was the lowest ecologically significant no effect dose and was administered to the sensitive life stage of the test organism; thus, it was used in deriving the low TRV.

Bakalli and others (1995a) administered cupric sulfate pentahydrate in food to one-day-old broiler cockerels for 42 days. This study reported increased body weights and decreased total cholesterol at a dose of 22.36 mg/kg-day. Because this was a breeder experiment designed to investigate methods for raising low-cholesterol, high-weight chickens, the effects at dose 22.36 mg/kg-day were not considered for TRV development.

In Jensen and Maurice (1978), cobb broiler chicks were administered daily doses of cupric sulfate pentahydrate in feed for 4 weeks. A dose of 26.13 mg/kg-day caused a decrease in body weight, but caused no effect on the gizzard or feed:weight gain ratio. At a dose of 52.26 mg/kg-day gizzard erosion was reported. This dose was chosen for the high TRV because gizzard erosion affects feed consumption; this dose was in the mid-range of effects.

In Shivanandappa and others (1983), white leghorn chickens were exposed to a single dose of copper in gelatin capsules. At a dose of 200 mg/kg, reproductive effects occurred. An LD_{50} (a dose at which mortality occurs in 50 percent of the test organisms) was also reported at a dose of 693 mg/kg-day. This study provided the only reproductive effect in the data set. However, this dose of 200 mg/kg-day was above a dose from another study that increased mortality. It was not considered for deriving a high TRV.

In Van Vleet and others (1981), a dose of 149.16 mg/kg-day caused an increase in mortality. This study exposed hatchling white pekin ducks to copper in feed for 15 days. The selected high TRV was below this dose.

COPPER TOXICITY DATA (AVIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Broiler cockerels	1 d	Increase in body weight gain. Decrease in feed conversion, in total cholesterol and breast muscle cholesterol	EL	42 d	F	22.36	Bakalli and others 1995a
Cobb broiler	chicks	Decrease in body weight	EL	4 wk	F	26.13	Jensen and Maurice 1978

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Cobb broiler	chicks	No effect on gizzard erosion and feed to gain ratio	NOAEL	4 wk	F	26.13	Jensen and Maurice 1978
Cobb broiler	chicks	Increase in gizzard erosion and feed to gain ratio, increase in relative gizzard and proventriculus weight	NEL	4 wk	F	52.26[2]	Jensen and Maurice 1978
Broiler	1 d	Decrease in weight gain	LOAEL	8 wk	F	45.97	Norvell and others 1975
Broiler	1 d	No effect on weight gain	NOAEL	8 wk	F	22.99[1]	Norvell and others 1975
White Pekin ducks	hatchlings	Increase in mortality, and necrosis of gizzard, intestine, skeletal muscles and myocardium, decrease in blood glutathione peroxidase activity	EL	15 d	F	149.16	Van Vleet and others 1981
Single comb white leghorn chickens	25 wk	Mortality	LD50	single-dose	GC	693	Shivanandappa and others 1983
Single comb white leghorn chickens	25 wk	Dose-related atrophy and spermatogenetic arrest of testes and accumulation of dense lipid globules in interstitial cells and seminiferous tubules, and hypertrophy of liver (not statistically tested)	EL	single-dose	GC	200	Shivanandappa and others 1983

Notes:

1 Selected low avian dose; an uncertainty factor of 10 was applied for sub-chronic to chronic conversion giving a TRV = 2.3 mg/kg-day

2 Selected high avian TRV = 52.26 mg/kg-day

Highlighted row — The bases for high and low TRVs
NOAEL — No observed adverse effect level
NEL — No effect level
LOAEL — Lowest observed adverse effect level
EL — Effect level
LD50 — Dose resulting in 50% mortality
Exposure route: F = food; GC = gelatin capsule

5.7.4 Avian TRVs for Copper

The avian low TRV was based on a dose of 22.99 mg/kg-day reported in Norvell and others (1975). The TRV was divided by an uncertainty factor of 10 for a sub-chronic to chronic conversion, resulting in a low TRV of 2.3 mg/kg-day. The dose of 22.36 mg/kg-day in Bakalli and others (1995a) was not

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considered appropriate for deriving a low TRV because effects at this dose were not adverse. The TRV of 2.3 mg/kg-day is above nutrient levels reported for quails (1.1 mg/kg-day).

The data set of the effects of copper on birds (a) included exposure to the most sensitive life stage (+s); (b) did not address chronic exposures (–c); and (c) contained 3 different test species representing 2 different avian groups (3/2). The low and high TRV test organisms are both in the avian group of gallinaceous birds. This information should be included in the confidence rating for each of the TRVs as outlined in Section 3.4.

5.8 TOXICITY REFERENCE VALUES FOR DICHLORODIPHENYLTRICHLOROETHANE (DDT) AND MERCURY

As part of the Great Lakes Water Quality Initiative (EPA 1995a), the EPA developed wildlife criteria values for DDT (and its metabolites) and mercury analogous to low TRVs. The Great Lakes documents are well-respected and considered to be of high quality. In fact, the Navy's approach to deriving TRVs was modeled, in part, after the methods employed by the EPA in establishing wildlife criteria values. These methods included review of the primary literature, calculation of doses, and application of uncertainty factors in order to arrive at a dose-based TRV in mg/kg-day. In order to avoid a duplication of effort, the Great Lakes wildlife values were used in lieu of full TRV derivations for DDT and mercury. EPA did not, however, develop low and high wildlife criteria. The single value developed by EPA is equivalent to the Navy's low TRV. Thus, the low TRVs for DDT (and metabolites) and mercury were based on EPA's Great Lakes Water Quality Initiative wildlife criteria for total DDT and for mercury (EPA 1995a). The rodent and avian high TRVs for DDT were selected from the data presented in summary tables 1-2 and 1-6, respectively, in the Great Lakes document (EPA 1995a). The rodent and avian high TRVs for mercury were selected from data presented in tables 2-2 and 2-6, respectively, in the Great Lakes document (EPA 1995a). These tables present a range of doses and effects. Mammalian and avian TRVs for mercury were based on studies using organic mercury. Since the entire data set used to develop the Great Lakes wildlife criteria was not presented in the Great Lakes documents, confidence ratings were not applied to TRVs derived from the Great Lakes documents.

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5.8.1 TRVs for DDT and Metabolites

This section contains mammalian and avian TRVs for DDT and its metabolites. Section 5.8.2 presents TRVs for methylmercury.

5.8.1.1 Mammalian TRVs

The mammalian TRVs for DDT, DDD and DDE were derived based on EPA's wildlife criterion for mammals. In the Great Lakes effort, the EPA reviewed toxicological data on DDT and its metabolites from the primary literature on rodents, monkeys, and minks. The EPA based its criterion on a NOAEL for reproductive effects in rats exposed at 0.8 mg/kg-day for 2 years (Fitzhugh 1948, as cited in EPA 1995a). They applied an interspecies uncertainty factor (UF) of 10 in order to extrapolate from the rat to the mink and otter, which were of primary concern in the Great Lakes region. The unadjusted dose of 0.8 mg/kg-day was selected as the low TRV.

The high TRV was based on a LOAEL of 16 mg/kg-day from Clement and Okey (1974 as cited in EPA 1995a) in which adverse effects on offspring growth in Wistar rats were observed after oral exposure to DDT for 6 months.

The unadjusted dose of 0.8 mg/kg-day from Fitzhugh (1948, as cited in EPA 1995a) was used as the low TRV. This dose should be allometrically converted to account for differences between the body weight of the test organism and the mammalian receptor species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.8 \text{ mg/kg-day } (320 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

This dose should also be allometrically converted to account for differences in body weight between the test organisms and receptor species. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 16 \text{ mg/kg-day } (320 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

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5.8.1.2 Avian TRVs

The avian TRVs for DDT, DDD and DDE were derived based on EPA's wildlife criterion for birds. In the Great Lakes documents, the EPA reviewed toxicological data on DDT and its metabolites from the primary literature on robins, clapper rails, chickens, pheasants, quail, kestrels, eagles, pelicans, and mallards to derive criteria for the kingfisher, herring gull, and bald eagle, which were the receptors of concern in the Great Lakes Area. The EPA based its criterion on a LOAEL for reproductive effects in pelicans exposed at 0.027 mg/kg-day (Anderson and others 1975 and 1977, as cited in EPA 1995b). They applied an UF of 3 to convert from a LOAEL to a NOAEL.

The high TRV was selected from a subset of the studies reviewed by the EPA. Heath and others (1969, as cited in EPA 1995a) reported reproductive LOAELs for DDT and DDE in a two year study on mallards. Since the study reported LOAELs for both DDT (1.5 mg/kg-day) and DDE (0.60 mg/kg-day), both LOAELs were selected as high TRVs.

5.8.2 TRVs for Mercury

The following sections describe the process for selection of TRVs for mercury using the Great Lakes documents. Both mammalian and avian TRVs are based on studies using methylmercury.

5.8.2.1 Mammalian TRVs

The rodent TRVs for methylmercury were derived based on EPA's wildlife criterion for mammals. In the Great Lakes documents, the EPA reviewed toxicological data on mercury from the primary literature on deer, seals, mink, cats, and rodents in order to derive a criterion for the mink and otter, which were the receptors of concern in the Great Lakes area. The EPA based its TRV on a NOAEL for anorexia, ataxia, and death in minks exposed at 0.16 mg/kg-day (Wobeser and others 1976, as cited in EPA 1995a). This dose was also a LOAEL for effects on the nervous system. The report that the nervous system effects were not associated with clinical evidence of toxicity but argued that had the experiment run longer, clinical signs of toxicity may have developed (EPA 1995a). Because of the uncertainty in these findings, the low and high TRVs for larger mammals were based on the LOAEL of 0.27 mg/kg-day for anorexia, ataxia, and death that corresponded to the NOAEL (0.16 mg/kg-day) for these effects (Wobeser and others 1976, as cited in EPA 1995a). An uncertainty factor of 10 was applied to this dose to convert the LOAEL to a no effect level equivalent resulting in a low TRV of 0.027 mg/kg-day for larger mammals.

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The low TRV (0.027 mg/kg-day) should be allometrically converted to account for differences in body size between the test organisms and the receptor species of concern. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.027 \text{ mg/kg-day } (800 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The unadjusted dose of 0.27 mg/kg-day was selected as the high TRV. This dose should be allometrically converted to account for differences in body size between the test organisms and the receptor species of concern. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 0.27 \text{ mg/kg-day } (800 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The EPA based its wildlife criterion on a mink study because the mink was a receptor of concern in the Great Lakes region. However, in the data summarized by the EPA, rats appeared to be less sensitive than mink to the effects of mercury. In order to avoid choosing a TRV that was too conservative for rodents, the studies on rats were used in place of the mink study selected by the EPA for the TRVs for small mammals. Khera and Tabacova (1973) (as cited in EPA 1995a) reported no adverse reproductive or developmental effects in rats exposed to 0.25 mg/kg-day of methylmercury for 122 days. This chronic NOAEL was selected as the low TRV for rodents.

The low TRV (0.25 mg/kg-day) should be allometrically converted to account for differences in body size between the test organisms and the receptor species of concern. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.25 \text{ mg/kg-day } (187.5 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The high TRV was based on Fuyuta and others (1978, as cited in EPA 1995a). In this study, developmental effects were observed in the offspring of rats given 4.0 mg/kg-day of methylmercury in feed.

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This dose (4.0 mg/kg-day) should be allometrically converted to account for differences in body size between test organisms and small mammal receptor species of concern. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{receptor} = 4.0 \text{ mg/kg-day } (428 \text{ g/Body Weight}_{receptor})^{1/4}$$

5.8.2.2 Avian TRVs

The avian TRVs for mercury were derived based on EPA's wildlife criterion for birds. In the Great Lakes documents, the EPA reviewed toxicological data on mercury from the primary literature on quail, ducks, pheasants, sparrows, chukars, doves, chickens, partridges, hawks, and finches to derive a criterion for the kingfisher, herring gull, and bald eagle, which were the receptors of concern. EPA based its wildlife criterion on a LOAEL for reproductive effects in mallards exposed at 0.078 mg/kg-day (Heinz 1974, 1975, 1976, and 1979, as cited in EPA 1995a). EPA applied an UF of 2 to convert from a LOAEL to a NOAEL. The adjusted dose (0.039 mg/kg-day) was used as the low TRV. A dose of 0.18 mg/kg-day from a 1.5 year mallard study (Heinz and Locke 1976) was selected as the high TRV.

5.9 TOXICITY REFERENCE VALUES FOR HEPTACHLOR

In a review of the literature on the toxicity of heptachlor to rodent and avian test organisms, 4 studies on rodents and no studies on birds were considered relevant for deriving TRVs. The adverse effects levels for rodents ranged from 1.29 mg/kg-day (Shain and others 1977) to 60 mg/kg-day (Krampi 1971). In the rodent data set considered, the effects reported were mostly reproductive and systemic, such as reduction in pup weights and reduced body weight.

5.9.1 Effects of Heptachlor on Rodents

Shain and others (1977) administered heptachlor in food to Sprague-Dawley rats for 90 days. At a dose of 1.29 mg/kg-day a reduction in weekly weight gain and adverse effects on the prostate of male rats were reported. This dose was used to derive the low TRV because it was the lowest effect level with an ecologically relevant endpoint.

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Narotsky and others (1995) conducted a study on the effects of heptachlor on Fischer rats resulting from exposure of pregnant females by gavage during gestation days 6 through 15. At a dose of 6.8 mg/kg-day a reduction in pup weight was reported. This dose was in the mid-range of adverse effects. Although the rats were dosed using gavage, the study was considered suitable for TRV derivation because the effects were observed in the pups, which were exposed in utero. The exposure to the pups was considered ecologically relevant, and the dose of 6.8 mg/kg-day was chosen for the high TRV.

Krampi (1971) administered a single dose of heptachlor by gavage to Wistar rats. At a dose of 60 mg/kg-day systemic adverse effects were reported. This study was not considered appropriate as the basis for the TRV because the single exposure dose was acute; therefore, the study was considered to be of low quality for deriving TRVs. This was the highest effect level reported in the data set and represented the extreme high end of adverse effects.

HEPTACHLOR TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Sprague-Dawley rats	76 or 91 d	Inhibition of 5alpha-DHT binding to ventral prostrate androgen receptors	EL	90 d	F	1.29[1]	Shain and others 1977
Sprague-Dawley rats	76 or 91 d	Decrease in weekly weight gain	EL	90 d	F	1.29[1]	Shain and others 1977
Sprague-Dawley rats	76 or 91 d	Decrease in total androgen receptor content in ventral prostate, available ventral prostrate cytoplasmic androgen receptor sites, and ventral prostrate protein and cell number per gram prostrate	EL	90 d	F	1.29[1]	Shain and others 1977
Fischer-344 rats	90 d	Decrease in pup weights	LOAEL	gestation d 6-15	G	6.8[2]	Narotsky and others 1995
Wistar rats	NG	Increase in activity of ALD and GPT in liver at 2 hours after single dose, then slight decrease, and below normal at 72 hours; increase in serum ALD and GPT activities until a maximum at 72 hours	EL	1 dose	G	60	Krampi 1971

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Notes:

1 Selected low mammalian TRV; uncertainty factor of 10 was applied for EL to NEL conversion giving a TRV = 1.29 mg/kg-day

2 Selected high mammalian TRV = 6.8 mg/kg-day

Highlighted rows	The bases for high and low TRVs
NEL	No effect level
LOAEL	Lowest observed adverse effect level
EL	Effect level
NG	Not given
Exposure route	F = food
	G = gavage

5.9.2 Mammalian TRVs for Heptachlor

The low TRV was based on Shain and others (1977). At a dose of 1.29 mg/kg-day adverse systemic and reproductive effects were reported. This dose was divided by an uncertainty factor of 10 for a effect level to no effect level conversion, resulting in a low TRV of 0.13 mg/kg-day. This study not only had a reproductive endpoint but also used a chronic exposure on a sensitive endpoint.

The high TRV was based on Narotsky and others (1995) at a dose of 6.8 mg/kg-day. This was an ecologically relevant dose in which a decrease in pup weight was reported. This dose was in the mid-range of effects with reproductive endpoints and therefore was an appropriate choice for the high TRV.

The low TRV should be allometrically converted to account for differences in body size between the test organism (laboratory rats) and the receptors species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.13 \text{ mg/kg-day} (100 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The high TRV (6.8 mg/kg-day) should be allometrically converted to account for body scaling differences between the test organism (Fischer rats) and the mammalian receptor species of concern. The following allometric equation as outlined in Section 3.4 can be used to arrive at a high TRV for a specific receptor species with the addition of the body weight in grams of the receptor:

$$\text{High TRV: Dose}_{\text{receptor}} = 6.8 \text{ mg/kg-day} (204 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

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The data set of the effects of heptachlor on rodents (a) included studies on the sensitive life stage of the test organism ($+_S$); (b) included chronic exposure duration ($+_C$); and (c) included 4 different test organisms representing 2 different mammalian groups. The low and high TRV test organisms were from the Laboratory Rat mammalian group. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.10 TOXICITY REFERENCE VALUES FOR LEAD

In review of the literature on the toxicity of lead to rodent and avian test organisms, 15 studies on rodents and 27 studies on birds were considered relevant for deriving TRVs. In deriving TRVs for mammals, the data set was supplemented with data from the ATSDR toxicity profiles (ATSDR 1993f). The adverse effects on rodents ranged from 4.62 mg/kg-day (Schroeder and Mitchener 1971) to 2,237.96 mg/kg-day (Ogilvie 1977), and for birds from 0.10 mg/kg-day (Bakalli and others 1995b) to 957.32 mg/kg-day (Donaldson 1986). In the data considered for deriving TRVs the effects reported for rodents were mostly reproductive and behavioral, such as increases in sterility, decreases in litter size, and failure in maze tests. For birds, the effects were systemic and reproductive, including decreases in egg production, body weight, and testes weight.

5.10.1 Effects of Lead on Rodents

In a multigenerational study by Draski and others (1989) laboratory mice were given lead acetate in drinking water. No effects on pup weight at birth, righting reflex, or eye-opening were reported at a dose of 0.88 mg/kg-day. This was the lowest reported no effect level for laboratory mice in the data set. In the same study, a dose of 14.6 mg/kg-day caused a decrease in pup weight at birth and reduced performance in behavioral tests.

Donovick and Burright (1986) exposed adult laboratory mice to 1.03 mg/kg-day of lead acetate in drinking water for 27 days. At this dose, no effects were observed on wheel running activity or body weight. This study was representative of the behavioral tests conducted on rodents in lead toxicity experiments. These studies are often conducted to characterize hyperactivity caused by lead poisoning in humans; wheel running activity is not considered as ecologically relevant as reproductive effects.

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In ATSDR study number 58A (ATSDR 1993f), Krasovskii and others (1979) administered lead acetate in drinking water to white rats for 6 to 12 months. Reproductive, hematological and neurological effects were observed at a dose of 0.01 mg/kg-day. No effects were reported at a dose of 0.0015 mg/kg day. This study contained the lowest no effect level in the data set, and was chosen for deriving the low TRV. Additionally, the effects reported in this study were considered to be ecologically important.

In ATSDR record number 67, Azar and others (1973) administered lead acetate in feed to laboratory rats at several concentrations. At a daily dose of 3.1 mg/kg-day, D-aminolevulinic acid dehydrase (ALAD) activity decreased. Measurements of ALAD, a specific enzyme, are typically used as biomarkers to indicate exposure to lead, but ALAD activity has not been correlated with adverse effects. No effects on ALAD activity were reported at a dose of 0.9 mg/kg-day. Because changes in ALAD activity are not considered ecologically relevant effects, this paper was not used for TRV derivation.

In ATSDR record number 56, Hilderbrand and others (1973) administered lead acetate by gavage to laboratory rats for 30 days. At the high dose, impotence in males and persistent estrous in females was reported. At the low dose of 0.013 mg/kg-day, prostate weight in males increased and estrus cycles in females became irregular. This study was not considered for low TRV development because it did not include doses at which no effects occurred. Also, gavage is not representative of field exposure.
In ATSDR record number 59, Chowdhury and others (1984) exposed laboratory rats to lead acetate in drinking water for 60 days. At a dose of 45 mg/kg-day, testis weight and spermatogenesis decreased. At 22 mg/kg-day, no effects were observed. This study was considered for the high TRV because of the ecologically important effects, but was rejected because the doses were at the low end of the range of effects.

In Wise (1981), lead acetate was administered in food to female laboratory mice for eight days. A dose of 240.64 mg/kg-day caused a decrease in body and organ weights. This dose was in the middle of the range of reported effects and was chosen as the basis for the high TRV.

In a study by Rasile and others (1995), lead acetate was administered to laboratory mice in drinking water. Adverse reproductive effects were observed at a dose of 680.56 mg/kg-day. This was a three-generation study, in which the daily dose caused an increase in sterility and mortality. This was considered for the high TRV, but there were many relevant reproductive and systemic effects below this dose, which put it at the high end of the range of effects. Lead acetate was administered to laboratory

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mice in feed for 15 weeks in a study by Morrisey and others (1989). A dose of 1,000 mg/kg-day caused a decrease in the average number of litters and a decrease in live pups per mated pair. This study was the highest reported dose for reproductive effects in the data set.

LEAD TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Binghamton HET stock mice	adult	Increased sterility and mortality in the F_1 and F_2 generations. Decrease in body wt., floating ability, litter viability; increase in latency to eye-opening with age and generation	LOAEL	multi-generational	DW	680.56	Rasile 1995
Binghamton HET stock mice	adult	No effect on litter size, sterility or mortality in the F_0 generation. No effect on return to home nest, jumps, holes poked, swim tests, assisted standups.	NOAEL	multi-generational	DW	680.56	Rasile 1995
Binghamton HET stock mice	adult	No effect on pup weight at birth, righting reflex, eye-opening.	NEL	multi-generational	DW	0.88	Draski and others 1989
Binghamton HET stock mice	adult	Decrease in square crossing. Decrease body weight for postnatally exposed pups. Increased latency to return home, and other behavioral tests.	EL	multi-generational	DW	14.60	Draski and others 1989
Charles Rivers CD mice	weaning	Increase in young deaths and number of runts	EL	multi-generational	DW	4.62	Schroeder and Mitchener 1971
Charles Rivers CD mice	weaning	No effects on maternal deaths; dead litters; failures to breed; number of mice; number of litters; pair age at first litter; intervals between litters; average litter size; male/female ratio	NEL	24 wk	DW	4.62	Schroeder and Mitchener 1971
MF 1 mice	not given	Decrease in body weight, liver weight, and kidney weight	EL	8 d	F	240.64	Wise 1981

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Binghamton HET stock mice	365, 220, 75 d	No effect on wheel running or body wt. before, during, or after food deprivation.	NEL	27 d	DW	1.03	Donovick and others 1986
CD-1 mice	adult	Decrease in mean number of litters/pair and mean number of live pups/pair	LOAEL	15 wk	F	1000	Morrissey and others 1989
CD-1 mice	adult	No effect on mean number of litters/pair or number of live pups/pair	NOAEL	15 wk	F	670	Morrissey and others 1989
CF-1 mice	NG	Decreases in Y-maze swimming time and increases in errors	EL	20 d	DW	2237.96	Ogilvie 1977
White rats	*adult*	*Adverse effects on reproductive, hematological and neurological systems*	*EL*	*6-12 mos*	*DW*	*0.01*	*Krasovskii and others 1979 (in ATSDR 1993f)*
White rats	*adult*	*No effects on reproductive, hematological and neurological systems*	*NEL*	*6-12 mos*	*DW*	*0.0015*	*Krasovskii and others 1979 (in ATSDR 1993f)*
Laboratory rats	*adult*	*Decreased ALAD activity*	*EL*	*2 years*	*F*	*3*	*Azar and others 1973 (in ATSDR 1993f)*
Laboratory rats	*adult*	*No effects on ALAD activity*	*NEL*	*2 years*	*F*	*0.9*	*Azar and others 1973 (in ATSDR 1993f)*
Sessco rats	*adult*	*Increased impotence and prostate weight; ovarian cysts and persistent aginal estrous*	*EL*	*30 d*	*G*	*0.26*	*Hilderbrand and others 1973 (in ATSDR 1993f)*
Sessco rats	*adult*	*Increased prostate weight in males and irregular estrous cycle in females*	*EL*	*30 d*	*G*	*0.013*	*Hilderbrand and others 1973 (in ATSDR 1993f)*
Albino rats	*adult*	*Decreased testis weight and spermatogenesis*	*EL*	*60 d*	*DW*	*45*	*Chowdhury and others 1984 (in ATSDR 1993f)*
Albino rats	*adult*	*No effects on testis weight and spermatogenesis*	*NEL*	*60 d*	*DW*	*22*	*Chowdhury and others 1984 (in ATSDR 1993f)*

Notes:

1 Selected low mammalian TRV = 0.0015 mg/kg-day

2 Selected high mammalian TRV = 240.64 mg/kg-day

Italic Text Information associated with a study presented in ATSDR

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Highlighted rows	The bases for high and low TRVs
NOAEL	No observed adverse effect level
NEL	No effect level
LOAEL	Lowest observed adverse effect level
EL	Effect level
Exposure route:	DW = drinking water, F = food, G = gavage

5.10.2 Mammalian TRVs for Lead

The low TRV for rodents was based on Krasovskii and others (1979). The dose of 0.0015 mg/kg-day was the lowest no effect in the data set. Since reproductive effects were reported at 0.01 mg/kg-day (Krasovskii and others 1979) and 0.013 mg/kg-day (Hildebrand and others 1973), a lower dose was selected as the low TRV.

The high TRV was based on Wise (1981). The dose of 240.64 mg/kg-day was in the mid-range of effects in the data set. The dose of 680.56 mg/kg-day was not chosen because there were many relevant adverse effects at lower doses.

The dose should be allometrically converted to account for differences in body size between the test organism (white rats) and the receptor species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.0015 \text{ mg/kg-day } (208 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The dose of 240.65 mg/kg-day should be allometrically converted to account for differences in body scaling between the test organism and the receptor species of concern. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 240.65 \text{ mg/kg-day } (18.7 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The data set of the effects of lead on rodents (a) included exposure to the most sensitive life stage (+s); (b) included chronic exposures (+c); and (c) contained 2 different test species representing 2 different mammalian groups (2/2). The low TRV test organism is in the mammalian group of laboratory rats and

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the high TRV test organism is in the mammalian group of laboratory mice. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.10.3 Effects of Lead on Birds

In Edens and Garlich (1983), several concentrations of lead acetate were administered in feed to both chickens and Japanese quail for five weeks. At a dose of 0.13 mg/kg-day, no effects were reported on egg production or total plasma calcium. At a dose of 1.29 mg/kg-day, adverse effects were reported on egg production and total plasma calcium in Japanese quail. In the same study, lead acetate was administered to adult chickens for six weeks. A dose of 8.75 mg/kg-day decreased egg production. This dose was used to derive the high TRV because it was an ecologically relevant reproductive effect in the mid-range of effects.

Edens and others (1976) fed Japanese quail hatchlings lead acetate in feed for 12 weeks. Adverse effects on egg production and testicular weight were observed at a dose of 0.14 mg/kg-day. This was an important reproductive effect and was selected as the low TRV.

In Bakalli and others (1995b), a dose of 0.10 mg/kg-day in feed caused a decrease in body weight. A dose of 0.05 mg/kg-day did not effect body weight. In this study lead acetate and lead sulfate were administered to hatchling chickens for 42 days. At a dose of 0.10 mg/kg-day, a decrease in ALAD activity was also reported. This effect was not considered in TRV development because ALAD activity is a biomarker that has not been correlated to adverse effects.

Morgan and others (1975) administered lead acetate in feed to Japanese quail hatchlings for 5 weeks. A dose of 90.94 mg/kg-day caused a decrease in growth, hemoglobin, adrenal weights, and testes weights. This was among the highest reproductive adverse effects in the data set.

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LEAD TOXICITY DATA (AVIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Japanese quail	0-12 wk	Decrease in females egg production and plasma calcium. Decrease in males testicular and liver weights	EL	12 wk	F	0.14[1]	Edens and others 1976
Japanese quail	6 wk	Decrease in egg production and in plasma total calcium	LOAEL	5 wk	F	1.29	Edens and Garlich 1983
Japanese quail	6 wk	No effect in egg production or plasma total calcium	NOAEL	5 wk	F	0.13	Edens and Garlich 1983
Chicken	adult	Decrease in egg production	EL	10 wk dosed, 8 wk undosed	F	8.75[2]	Edens and Garlich 1983 EXP. 3
Japanese quail	hatchling	Decrease in growth, hemoglobin, adrenal weight and testes weight	LOAEL	5 wk	F	90.94	Morgan and others 1975
Chicken	hatchling	Decrease in body weight	LOAEL	42 d	F	0.10	Bakalli and others 1995b
Chicken	hatchling	No effect on body weight	NOAEL	42 d	F	0.05	Bakalli and others 1995b
Chicken	hatchling	Decrease in ALAD	EL	42 d	F	0.10	Bakalli and others 1995b
Chicken	1 d	Decrease in body weight gain	EL	19 d	F	957.32	Donaldson 1986

Notes:

1 Selected low avian TRV; an uncertainty factor of 10 was applied for EL to NEL conversion giving a TRV = 0.014 mg/kg-day

2 Selected high avian TRV = 8.75 mg/kg-day

Highlighted rows — The bases for high and low TRVs
NOAEL — No observed adverse effect level
NEL — No effect level
LOAEL — Lowest observed adverse effect level
EL — Effect level
Exposure route: F = food

5.10.4 Avian TRVs for Lead

The low TRV was based on a dose of 0.14 mg/kg-day in Edens and others (1976). The dose was adjusted by an UF of 10 to convert the effect level to a no effect level equivalent, resulting in an avian low TRV of 0.014 mg/kg-day.

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The high TRV for birds was 8.75 mg/kg-day based on Edens and Garlich (1983) in which a decrease in egg production was observed. The high TRV was based on an ecologically significant effect and was in the mid-range of adverse reproductive effects.

The data set of the effects of lead on birds (a) included exposure to the most sensitive life stage (+s); (b) addressed chronic exposures (+c); and (c) contained 8 different test species representing 4 different groups (8/4). The low and high TRV test organisms are both in the avian group of gallinaceous birds. This information should be included in the confidence rating for the TRVs as outlined in Section 3.4.

5.11 TOXICITY REFERENCE VALUES FOR LINDANE

In review of the literature on the toxicity of lindane to rodent and avian test organisms, 21 studies on rodents but no studies on birds were considered relevant for deriving TRVs. The doses at which adverse effects occurred for rodents ranged from 0.05 mg/kg-day (Naishtein and Leibovich 1971) to 104.55 mg/kg-day (Nigam and others 1979). The majority of adverse effect in the rodent data set were reproductive, including effects such as increased pup mortality, decreased implantation of the fetus, and reduced ovary weight.

5.11.1 Effects of Lindane on Rodents

Naishtein and Leibovich (1971) administered lindane to laboratory rats orally for 4 months. At a dose of 0.05 mg/kg-day no effects were reported on the duration of the estrous cycle, the number of cycles per month, the development of pups, or pup weights. This was the lowest no effect level with a reproductive endpoint and was chosen for the low TRV. Effects were observed at a dose of 0.5 mg/kg-day. This dose of 0.5 mg/kg-day was the lowest effect level reported in the data set.

Cooper and others (1989), administered lindane by gavage to Fischer rats for approximately 100 days. At a dose of 10 mg/kg-day, the mean age of vaginal opening and serum estradiol levels increased, and pituitary gland weights decreased. A decrease in pituitary weight can alter the hormonal control of ovarian function. Although this paper was considered for the high TRV because it had a reproductive endpoint and was in the mid-range of effects, it was not used as the basis for the low TRV because it was above a significant dose at which pup mortality was reported, and because gavage was not considered an ecologically relevant exposure route.

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Sircar and Lahiri (1989) administered lindane by gavage to Swiss mice on days 14 through 19 of gestation. At a dose of 6.25 mg/kg-day, complete resorption of fetuses and reduction in ovary weight were reported. Also in this report, at a dose of 3.75 mg/kg-day a significant reduction in the average weight of pups and an increase in pup mortality were reported. This dose of 3.75 mg/kg-day was considered to be ecologically relevant and to be the high end of the TRV range. Generally, TRVs were not derived from studies using gavage as the exposure route. In a few cases, such as this, an exception was made. When looking at the data set as a whole, this exposure dose was the most appropriate dose on which to base the high TRV. For these reasons, the dose of 3.75 mg/kg-day was chosen for the high TRV.

Palmer and others (1978) reported that an increase in incidence of pups with extra ribs occurred at a dose of 20 mg/kg-day. In this study, laboratory rats were administered lindane by gastric intubation on days 6 through 15 of gestation. This was considered for the high TRV, but the dose of 20 mg/kg-day was rejected due to the pup mortality reported at a lower dose and questions about the ecological relevance of the exposure route.

Nigam and others (1979) administered lindane through food to Swiss mice for 10 months. At a dose of 104.55 mg/kg-day an increase in testis weight and degenerative changes in seminiferous epithelium and tubules were reported. This was the highest adverse reproductive effect reported in the data set.

LINDANE TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Laboratory rats	adult	Increase in duration of estrous cycle, duration of diestrus and estrous, in # of cycles per month and # of offspring, in pup body weight, and physical development	LOAEL	4 mos	0	0.5	Naishtein and Leibovich 1971
Laboratory rats	adult	No effect on duration of estrous cycle, # of cycles/month, duration of diestrous and estrous, # of offspring, development of pups, and pup weight	NOAEL	4 mos	0	0.05[1]	Naishtein and Leibovich 1971
Fischer-344 rats	21 d	Increase in the mean age of vaginal opening and in serum estradiol levels; decrease in pituitaries	LOAEL	100 d	G	10	Cooper and others 1989

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Swiss mice	adult	Complete resorption of fetuses; average implantation of fetuses within uterus; decrease in weight of ovary	EL	gestation d 6-12	G	6.25	Sircar and Lahiri 1989
Swiss mice	adult	Decrease in average weight of pups; 100% pup mortality	EL	gestation d 14-19	G	3.75[2]	Sircar and Lahiri 1989
CFY rats	adult	Increase in incidence of young with extra ribs	LOAEL	gestation d 6-15	G	20	Palmer and others 1978
Swiss mice	NG	Increase in testis weight; degenerative changes in the seminiferous epithelium	EL	10 mos	G	104.55	Nigam and others 1978

Notes:

1 Selected low mammalian TRV; uncertainty factor of 10 was applied for EL to NEL conversion giving a TRV = 0.05 mg/kg-day

2 Selected high mammalian TRV = 3.75 mg/kg-day

Highlighted rows — The bases for high and low TRVs
NEL — No effect level
NOAEL — No observed adverse effect level
EL — Effect level
LOAEL — Lowest observed adverse effect level
NG — Not given
Exposure route: — O = oral; F = food, G = gavage

5.11.2 Mammalian TRVs for Lindane

The mammalian dose of 0.05 mg/kg-day from Naishtein and Leibovich (1971) was chosen for the low TRV. This was the lowest no effect level in the data set and had a reproductive endpoint. No effects on reproductive cycles, number of offspring, pup weight, or the development of pups were observed at this dose.

The high TRV (3.75 mg/kg-day) should be allometrically converted to account for body scaling differences between the test organism (Swiss mice) and the mammalian receptor species of concern. The following allometric equation as outlined in Section 3.3 can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

The low TRV should be allometrically converted to account for differences in body size between the test organism (laboratory rats) and the receptors species. The following allometric equation as outlined in Section 3.4 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

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$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.05 \text{ mg/kg-day } (176 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The high TRV was based on Sircar and Lahiri (1989) at a dose of 3.75 mg/kg-day. This was an ecologically relevant dose in which both an increase in pup mortality and a decrease in pup weight were reported.

$$\text{High TRV: Dose}_{\text{receptor}} = 3.75 \text{ mg/kg-day } (24 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The data set of the effects of lindane on rodents (a) included studies on the sensitive life stage of the test organism ($+_S$); (b) included chronic exposure durations ($+_C$); and (c) included 4 different test organisms representing 3 different mammalian groups (4/3). The low TRV test organism is from the laboratory rat mammalian group and the high TRV test organism is from the laboratory mice mammalian group. This information would be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.12 TOXICITY REFERENCE VALUES FOR MANGANESE

In review of the literature on the toxicity of manganese to rodent and avian test organisms, 7 studies on rodents and 2 studies on birds were considered relevant for deriving TRVs. The doses at which adverse effects occur for rodents ranged from 71 mg/kg-day (Laskey and others 1985) to 2,145.59 mg/kg-day (Gianutsos and Murray 1982) and for birds ranged from 562.98 mg/kg-day (Southern and Baker 1983) to 776 mg/kg-day (Laskey and Edens 1985). The effects in the rodent data set were mostly reproductive and cytotoxic including reduction in testicular growth and chromosomal aberrations. For the bird data set, the adverse effects were mostly systemic, including reduced weight gain and liver/hematocrit iron concentrations.

5.12.1 Effects of Manganese on Rodents

In Gray and Laskey (1980), CD-1 mice were administered manganese in food for 90 days. At a dose of 136.56 mg/kg-day, decreases in paired testes weight and seminal vesicle weight were reported. Also at this dose a decrease in the preputial gland was reported. This dose was considered to have an ecologically relevant reproductive endpoint and was used to derive the low TRV. At a dose of 159.56

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mg/kg-day, the mice were reported to have decreased testes, seminal vesicle, and preputial gland weights at 73 days. This dose was considered to have an ecologically relevant endpoint and to be in the mid-range of effects. Therefore, the dose of 159.56 mg/kg-day was chosen for the high TRV.

Laskey and others (1985) administered manganese oxide by gavage to Long-Evans rats for 21 days. At a dose of 71 mg/kg-day, decreases in serum testosterone and increase in body, testes, and seminal vesicle weight were reported. This was the lowest adverse effect level in the data set.

Kontur and Fetcher (1988) administered manganese chloride by gastric intubation to Long Evans rats for 14 to 21 days. At a dose of 13.8 mg/kg-day, no effects were reported on levels of neurotransmitters or their metabolites. This study was considered for the low TRV, but neither the neurological endpoint nor the exposure route were considered as ecologically relevant as other studies in the data set.

Joardar and Sharma (1990) administered potassium permanganate through drinking water to Swiss albino rats for 7 to 21 days. At a dose of 65 mg/kg-day, chromosomal aberrations, cell breaks, and sperm-head abnormalities were reported. This was considered for the derivation of the low TRV, but application of an uncertainty factor resulted in a dose approximating nutritional levels for rodents (4.67 mg/kg-day).

MANGANESE TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
CD-1 mice	90 d	Decrease in paired testes weight, seminal vesicle weight, and preputial gland weight	EL	90 d	F	136.56	Gray and Laskey1980
CD-1 mice	90 d	Decrease in paired testes weight, seminal vesicle weight, and preputial gland weight	EL	73 d	F	159.09	Gray and Laskey1980
Long-Evans rat	21 d	Decrease in serum testosterone and increase in body, testes, and seminal vesicle weight following hCG treatment	EL	21 d	G	71	Laskey and others 1985
Long-Evans rat	pup	No effect on no neurotransmitter levels and their metabolites in the striatium, hypothalamus or nucleus accumbens	NEL	14 to 21 d	G	13.8	Kontur and Fechter 1988
Swiss albino rat	8 to 10 wk	Increases in chromosomal aberrations, higher frequency of breaks per cell, micronucleus formation and sperm-head	EL	7, 14, and 21 d	DW	65	Joardar and Sharma 1990

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
		abnormalities					

Notes:

1 Selected low mammalian TRV; an uncertainty factor of 10 was applied for EL to NEL conversion giving a TRV = 13.7 mg/kg-day

2 Selected high mammalian TRV = 159.09 mg/kg-day

Highlighted rows The bases for high and low TRVs

NEL No effect level

EL Effect level

Exposure route: G =gavage, DW = drinking water, F = feed

5.12.2 Mammalian TRVs for Manganese

The mammalian low TRV was based on Gray and Laskey (1980), which reported adverse effects at a dose of 136.56 mg/kg-day. This dose was divided by an uncertainty factor of 10 for an effect level to a no effect level conversion resulting in a dose of 13.7 mg/kg-day for the low TRV. This dose was considered to be more ecologically relevant than the cytotoxic and neurological endpoints and was above the nutritional requirement of manganese for rodents.

The mammalian high TRV was based on Gray and Laskey (1980), which reported adverse effects at a dose of 159.09 mg/kg-day. This dose had significant reproductive endpoints of greater ecological relevance than other reported endpoints in the data set. The dose of 159.09 mg/kg-day was in the mid-range of adverse effects.

The low TRV should be allometrically converted to account for size scaling between the test organism (laboratory mice) and the mammalian receptor species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 13.7 \text{ mg/kg-day } (34.6 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

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This dose should be allometrically converted to account for size differences between the test organism (laboratory mice) and the receptor species. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the body weight in grams of the receptor:

$$\text{High TRV: Dose}_{\text{receptor}} = 159.09 \text{ mg/kg-day } (29.7 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The data set of the effects of manganese on rodents (a) included studies on the sensitive life stage of the test organism (+s); (d) included chronic exposure durations (+c); and (c) included 2 different test organisms representing 2 different mammalian groups (2/2). The low and high TRV test organisms are both in the mammalian group of laboratory rats. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.12.3 Effects of Manganese on Birds

In Laskey and Edens (1985), Japanese quail were given manganese oxide in food for 75-80 days. At a dose of 776 mg/kg-day, reduction in motor skills and aggressive behavior were reported. Also at this dose, no significant effects were reported on serum testosterone levels. The effect dose was used to derive the low and high TRVs. This was the only study in the data set that had reproductive and systemic endpoints. This dose was at the high end of the range of effects.

Southern and Baker (1983) administered manganese oxide in food to hybrid chicks for 13 days. In this study there was a large range of effect levels and no effect levels. At a dose of 562.98 mg/kg-day, a reduction in hemoglobin and liver hematocrit iron levels were reported. This was the lowest effect in the data set. The highest no effect level in the data set was also from this study (973.33 mg/kg-day).

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MANGANESE TOXICITY DATA (AVIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Japanese quail	hatchling	Decrease in rate of motor development and aggressive behavior	EL	75-80 d	F	7761.2	Laskey and Edens 1985
Japanese quail	hatchling	No effect on serum testosterone levels	NEL	75-80 d	F	776	Laskey and Edens 1985
Hybrid chicks	7 d	Decrease in hemoglobin, hematocrit, and liver iron concentrations; increase in manganese in bile and liver	EL	13 d	F	562.98	Southern and Baker 1983
Hybrid chicks	7 d	No effect on efficiency of feed utilization	NEL	13 d	F	973.33	Southern and Baker 1983

Notes:

1 Selected low avian TRV; an uncertainty factor of 10 was applied for EL to NEL conversion giving a TRV = 77.6 mg/kg-day

2 Selected high avian TRV = 776 mg/kg-day

Highlighted rows The bases for high and low TRVs

NEL No effect level

EL Effect level

Exposure route F =food

5.12.4 Avian TRVs for Manganese

The low TRV was based on Laskey and Edens (1985). A dose of 776 mg/kg-day caused adverse systemic and behavioral effects. An uncertainty factor of 10 was applied for effect to no effect conversion resulting in a low TRV of 77.6 mg/kg-day. This dose is above nutrient levels of manganese for birds in a basal diet containing 56 parts per million (ppm) manganese as reported by Laskey and Edens (1985).

The high TRV was also based on Laskey and Edens (1985). This study measured behavioral and reproductive endpoints at a dose of 776 mg/kg-day. This dose was at the high end of the range of effects, but was chosen for the high TRV because of corroborating data in Southern and Baker (1983).

The data set of the effects of manganese on birds (a) included exposure to a sensitive life stage of the test organism (+s); (b) did not include chronic exposures (−c); and (c) contained 2 different test species representing 1 avian group (2/1). The low and high TRV test organisms are both in the avian group of

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gallinaceous birds. This information should be included in the confidence rating for each of the TRVs as outlined in Section 3.4.

5.13 TOXICITY REFERENCE VALUE FOR METHOXYCHLOR

In review of the literature on the toxicity of methoxychlor to rodent and avian test organisms, 11 studies on rodents but no studies on birds were considered appropriate for deriving TRVs. Due to insufficient data, avian TRVs were not derived. Adverse effects for rodents ranged from 9.13 mg/kg-day (Davison and Cox 1976) to 1,000 mg/kg-day (Dikshith and others 1990). The majority of adverse effects were reproductive, including effects such as decreases in weight of offspring, atrophy of the ovary and uterus, and infertility.

5.13.1 Effects of Methoxychlor on Rodents

In Gray and others (1989), Long-Evans rats were administered methoxychlor by gavage from weaning to puberty and gestation day 15. At a dose of 25 mg/kg-day an increase in the prolactin content in the pituitary gland and accelerated vaginal opening and onset of estrous cyclicity were reported. This was the lowest dose in the data set that was ecologically relevant, and was used to derive the low TRV. At a dose of 50 mg/kg-day first generation female rats displayed reduced time to vaginal opening, reduced fertility, fewer litters, and acyclic estrous. This was in the mid-range of adverse effects and had an ecologically relevant endpoint. This dose of 50 mg/kg-day was chosen for the high TRV.

Harris and others (1974) fed methoxychlor to Sprague-Dawley rats for 9 weeks. At a dose of 71.03 mg/kg-day, reduced time to vaginal opening, reproduction rate, and ovarian weights were reported. This was considered for the high TRV but was not selected because it was on the high end of the range of reproductive effects.

Davison and Cox (1976) administered methoxychlor in food to Sprague-Dawley rats for 16 weeks. At a dose of 9.13 mg/kg-day a decrease in the hepatic storage of vitamin A was observed. This was the lowest effect level in the data set.

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Dikshith and others (1990) administered methoxychlor technical (MT) by gavage to albino rats for 90 days. At a dose of 1,000 mg/kg-day an increase in liver weight and induced body tremor, diarrhea, lachrymation, salivation, and death were reported. This was the highest adverse effect in the data set.

METHOXYCHLOR TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Long-Evans rats	weanling	Depressed growth rates	LOAEL	weaning to puberty, gestation, d 15 of lactation	G	25[1]	Gray and others 1989
Long-Evans rats	weanling	Increase in pituitary prolactin content	EL	weaning to puberty, gestation, d 15 of lactation	G	25[1]	Gray and others 1989
Long-Evans rats	weanling	Decrease in time to vaginal opening in F_1 females, in fertility and fewer litters, acyclic estrous	EL	weaning to puberty, gestation, day 15 of lactation	G	50[2]	Gray and others 1989
Sprague-Dawley rats	60-90 d	Decrease in time to vaginal opening in female pups of treated mothers, in reproduction rate in F_1 males and females, and in ovarian weight	LOAEL	9 wk	F	71.13	Harris and others 1974
Sprague-Dawley rats	23 d	Decrease in hepatic storage of vitamin A	LOAEL	16 wk	F	9.13	Davison and Cox 1976
Albino rats	NG	Increase in liver weight	LOAEL	90 d	G	1,000	Dikshith and others 1990
Albino rats	NG	Induced body tremor, diarrhea, lachrymation, salivation, and death	LOAEL	90 d	G	1,000	Dikshith and others 1990

Notes:

1 Selected low mammalian TRV; an uncertainty factor of 10 was applied for EL to NEL conversion giving a TRV = 2.5 mg/kg-day

2 Selected high mammalian TRV = 50 mg/kg-day

Highlighted rows The bases for high and low TRVs

LOAEL Lowest observed adverse effect level

EL Effect level

NG Not given

Exposure route F = food, G = gavage

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5.13.2 Mammalian TRVs for Methoxychlor

In Gray and others (1989), Long-Evans rats were administered methoxychlor by gavage from weaning through day 15 of gestation. At a dose of 25 mg/kg-day an increase in the prolactin content in the pituitary gland and accelerated vaginal opening and onset of estrous cyclicity were reported. This dose was used to derive the low TRV. At a dose of 50 mg/kg-day first generation female rats displayed reduced time to vaginal opening, reduced fertility, fewer litters, and acyclic estrous. This dose was in the mid-range of adverse effects and was the basis of the high TRV. The data set for methoxychlor contained 12 studies, 4 of which exposed the test organisms orally. The remaining eight studies used gavage. This study was used for TRV derivation, even though the exposure was through gavage, because very few studies using oral exposure were available, and because this was a multigenerational study that included dosing of the mother during pregnancy and lactation.

The mammalian high TRV was based on Gray and others (1989). At a dose of 50 mg/kg-day significant adverse reproductive effects, such as reduced fertility, were reported. This dose was in the mid-range of effects, and due to the significance of the endpoints, was selected as the high TRV.

The low TRV (2.5 mg/kg-day) should be allometrically converted to account for differences in body size between the test organism (Long-Evans rats) and the receptors species of concern. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 2.5 \text{ mg/kg-day } (332 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The high TRV should be allometrically converted to account for body scaling differences between the test organism (Long-Evans rats) and the mammalian receptor species of concern. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 50 \text{ mg/kg-day } (332/\text{Body Weight}_{\text{receptor}})^{1/4}$$

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The data set of the effects of methoxychlor on rodents (a) included studies on the sensitive life stage of the test organism ($+_S$); (d) included chronic exposure durations ($+_C$); and (c) included 2 different test organisms representing 2 different mammalian groups (2/2). The low and high TRV test organisms are both in the laboratory rat mammalian group. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.14 TOXICITY REFERENCE VALUES FOR NAPTHALENE

In a review of the literature on the toxicity of naphthalene to rodent and avian test organisms, 3 studies on rodents, but no studies on birds, were considered appropriate for deriving TRVs. Due to insufficient data, avian TRVs were not derived. The adverse effects for rodents ranged from 5.3 mg/kg-day (Shopp and others 1984) to 300 mg/kg-day (Plasterer and others 1985). The majority of these adverse effects were systemic; some hematological and reproductive effects were reported. The data set included effects such as decreases in renal functions, number of live offspring, and altered serum calcium concentration.

5.14.1 Effects of Naphthalene on Rodents

In Navarro and others (1991), naphthalene was administered by gavage to laboratory rats during gestation days 6-15 mg/kg-day. At a dose of 50 mg/kg-day, no effects were reported on weight gain or water consumption. At the same dose, maternal lethargy was reported. A daily dose of 150 mg/kg-day caused decreases in body weight and water consumption. At 300 mg/kg-day, reduced maternal survival and decreased average number of live offspring were reported. This study was used for both the low and high TRV. The exposure route of gavage, though not representative of field exposures, was used in all studies in the data set. Moreover, this was the only study that focused on reproductive and systemic endpoints. The low TRV was based on the no effect dose of 50 mg/kg-day, and the high TRV was based on the effect dose of 150 mg/kg-day. The dose of 150 mg/kg-day was in the mid-range of adverse effects in the data set.

Shopp and others (1984) administered naphthalene by gavage to laboratory mice for 90 days. At a dose of 27 mg/kg-day, decreases in serum concentration of blood urea nitrogen (BUN) and creatinine were reported. BUN is the breakdown of protein products in the serum that are filtered out of the blood by the kidney. Creatinine is the byproduct of the muscle enzyme creatine, and is also filtered by the kidney. The effect of the decrease in these by-products in serum was not observed consistently at higher doses of

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naphthalene. These effects were not considered for TRV development because no correlation to adverse effects in field animals has been demonstrated.

NAPTHALENE TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
CD-1 mice	6 wk	Decrease in concentration of BUN in serum; ratio of BUN/creatinine; decrease in BUN at high dose, but not at middle dose; increase in cholesterol concentration in serum	EL	14 d	G	27	Shopp and others 1984
CD-1 mice	6 wk	Decrease in serum concentration of BUN and creatinine (creatinine levels were normal at higher doses)	EL	90 d	G	5.3	Shopp and others 1984
CD-1 mice	adult	Decrease in maternal survival and average number of live offspring	EL	gestation d 7-14	G	300	Plasterer and others 1985
Sprague-Dawley rats	adult	Increase in maternal toxicity (lethargy, slow breathing, prone body posture and rooting); return to normal after dosing at 50 and 150 mg/kg-d, but continued after doing at 450 mg/kg-d level	LOAEL	gestation d 6-15	G	50	Navarro and others 1991
Sprague-Dawley rats	adult	Decrease in body weight gain during dosing, entire gestation period, and corrected body weight; decrease in water consumption on gestation days 6 to 9; increase in water consumption on gestation days 9 to 18	LOAEL	gestation d 6-15	G	150[2]	Navarro and others 1991
Sprague-Dawley rats	adult	No effect on body weight gain or water consumption during dosing, entire gestation period	NOAEL	gestation d 6-15	G	50[1]	Navarro and others 1991

Notes:

1 Selected low mammalian TRV = 50 mg/kg-day

2 Selected high mammalian TRV = 150 mg/kg-day

Highlighted rows The bases for high and low TRVs

NOAEL No observed adverse effect level

LOAEL Lowest observed adverse effect level

EL Effect level

Exposure route: G = gavage

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5.14.2 Mammalian TRVs for Naphthalene

The low TRV was based a dose of 50 mg/kg-day as reported in Navarro and others (1991). This study focused on both systemic and reproductive endpoints and was conducted on the sensitive life stage of the test organism.

The high TRV was also based on Navarro and others (1991). The dose of 150 mg/kg-day was in the mid-range of systemic and reproductive effects. This study was conducted using the sensitive life stage of the test organism, and the effects were ecologically important.

This dose should be allometrically converted to account for differences in body size between the test organism (laboratory rats) and the receptor species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 50 \text{ mg/kg-day } (276.5 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The dose for the high TRV should be allometrically converted to account for body scaling differences between the test organisms and the mammalian receptor species. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 150 \text{ mg/kg-day } (270.2 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The data set of the effects of naphthalene on rodents (a) included studies on the sensitive life stage of the test organism ($+_S$); (b) included chronic exposure durations ($+_C$); and (c) included 2 species representing 2 groups (2/2). The low and high TRV test organisms are both in the mammalian group of laboratory rats. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

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5.15 TOXICITY REFERENCE VALUES FOR NICKEL

In a review of the literature on the toxicity of nickel to rodent and avian test organisms, 4 studies on rodents and 5 studies on birds were considered relevant for deriving TRVs. The range of adverse effects for rodents extended from 1.33 mg/kg-day (Smith and others 1993) to 395.70 mg/kg-day (Dieter and others 1988), and for birds from 14.07 mg/kg-day (Cain and Pafford 1981) to 121.48 mg/kg-day (Eastin and O'Shea 1981). In the rodent data set, the majority of adverse effects were systemic, including nephrotoxicity and immunotoxicity. For birds, the adverse effects included decreases in body weight and humerus length.

5.15.1 Effects of Nickel on Rodents

Smith and others (1993) administered nickel chloride in drinking water to female laboratory rats for 4 months. At a dose of 1.33 mg/kg-day, no effects were observed on the first litter of pups, but pup mortality increased in the second litter. This was the lowest effect level in the data set. A dose of 31.6 mg/kg-day caused an increase in pups born dead or dying shortly after birth. These doses were the only reproductive effect levels in the data set. The dose of 1.33 mg/kg-day was selected for the low TRV and the dose of 31.6 mg/kg-day was chosen for the high TRV.

Vyskocil and others (1994) gave nickel sulfate in drinking water to laboratory rats for 6 months. At a dose of 6.91 mg/kg-day, no effects on weight gain were reported, but nephrotoxicity and increased kidney weight were reported. This dose was not considered for the low TRV because effects were reported at the same dose and significant reproductive effects were reported at a lower dose. The dose of 6.91 mg/kg-day was the lowest dose reported to cause systemic effects.

In Dieter and others (1988), reduced body and organ weights were reported at 395.7 mg/kg-day administered in water. This was the highest effect level in the data set. In this study, nickel sulfate was administered to 8 to 10 week old female laboratory mice for 180 days.

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NICKEL TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
B6C3F1 mice	8-10 wk	Decrease in body and organ weights	LOAEL	180 d	DW	395.7	Dieter and others 1988
Long-Evans rats	61-64 d	Increase in number and proportion of pups born dead or dying shortly after birth during G1; increase in food consumption and decrease in water intake in dams	LOAEL	4 mos (11 weeks pre-gestation plus 2 complete gestational and lactational periods)	DW	31.6[2]	Smith and others 1993
Long-Evans rats	61-64 d	Increase in number and proportion of pups born dead or dying shortly after birth during G2	EL	4 mos (11 weeks pre-gestation plus 2 complete gestational and lactational periods)	DW	1.33[1]	Smith and others 1993
Wistar rat	8 wk	Increase in nephrotoxicity, increase in kidney weights	LOAEL	6 mos	DW	6.91	Vyskocil and others 1994
Wistar rat	8 wk	No effect on weight gain	NOAEL	6 mos	DW	6.91	Vyskocil and others 1994

Notes:

1 Selected low mammalian TRV; an uncertainty factor of 10 was applied for EL to NEL conversion giving a TRV = 0.133 mg/kg-day

2 Selected high mammalian TRV = 31.6 mg/kg-day

Highlighted rows	The bases for high and low TRVs
NOAEL	No observed adverse effect level
NEL	No effect level
LOAEL	Lowest observed adverse effect level
EL	Effect level
Exposure route	DW = drinking water

5.15.2 Mammalian TRVs for Nickel

The mammalian low TRV was based on Smith and others (1993). The reported dose of 1.33 mg/kg-day was divided by an uncertainty factor of 10 to convert the effect level to a no effect level equivalent. The resulting low TRV was 0.133 mg/kg. This effect was the only reproductive effect in the data set.

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The high TRV was also based on Smith and others (1993). The dose of 31.6 mg/kg-day was the highest dose causing reproductive effects and was in the mid-range of the adverse effects in the data set.

This low TRV should be allometrically converted to account for the differences in body size between the test organism (laboratory rats) and the receptor species of concern. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.133 \text{ mg/kg-day } (248.6 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The high TRV should be allometrically converted as well to account for differences between the test organisms and the mammalian receptor of concern. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 31.6 \text{ mg/kg-day } (248.6 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The data set for the effects of nickel on rodents (a) included exposure to the most sensitive life stage (+s); (b) included chronic exposures (+c); and (c) contained two different species representing two different mammalian groups (2/2). The low and high TRV test organisms are both in the mammalian group of laboratory rats. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

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5.15.3 Effects of Nickel on Birds

In Cain and Pafford (1981), mallards were given nickel sulfate in feed for 90 days. At a dose of 13.79 mg/kg-day, no effects were observed on tremors or edema in toe and leg joints. These effects were observed at 55.16 mg/kg-day. A dose of 56.26 mg/kg-day caused a decrease in length to weight ratio of the humerus at 30 days. This effect did not occur at 14.07 mg/kg-day. The dose of 13.79 mg/kg-day was chosen as the low TRV and the dose of 55.16 mg/kg-day was chosen for the high TRV. This study was conducted on one-day old mallards, which is a sensitive life stage. Moreover, the low dose was the lowest no effect level in the reported data and the high dose was in the mid-range of effects.

In Eastin and O'Shea (1981), nickel sulfate was administered to 20-month-old mallards in feed for 90 days. At a dose of 121.48 mg/kg-day, black, tarry feces were observed. This was the highest effect level reported in the data set.

NICKEL TOXICITY DATA (AVIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Mallard	20 mos	Black, tarry feces	LOAEL	90 d	F	121.48	Eastin and O'Shea 1981
Mallard	1 day	Increase in tremors and edema in toe and leg joints	LOAEL	90 d	F	55.16	Cain and Pafford 1981
Mallard	1 day	No effect on tremors and edema in toe and leg joints	NOAEL	90 d	F	13.79[1]	Cain and Pafford 1981
Mallard	1 day	Decrease in length:weight ratio of humerus at 30 days	LOAEL	90 d	F	56.16[2]	Cain and Pafford 1981
Mallard	1 day	No effect on length:weight ratio of humerus at 30 days	NOAEL	90 d	F	14.07	Cain and Pafford 1981
Mallard	1 day	Decrease in length:weight ratio of humerus at 60 days	EL	90 d	F	14.07	Cain and Pafford 1981

Notes:

1 Selected low avian TRV; an uncertainty factor of 10 was applied for sub-chronic to chronic conversion giving a TRV = 1.38 mg/kg-day

2 Selected high avian TRV = 55.16 mg/kg-day

Highlighted rows The bases for high and low TRVs

NOAEL No observed adverse effect level

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LOAEL	Lowest observed adverse effect level
EL	Effect level
Exposure route:	F = food

5.15.4 Avian TRVs for Nickel

The low TRV was based on Cain and Pafford (1981). The dose of 13.79 mg/kg-day was the lowest no effect level in the data set. The study was conducted on mallards which, based on the data set, appear to be more sensitive than chickens to nickel toxicity. The reported dose of 13.79 mg/kg-day was divided by an uncertainty factor of 10 for a sub-chronic to chronic conversion. This resulted in an avian low TRV of 1.38 mg/kg-day.

The high TRV was based on Cain and Pafford (1981). The reported dose of 55.16 mg/kg-day caused adverse systemic effects on mallards. This dose was in the mid-range of systemic effects. In addition, effects on the humerus were considered ecologically relevant and were supported by increases in tremors and edema in toe and leg joints at a similar dose.

The data set of the effects of nickel on birds (a) included exposure to the most sensitive life stage (+s); (b) did not address chronic exposures (−c); and (c) contained 2 different test species representing 2 different avian groups (2/2). The low and high TRV test organisms are both in the Duck avian group. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.16 TOXICITY REFERENCE VALUE FOR PCBS

In a review of the literature on the toxicity of polychlorinated biphenyls (PCBs) to rodents and avian test organisms, 19 studies on rodents and 26 studies on birds were considered relevant for deriving TRVs. The range of adverse effects for rodents extended from 0.36 mg/kg-day (Simmons and McKee 1992) to 140.36 mg/kg-day (Sanders and others 1974) and for birds from 0.05 mg/kg-day (Elliott and others 1991) to 642.72 mg/kg-day (Call and Harrell 1974). For rodents, most studies measured reproductive and systemic endpoints. Studies on birds largely reported reproductive endpoints, while some systemic effects were also evident.

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5.16.1 Effects of PCBs on Rodents

McCoy and others (1995) administered Aroclor 1254 in feed to oldfield mice over several generations. (Aroclors are mixtures of PCB congeners.) No effects were reported on litter size at a dose of 0.71 mg/kg-day. The same dose did, however, result in decreases in the number of litters produced per month, the number weaned per month, the percentage of pups surviving to weaning, and mean body weight at birth and at weaning. This was the lowest reproductive effect level in the data set, but was rejected as the low TRV because ecologically significant reproductive effects were observed at this dose. The low TRV is meant to be a dose at which adverse effects are not expected to occur.

In Simmons and McKee (1992), white-footed mice were given Aroclor 1254 in feed for 21 days. A dose of 0.36 mg/kg-day had no effect on liver weight, enzyme activity, or pentobarbitol-induced sleep time. This dose was selected as the low TRV because it was the lowest no effect level in the data set, and because reproductive effects were observed at the next highest dose of 0.71 mg/kg-day (in McCoy and others 1995). Simmons and McKee (1992) did report that 0.36 mg/kg-day caused an increase in the activity of a specific enzyme (ethoxyresorufin-O-dealkylase). This enzymatic effect was not considered ecologically relevant because it was not linked with adverse effects and had no effect on the percentage of choroid epithelial cells with blebs or bald patches.

In Sanders and others (1974), Aroclor 1254 was administered to laboratory mice in feed for two weeks. A dose of 140.36 mg/kg-day resulted in increased adrenal weights. This was the highest effect level in the data set. The same dose had no effect on testes weights or on preputial or vesicular gland weights.

Linzey (1987) administered Aroclor 1254 to white-footed mice in feed for up to 18 months at a single dose level of 1.28 mg/kg-day. This dose resulted in decreased survival of pups to 28 days of age, increased birth intervals, and decreased numbers of young per litter. Linzey (1988) confirmed impaired reproduction at this dose in a later multigenerational study showing reduced reproductive success in the second generation. This dose (1.28 mg/kg-day) was chosen for the high TRV because important reproductive effects were observed at lower doses, and because the endpoints measured are ecologically significant.

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PCB TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
White-footed mice	field collected	Decrease in survival/litter to 28 d	EL	18 mos	F	1.28[2]	Linzey 1987
White-footed mice	12 wk	Increase in birth interval, decrease number of young per litter	EL	9-15 mos	F	1.28[2]	Linzey 1987
White-footed mice	adult	Decrease in reproductive success in second generation (fewer pairs produced litters, fewer young survived to 12 weeks)	EL	multi-generational	F	1.28[2]	Linzey 1987
White-footed mice	90 d	No effect on liver weight, PROD activity (hepatic pentoxyresorufin-O-dealkylase), or on pentobarbitol-induced sleep time	NOAEL	21 d	F	0.361	Simmons and McKee 1992
White-footed mice	90 d	Increase in EROD activity (hepatic ethoxyresorufin-O-dealkylase)	EL	21 d	F	0.36	Simmons and McKee 1992
Oldfield mice (*Peromyscus polionotus*)	adult	No effect on weight gain and litter size	NEL	multi-generational	F	0.71	McCoy and others 1995
Oldfield mice	adult	Fewer litters/month; longer interval to first litter; decrease in mean birth weights and weaning weights and % survival to weaning	EL	multi-generational	F	0.71	McCoy and others 1995
ICR albino mice	adult	No effect on testes, preputial and vesicular gland weights	NEL	2 wk	F	140.36	Sanders and others 1974
ICR albino mice	adult	Increase in adrenal weight	LOAEL	2 wk	F	140.36	Sanders and others 1974
ICR albino mice	adult	No effect on adrenal weight	NOAEL	2 wk	F	39.43	Sanders and others 1974

Notes:

1 Selected low mammalian TRV = 0.36 mg/kg-day

2 Selected high mammalian TRV = 1.28 mg/kg-day

Highlighted rows	The bases for high and low TRVs
NOAEL	No observed adverse effect level
NEL	No effect level
LOAEL	Lowest observed adverse effect level
EL	Effect level
Exposure route	F = food

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5.16.2 Mammalian TRVs for PCBs

The mammalian low TRV was based on Simmons and McKee (1992), in which 0.36 mg/kg-day had no effect on liver weight, pentobarbitol-induced sleep time, or enzyme activity.

The high TRV was based on Linzey (1987), in which a dose of 1.28 mg/kg-day resulted in reduced reproductive capacity. There was a high degree of confidence in this study because the adverse effects were confirmed in a later study by Linzey (1988).

The low TRV should be allometrically converted to account for differences in body size between the test organism (white-footed mice) and the receptor species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.36 \text{ mg/kg-day } (20.62 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

This dose should be allometrically converted to account for differences in body scaling between the test organism and the receptor species. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 1.28 \text{ mg/kg-day } (22.85 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The data set of the effects of PCB on rodents (a) included studies looking at the sensitive life stage of the test organism ($+_S$); (b) included chronic exposure durations ($+_C$); and (c) included 3 different test species representing 3 different mammalian groups (3/3). The low and high TRV test organisms are both in the mammalian group of laboratory rats. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.16.3 Effects of PCBs on Birds

In Elliott and others (1991), PCB congeners were administered individually in gelatin capsules to American kestrels three times per week for four weeks. At a dose of 0.05 mg/kg-day, no effects were

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reported on liver weights, microsomal protein or specific enzyme activity. At the same dose, increases in activity of other enzymes occurred. This was the lowest dose level in the core data set.

The lowest reproductive dose in the avian PCB data was reported in Scott and others (1975). In this study, a dose of 0.06 mg/kg-day had no effect on hatchability in chickens fed Aroclor 1248 for eight weeks. This dose was the lowest reproductive no effect level in the data set. This study was considered for the low TRV but was rejected in favor of a study using a longer exposure duration.

Platonow and Reinhart (1973) administered Aroclor 1254 in feed to chickens for 39 weeks. A dose of 0.88 mg/kg-day resulted in reduced egg production. This study reported that PCBs accumulated in tissues are transferred to the egg during laying. Concentrations passed to the egg reach a maximum after several months of ingestion by the hen. This finding suggests that longer exposure durations may more accurately predict reproductive effects caused by PCBs. Because this study exposed chickens for 39 weeks, it was the basis for the low TRV. An uncertainty factor of 10 was applied to the dose to convert the effect level to a no effect level equivalent. The resulting avian low TRV is 0.09 mg/kg-day.

In Call and Harrell (1974), Japanese quail were given different Aroclors in feed for 21 days. A dose of 642.72 mg/kg-day of Aroclor 1242 resulted in interrupted egg laying patterns and shorter, narrower eggs. This was the highest dose level in the data set.

Britton and Huston (1973) administered Aroclor 1242 to chickens in feed for 6 weeks. At a dose of 1.27 mg/kg-day, a decrease in hatchability was observed. This dose was selected as the high TRV because of the highly significant reproductive effects, and because it was in the mid-range of the majority of adverse reproductive effects in the data set. Adverse effects were also reported at this dose in Harris and others (1976), including a decrease in the weight of the bursa of Fabricus in the progeny of hens fed a variety of Aroclors. The bursa of Fabricus is a thymus-like organ with immunologic functions.

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PCB TOXICITY DATA (AVIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
American kestrel	1 yr	No effect on total microsomal protein, and ANPD activity or mean hepatic porphyrin activity; no significant difference in liver weight	NEL	4wk (3times/ wk)	GC	0.05	Elliot and others 1991
American kestrel	1 yr	Increase in EROD and AE activity	EL	4wk (3 times/ wk)	GC	0.05	Elliot and others 1991
White-leghorn chickens	adult	No effect on hatchability	NOAEL	8 wk	F	0.06	Scott and others 1975
Japanese quail	7 wk	Interrupted egg laying pattern, shorter and narrower eggs	LOAEL	21 d	F	642.72	Call and Harrell 1974
Single comb white-leghorn	10 mos	Decrease in hatchability	LOAEL	6 wk dose, 6 wk elimination period	F	1.27[2]	Britton and Huston 1973
Chicken	adult	Decrease in egg production	EL	39 wk	F	0.88[1]	Platonow and Reinhart 1973
White-leghorn chickens	mature	Decrease in the weight of the bursa of Fabricius in progeny	LOAEL	8 wk	F	1.27	Harris and others 1976

Notes:

1 Selected low avian TRV; an uncertainty factor of 10 was applied for EL to NEL conversion giving a TRV = 0.09 mg/kg-day

2 Selected high avian TRV = 1.27 mg/kg-day

Highlighted rows — The bases for high and low TRVs
NOAEL — No observed adverse effect level
NEL — No effect level
LOAEL — Lowest observed adverse effect level
EL — Effect level
Exposure route: — GC = gelatin capsule, F= food

5.16.4 Avian TRVs for PCBs

The low TRV was based on Platonow and Reinhart (1973), in which reduced egg production occurred in chickens given PCBs in food at a dose of 0.88 mg/kg-day. The reported dose was divided by an uncertainty factor of 10 to convert the effect level to a no effect level equivalent. The resulting avian low TRV is 0.09 mg/kg-day.

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The high TRV was based on Britton and Huston (1973). A dose of 1.27 mg/kg-day resulted in a decrease in egg hatchability in chickens. This dose was in the mid-range of the reproductive effects and was supported by adverse effects reported by Harris and others (1976) at the same dose.

The data set for the effects of PCB on birds (a) included exposure to the most sensitive life stage of the test organism ($+_S$); (b) included chronic exposures ($+_C$); and (c) contained 14 different test species representing 5 different avian groups (14/5). The low and high TRV test organisms are both in the mammalian group of gallinaceous birds. This information should be included in the confidence rating for each of the TRVs as outlined in Section 3.4.

5.17 TOXICITY REFERENCE VALUES FOR SELENIUM

In a review of the literature on the toxicity of selenium to rodent and avian test organisms, 7 studies on rodents and 18 studies on birds were considered relevant for deriving TRVs. The adverse effects on rodents occurred at doses from 0.05 mg/kg-day (Harr and others 1966) to 23.43 mg/kg-days (Jacobs and Forst 1981) and on birds ranged from 0.32 mg/kg-day (Fairbrother and Fowles 1990) to 10.7 mg/kg-day (Cantor and others 1984). In the rodent data set, the majority of adverse effects were systemic and reproductive, including effects on body weight, and increases in young deaths and frequency of runts. For birds, the majority of adverse effects were reproductive and systemic including increased malformed embryos, and decreased hatchling and adult weight.

5.17.1 Effects of Selenium on Rodents

Nobunaga and others (1979) administered sodium selenite in drinking water to laboratory mice for 48 days. At a dose of 0.48 mg/kg-day, no effects were reported on fetal body weight or fetal skeletal development. At this dose water uptake decreased. This was the lowest dose in the data set at which no reproductive effects were reported. This dose was considered for the low TRV because reproductive endpoints were considered more ecologically relevant than systemic endpoints; however, because significant effects at the same dose were reported, it was considered inappropriate for a low TRV.

In Schroeder and Mitchener (1971), laboratory weanling mice were given selenate in drinking water for 6 months. At a dose of 1.21 mg/kg-day, increases in young deaths and runts were reported in the first

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generation. This significant reproductive endpoint was chosen for the high TRV. This dose was also in the mid-range of effects in the data set.

In Schroeder and Mitchener (1972), laboratory mice were administered sodium selenite in drinking water for their lifetime. In this study, a dose of 0.86 mg/kg-day resulted in a decreased longevity. This effect was not considered appropriate for TRV development because a lifetime of exposure for laboratory mice is much longer than the typical life span of wild mice, which are normally preyed on within the first year of life.

Jacobs and Forst (1981) administered sodium selenite to laboratory mice in drinking water for 46 days. At a dose of 23.43 mg/kg-day, decreases in weight gain were reported. This was the highest effect level reported in the data set.

Harr and others (1966) administered selenate to Wistar rats in food for their lifetime. At a dose of 0.05 mg/kg-day no hepatic lesions were reported. This chronic study, the lowest no effect level in the data set, was chosen for the low TRV.

SELENIUM TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
IVCS mice	60 d	No effect on fetal body weight or fetal skeletal development (reduced number of ossified vertebrae)	NOAEL	48 d	DW	0.48	Nobunaga and others 1979
IVCS mice	60 d	Decrease in daily water intake	EL	48 d	DW	0.48	Nobunaga and others 1979
CD mice	weanling	Increase in F1 generation of young deaths and the number of runts; F2 generation had a significant increase in the number of runts; F3 generation had a significant increase in the number of runts	EL	6 mo	DW	1.21	Schroeder and Mitchener 1971
Charles River Swiss CD mice	weanling	Decrease in longevity	EL	lifetime	DW	0.86	Schroeder and Mitchener 1972
Swiss mice	18 wk	Decrease in weight gain	LOAEL	46 d	DW	23.43	Jacobs and Forst 1981

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Wistar rats	adults	No effect on hepatic lesions	NEL	lifetime	F	0.05[1]	Harr and others 1966

Notes:
1 Selected low mammalian TRV = 0.05 mg/kg-day
2 Selected high mammalian TRV = 1.21 mg/kg-day
Highlighted rows The bases for high and low TRVs
NOAEL No observed adverse effect level
NEL No effect level
LOAEL Lowest observed adverse effect level
EL Effect level
Exposure route: DW = drinking water, F = food

5.17.2 Mammalian TRVs for Selenium

The low TRV was based on Harr and others (1966). At a dose of 0.05 mg/kg-day, no hepatic lesions were reported. For selenium, the reproductive endpoints were considered to have more ecological relevance than were systemic endpoints. Systemic endpoints included a decrease in longevity observed at 0.86 mg/kg-day (Schroeder and Mitchener 1972) and decrease in water intake at 0.48 mg/kg-day (Nobunaga and others 1979).

The high TRV was based on Schroeder and Mitchener (1971). At a dose of 1.21 mg/kg-day, reproductive effects were reported. This was in the mid-range of effects of the data set.

The low TRV should be allometrically converted to account for differences in body scaling between the test organism and the receptor species. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.05 \text{ mg/kg-day} (24.6 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

This dose (1.21 mg/kg-day) should be allometrically converted to account for differences in body sizes between the test organism and the mammalian receptors of concern. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

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High TRV: $\text{Dose}_{receptor} = 1.21 \text{ mg/kg-day } (24.6 \text{ g/Body Weight}_{receptor})^{1/4}$

The data set on the effects of selenium on rodents (a) did not include exposure to the sensitive life stage of the test organisms (−s) (b) included chronic exposures (+c) and (c) included 2 different test species representing 2 different mammalian groups (2/2). The low TRV test organism is in the mammalian group of laboratory rats and the high TRV test organism is in the mammalian group of laboratory mice. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.17.3 Effects of Selenium on Birds

Heinz and others (1989) administered seleno-DL-methionine in food to female mallard adults for 40 to 50 days. At a dose of 0.23 mg/kg-day no effects were reported on hatchling body weights, survival, and reproductive parameters. This was in the mid-range of the reproductive no effect doses. Also in this study at a dose of 0.93 mg/kg-day a decrease in hatching success was reported. This was in the mid-range of adverse effects in the data set. The endpoints for this study were considered the most ecologically relevant in the data set because selenium targets the reproductive system in birds. The 0.23 mg/kg-day dose was chosen for the low TRV and 0.93 mg/kg-day for the high TRV.

In Fairbrother and Fowles (1990), selenomethionine was administered in drinking water to mallards for 12 weeks. At a dose of 0.32 mg/kg-day decreased response to bovine antigens was reported. This was not considered to be ecologically relevant because the mallards were injected with antigens to which birds are not exposed in the field. This was the lowest effect level dose in the data set.

Hoffman and others (1992) administered seleno-DL-methionene in food to one-day-old mallards for 4 weeks. At a dose of 10.7 mg/kg-day, decreases in body, spleen, and liver weight, and tarsal length were reported. This was the highest effect level in the data set.

SELENIUM TOXICITY DATA (AVIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Mallard	1 d	Decrease in body, spleen, liver weight, tarsal length	LOAEL	4 wk	F	10.7	Hoffman and others 1992

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Mallard	adult	Decrease in hatching success	LOAEL	40 -50 d	F	0.93[2]	Heinz and others 1989
Mallard	adult	No effect in hatchling body weight, and survival; no effect on number of hatchlings produced per hen, and no malformed embryos	NOAEL	40 -50 d	F	0.23[1]	Heinz and others 1989
Mallard	9 mos	Decrease in number of birds exhibiting a delayed type hypersensitivity (DTH) response to M. bovis (tuberculin antigens) purified protein derivative (PPD)	EL	12 wk	DW	0.32	Fairbrother and Fowles 1990

Notes:
1 Selected low avian TRV = 0.23 mg/kg-day
2 Selected high avian TRV = 0.93 mg/kg-day

Highlighted rows	The bases for high and low TRVs
NOAEL	No observed adverse effect level
NEL	No effect level
LOAEL	Lowest observed adverse effect level
EL	Effect level
Exposure route:	F = food
	DW = drinking water

5.17.4 Avian TRVs for Selenium

The low TRV was based on Heinz and others (1989). At a dose of 0.23 mg/kg-day, no reproductive effects were reported. This study was conducted on mallards which, based on the data set, may be more sensitive than chickens to selenium toxicity.

The high TRV was based on Heinz and other (1989). At a dose of 0.93 mg/kg-day, a significant decrease in hatching success was reported. This was in the mid-range of effects and was an ecologically relevant endpoint. This study was on mallards which, based on the reported effects, are more sensitive than other test organisms.

The risk threshold developed by the US Fish and Wildlife Service (FWS) (2.6 mg/kg selenium dry weight in food) will prove useful in the evaluation of potential selenium effects at hazardous waste sites, but was not considered appropriate for deriving the avian TRV for selenium. FWS based its risk value on a field-established hatchability threshold and observed effects of reproductive performance in Black-

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necked Stilt and American Avocet breeding in aggregations at evaporation basins in the Tulare Basin of California. This study reported 8.0 mg/kg as a threshold resulting in egg concentration of selenium; 2.9 mg/kg selenium dry weight was determined to be the reproductive lethality threshold and 2.6 mg/kg selenium was selected as the dilution standard (Skorupa and Schwarzbach 1995, Skorupa and Ohlendorf 1991).

The low TRV for selenium of 0.23 mg/kg/day for avian receptors was based on a NOAEL from a laboratory study by Heinz and others (1989). This study determined that the NOAEL for reproductive impairment in mallards was between 4.0 and 8.0 ppm selenium as selenomethionine; 4.0 ppm was chosen to represent this NOAEL. This study also states that embryo development and survival are thought to be the most sensitive measure of selenomethionine poisoning in mallards (Heinz and others 1989). Dabbling ducks are cited as among the more sensitive birds to embryonic effects from *in ovo* selenium exposure (Skorupa and others 1996), making mallards a reasonable test species on which to base the TRV value. TRV derivation is based on controlled laboratory studies only, not field studies. The risk guideline established by the FWS may, however, be used as another line of evidence to support decisions of selenium risk at installations.

The data set of the effects of selenium on birds (a) included exposure to the most sensitive life stage (+s); (b) addressed chronic exposure (+c); and (c) contained two different test species representing two different avian groups (2/2). The low and high TRV test organisms are both in the duck avian group. This information should be included in the confidence rating for each of the TRVs as outlined in Section 3.4.

5.18 Toxicity Reference Values for Thallium

In a review of the literature on the toxicity of thallium to rodent and avian test organisms, 1 study on rodents but no studies on birds were considered relevant for deriving TRVs. The rodent data were supplemented by 3 studies from ATSDR toxicity profiles (ATSDR 1992c) for deriving TRVs. The range of effects for rodents extended from 0.25 mg/kg-day (Roll and Matthiasch 1981) to 3.34 mg/kg-day (Downs and others 1960). In the rodent data set the majority of adverse effects were systemic, such as hair loss, and changes in body weight.

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5.18.1 Effects of Thallium on Rodents

In Roll and Matthiasch (1981), laboratory rats were administered thallium acetate and thallium chloride by gastric intubation for gestation days 6-15. At a dose of 0.25 mg/kg-day, both forms of thallium caused increased skeletal abnormalities. At the same dose, thallium chloride did not cause embryo toxicity. This was the lowest adverse effect in the considered data. Because this was a study of short duration and the exposure route was not as ecologically relevant as other routes, it was not considered for deriving TRVs.

In Downs and others (1960), laboratory rats were administered thallous acetate in feed for 15 weeks. At a dose of 1.43 mg/kg-day, hair loss was observed. These effects were not seen at a dose of 0.48 mg/kg-day. At a dose of 1.91 mg/kg-day, weight loss, hair loss, and histological changes occurred. The highest effect reported in the considered data was a dose of 3.34 mg/kg-day, which caused an increase in mortality. The no effect level at 0.48 mg/kg-day was chosen as the low TRV because it was a long duration study with a significant endpoint. A dose at 1.43 mg/kg-day causing increased hair loss was chosen for the high TRV. This dose was below a mortality effect and was in the mid-range of adverse effects. Hair loss was considered ecologically relevant because of possible effects such as behavioral changes, decreased sensory capabilities, or reduced conservation of body heat.

In Manzo and others (1983), thallium sulfate was administered in drinking water to rats for 36 weeks. At a dose of 1.60 mg/kg-day, 21 percent mortality and neuromorphological changes were reported. This was the lowest dose at which increases in mortality occurred. For this reason, the high TRV could not exceed this dose.

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THALLIUM TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Wistar rats	adult	No observed embryo-toxic effects	NEL	gestation 6-15 d	G	0.25	Roll and Matthiasch 1981
Wistar rats	adult	Increased frequency of skeletal anomalies	EL	gestation 6-15 d	G	0.25	Roll and Matthiasch 1981
Wistar rats	weanling	No effect on hair loss	NOAEL	15 wk	F	0.48[1]	Downs and others 1960
Wistar rats	weanling	Increase in hair loss	LOAEL	15 wk	F	1.43[2]	Downs and others 1960
Wistar rats	weanling	Weight loss in males, hair loss, histological changes in skin, and increase in kidney weight in males and females	EL	15 wk	F	1.91	Downs and others 1960
Wistar rats	weanling	Increase in male mortality	EL	15 wk	F	3.34	Downs and others 1960
Sprague-Dawley rats	adult	Increase in mortality (21%), abnormalities in caudal nerve, hair loss, neuromorphological changes	EL	36 wk	DW	1.60	Manzo and others 1983

Notes:

1 Selected low mammalian TRV = 0.48 mg/kg-day

2 Selected high mammalian TRV = 1.43 mg/kg-day

Highlighted rows — The bases for high and low TRVs

NOAEL — No observed adverse effect level

NEL — No effect level

LOAEL — Lowest observed adverse effect level

EL — Effect level

Exposure route: G = gavage, F = food, DW = drinking water

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5.18.2 Mammalian TRVs for Thallium

The low TRV was based on Downs and others (1960). At a dose of 0.48 mg/kg-day there was no reported hair loss.

The high TRV was based on Downs and others (1960). The dose of 1.43 mg/kg-day was below mortality doses and in the mid-range of effects reported.

The low TRV should be allometrically converted to account for differences in body size between the test organism (laboratory rats) and the mammalian receptors species of concern. The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 0.48 \text{ mg/kg-day } (65 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The high TRV should also be allometrically converted to account for differences in body size between the test organism and the receptor species. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 1.43 \text{ mg/kg-day } (65 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

The total data set of the effects of thallium on rodents (a) did not include exposure to the most sensitive life stage (–s); (b) did not address chronic exposures (–c); and (c) contained 1 test species representing 1 mammalian group (1/1). The low and high TRV test organisms are both in the mammalian group of laboratory rats. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

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5.19 TOXICITY REFERENCE VALUES FOR ZINC

In a review of literature on the toxicity of zinc to rodent and avian test organisms, 6 studies on rodents and 10 studies on birds were considered relevant for deriving TRVs. In deriving the rodent TRVs, the data set was supplemented with studies from ATSDR toxicity profiles (ATSDR 1994e). The range of adverse effects for rodents extended from doses of 70 mg/kg-day (Aughey and others 1977 as cited in ATSDR 1994e) to 4083.33 mg/kg-day (Maita and others 1981) and for birds from doses of 55.09 mg/kg-day (Lu and others 1990) to 2019.23 mg/kg-day (Hussein and others 1988). A large number of studies on the effects of zinc deficiency on mammals have been conducted. Only those studies measuring the effects of excess zinc were used in the TRV derivation. In general, these studies reported reproductive and hematological effects. For birds, the majority of studies measured organ weights, enzymatic effects and hematological effects in ducks, chickens, and quail; however, a few studies of pancreatic and reproductive effects were available.

5.19.1 Effects of Zinc on Rodents

Uriu-Hare and others (1989) exposed pregnant laboratory rats to dietary zinc carbonate in food at a single dose level of 39.13 mg/kg-day. After 20 days of dosing, the fetuses were analyzed and maternal hematological effects evaluated. No developmental effects were observed. This study represents the lowest dose given in a reproductive or developmental study in the core data set.

The highest dose in the data set was reported in Maita and others (1981). In this study, laboratory mice were given zinc sulfate in feed for five weeks at doses ranging from 40 to 4083.33 mg/kg-day. Hematological effects such as changes in hematocrit, glucose levels, and alkaline phosphatase were measured; some effects were reported at all dose levels.

In Walters and Roe ((1965), as cited in ATSDR 1994e), mice were given 68 mg/kg-day of zinc oleate for 9 months, resulting in severe anemia. This study was of questionable ecological relevance because zinc oleate is not a form of zinc usually found at military sites.

Aughey and others (1977) exposed mice to 96.08 mg/kg-day of zinc sulfate in water for up to 14 months. This dose resulted in hypertrophy (enlargement) and vacuolation (formation of cavities in cell

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protoplasm) of pancreatic islet cells and fasciculata cells in the adrenal cortex. This was a chronic study that had significant systemic effects and was the basis for the low TRV.

In Schlicker and Cox (1968), female rats were given 411.43 mg/kg-day zinc oxide in feed for up to 36 days, then their fetuses were analyzed. This dose resulted in fetal resorption and decreases in fetal weight and fetal liver weight. This study was the basis for the high TRV.

ZINC TOXICITY DATA (MAMMALIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
ICR strain mouse	5 wk	Decreased total leukocyte concentration	EL	13 wk	F	4083.33	Maita and others 1981
C3H strain	7 wk	Hypertrophy and vacuolation of pancreatic islet cells and fasciculata cells in the adrenal cortex	EL	14 mos	DW	96.08[1]	Aughey and others 1977
Sprague-Dawley rat	adult	No effect on maternal glucose levels, insulin levels, or hematocrit. No effect on litter number, live fetuses/litter, fetal length and weight, placental weight, resorptions/litter, fetal ossification centers, or fetal malformations	NEL	20 d	F	39.13	Uriu-Hare and others 1989
Sprague-Dawley rat	adult	Decreased levels iron and magnesium in maternal liver, calcium and magnesium in maternal kidney, and iron and magnesium maternal plasma concentrations; decreased calcium concentration in fetal livers; increased metallothionein conc. in maternal livers	EL	20 d	F	39.13	Uriu-Hare and others 1989
Nulliparous rat	adult	Decreased fetus weight, fetal liver weight, and body weight	EL	20 d	F	411.43[2]	Shlicker and Cox 1968
Nulliparous rat	adult	Total resorption of fetus	LOAEL	36 d	F	411.43[2]	Shlicker and Cox 1968
Nulliparous rat	adult	No effect on fetal resorption	NOAEL	36 d	F	205.71	Shlicker and Cox 1968
Laboratory mice	*adult*	*Severe anemia*	*EL*	*9 mos*	*F*	*68*	*Walters and Roe 1965 (In ATSDR 1994e)*

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Notes:

1 Selected low mammalian TRV; an uncertainty factor of 10 was applied for EL to NEL conversion giving a TRV = 9.60 mg/kg-day

2 Selected high mammalian TRV = 411.43 mg/kg-day

Italic Text	Information associated with a study presented in ATSDR
Highlighted rows	The bases for high and low TRVs
NOAEL	No observed adverse effect level
NEL	No effect level
LOAEL	Lowest observed adverse effect level
EL	Effect level
Exposure route:	DW = drinking water, F = food

5.19.2 Mammalian TRVs for Zinc

The low TRV was based on Aughey and others (1977), in which a dose of 96.08 mg/kg-day resulted in cellular changes in the pancreas and adrenal cortex. An uncertainty factor of 10 was applied to the TRV to convert the effect level to a no effect level equivalent.

The high TRV was based on Schlicker and Cox (1968), in which a dose of 411.43 mg/kg-day affected fetal developmental. The study was selected because the obvious adverse ecologically relevant effects represented the mid-range of adverse effects.

This dose should be allometrically converted to account for differences in body size between the test organism (laboratory mice) and the receptor species. Special consideration should be given to this TRV because it is very close to the minimum dietary requirement for rodents of 7.45 mg/kg-day reported in Fox and others (1984). The following allometric equation as outlined in Section 3.3 can be used to arrive at a low TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{Dose}_{\text{receptor}} = \text{Dose}_{\text{test organism}} (\text{Body Weight}_{\text{test organism}}/\text{Body Weight}_{\text{receptor}})^{1/4}$$

$$\text{Low TRV: Dose}_{\text{receptor}} = 9.608 \text{ mg/kg-day } (25.5 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

This dose (411.43 mg/kg-day) should be allometrically converted to account for differences between the test organism and the mammalian receptor species of concern. The following allometric equation can be used to arrive at a high TRV for a specific receptor species with the addition of the receptor body weight in grams:

$$\text{High TRV: Dose}_{\text{receptor}} = 411.43 \text{ mg/kg-day } (175 \text{ g/Body Weight}_{\text{receptor}})^{1/4}$$

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The total data set of the effects of zinc on rodents (a) included exposure to the most sensitive life stage of the test organism (+s); (b) included chronic exposure durations (+c); and (c) contained 2 different test species representing 2 different mammalian groups (2/2). The low TRV test organism is in the mammalian group of laboratory mice and the high TRV test organism is in the mammalian group of laboratory rats. This information should be included in the confidence rating for each of the allometrically converted TRVs as outlined in Section 3.4.

5.19.3 Effects of Zinc on Birds

In Lu and Combs (1988), a dose of 11.36 mg/kg-day resulted in no effect on food intake, no change in the concentration of zinc in the pancreas and liver, and no decrease in pancreatic enzymes in day-old chickens. In the same study, a dose of 138.45 mg/kg-day resulted in a decrease in weight gain and food intake in day-old chickens.

Hussein and others (1988) reported decreases in egg production and eggshell breaking strength resulting from a dose of 2,019.23 mg/kg-day given female quail for 23 weeks. This study represents the highest dose in the data set.

Gasaway and Buss (1972) found that giving 7-week-old ducklings 172 mg/kg-day of zinc carbonate for up to 60 days resulted in decreases in gonad, pancreas, and body weight. At this dose the authors also reported diarrhea and leg paralysis. This study was the basis for both the low and high TRVs.

Stahl and others (1990) reported that giving adult chickens 126.5 mg/kg-day in feed for 44 weeks did not affect body weight or reproduction. This study was not considered for TRV derivation because the test organisms were chickens, which appear to be less sensitive than ducks to the effects of zinc.

ZINC TOXICITY DATA (AVIAN)

Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Single Comb White Leghorn chickens	14 d	Increase in pancreatic amylase activity	EL	7 d	F	55.09	Lu and others 1990
Single Comb White Leghorn chickens	1 d	Decrease in weight gain and feed intake	LOAEL	9 d	F	138.45	Lu and Combs 1988

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Test Organism	Age	Measured Effect	Test Endpoint	Duration	Exposure Route	Dose (mg/kg-day)	Reference
Single Comb White Leghorn chickens	1 d	No effect on feed intake, concentration of copper in the liver, pancreatic amylase levels, alpha-tocopherol in plasma, liver, and pancreas; or liver ascorbate-induced TBA	NOAEL	9 d	F	11.36	Lu and Combs 1988
Single Comb White Leghorn chickens	24 wk	No effect on egg production, feed conversion, feed consumption, hen weight, fertility or hatchability, offspring body weight or incidence of frayed feathers; no effect on copper or iron concentrations in liver, pancreas or tibiatarsus of offspring	NEL	44 wk	F	126.5	Stahl and others 1990
Japanese quail	23 wk	Decreases in feed intake/hen, egg production, eggshell breaking strength, body weight	EL	7 d dosing, 6 wk post trtmt observation period	F	2019.23	Hussein and others 1988
Japanese quail	23 wk	No effect on egg production rates	NEL	7 d dosing, 6 wk post trtmt observation period	F	2019.23	Hussein and others 1988
Mallard ducks	7 wk	Decrease in body weight at 40 days; decrease in gonad weight; decrease in organ: body weight ratio (pancreas, adrenal and kidney); decreases in pancreas weight and liver weight, leg paralysis, diarrhea	EL	60 d	F	172[1,2]	Gasaway and Buss 1972

Notes:

1 Selected low avian TRV; an uncertainty factor of 10 was applied for El to NEL conversion giving a TRV = 17.2 mg/kg-day

2 Selected high avian TRV = 172 mg/kg-day

Highlighted rows The bases for high and low TRVs

NOAEL No observed adverse effect level

NEL No effect level

LOAEL Lowest observed adverse effect level

EL Effect level

Exposure route F = food

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5.19.4 Avian TRVs for Zinc

The low TRV was based on Gasaway and Buss (1972) which reported body weight, reproductive and pancreatic effects at a dose of 172 mg/kg-day. An uncertainty factor of 10 was applied to convert the effect level to a no effect level resulting in a low TRV of 17.2 mg/kg-day. No sub-chronic to chronic uncertainty factor was applied because the study evaluated effects on juvenile ducks during a sensitive life stage.

The effect level of 172 mg/kg-day in Gasaway and Bus (1972) was also the basis for the high TRV. Uncertainty factors are not applied to high TRVs, so the unadjusted dose was selected as the high TRV.

The data set of the effects of zinc on birds (a) included exposure to the most sensitive life stage of the test organism (+s); (b) included chronic exposures (+c); and (c) contained 3 different test species representing 2 different avian groups (3/2). The low and high TRV test organisms are both in the duck avian group. This information should be included in the confidence rating for each of the TRVs as outlined in Section 3.4.

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ATTACHMENT 1

SAN FRANCISCO BAY REGIONAL TOXICITY REFERENCE VALUES

ATTACHMENT 1
SAN FRANCISCO BAY REGIONAL TOXICITY REFERENCE VALUES

Contaminant		Regional TRVs - Mammals: High TRV (mg/kg-day)	Regional TRVs - Mammals: Low TRV (Unadjusted*) (mg/kg-day)	Regional TRVs - Birds: High TRV (mg/kg-day)	Regional TRVs - Birds: Low TRV (Unadjusted*) (mg/kg-day)
PESTICIDES, PCBs					
DDT, DDE DDD [2]	Dose	*16*	*0.8*[3]	*DDT - 1.5 DDE - 0.6*	*0.009*[3] *(0.027)*
	Reference	EPA-Great Lakes, Clement and Oakey 1974	EPA-Great Lakes, Fitzhugh 1948	EPA-Great Lakes, Heath et al. 1969	EPA-Great Lakes, Anderson et al. 1975
	Confidence	N/A		N/A	
PCBs	Dose	*1.28*	*0.36*	*1.27*	*0.09*[1] *(0.88)*
	Reference	Linzey 1987	Simmons and McKee 1992	Britton and Huston 1973	Platonow & Reinhart 1973
	Confidence	$+_s +_c$ 3/3		$+_s +_c$ 14/5	
Aldrin	Dose	*1.0*	*0.1*[1] *(1.0)*	No Avian TRV: Insufficient Data[11]	
	Reference	Paul & others 1992	Paul & others 1992		
	Confidence	$+_s +_c$ 2/2			
Lindane	Dose	*3.75*	*0.05*	No Avian TRV: Insufficient Data[11]	
	Reference	Sircaar & Lahiri 1989	Naishtein and Leibovich 1971		
	Confidence	$+_s +_c$ 4/3			
Heptachlor	Dose	*6.8*	*0.13*[1] *(1.29)*	No Avian TRV: Insufficient Data[11]	
	Reference	Norotsky & others 1995	Shain & others 1977		
	Confidence	$+_s +_c$ 4/2			
Methoxychlor	Dose	*50.0*	*2.5*[4] *(25)*	No Avian TRV: Insufficient Data[11]	
	Reference	Gray & others 1989	Gray & others 1989		
	Confidence	$+_s +_c$ 2/2			
ORGANOTINS					
Dibutyltin and Tributyltin	Dose	*15.0*	*0.25*[5] *(2.5)*	*45.85*	*0.73*[5] *(7.34)*
	Reference	Ema & others 1995	Smialowicz & others 1989	Schlatterer & others 1993	Schlatterer & others 1993
	Confidence	$+_s -_c$ 5/2		$+_s -_c$ 1/1	

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ATTAC ENT 1

SAN FRANCISCO BAY REGIONAL TOXICITY REFERENCE VALUES

Contaminant		Regional TRVs - Mammals		Regional TRVs - Birds	
		High TRV (mg/kg-day)	Low TRV (Unadjusted*) (mg/kg-day)	High TRV (mg/kg-day)	Low TRV (Unadjusted*) (mg/kg-day)
PAHs					
Benzo(a)pyrene	Dose	*32.79*	*1.31*	No Avian TRV: Insufficient Data	
	Reference	Rigdon & Neal 1969	Neal & Rigdon 1967		
	Confidence	$+_s +_c$ 2/2-			
Napthalene	Dose	*150.0*	*50.0*	No Avian TRV: Insufficient Data	
	Reference	Navarro & others 1991	Navarro & others 1991		
	Confidence	$+_s +_c$ 2/2			
METALS					
Arsenic	Dose	*4.70*	*0.32*	*22.01*[g]	*5.5*[g]
	Reference	Brown & others 1976	Schroeder & others 1968	Stanley,Jr. & others 1994	Stanley,Jr. & others 1994
	Confidence	$+_s +_c$ 2/2		$+_s +_c$ 1/1	
Barium	Dose	No Mammalian TRV: Insufficient Data		No Avian TRV: Insufficient Data	
	Reference				
	Confidence				
Beryllium	Dose	No Mammalian TRV: Insufficient Data		No Avian TRV: Insufficient Data	
	Reference				
	Confidence				
Cadmium	Dose	*2.64*	*0.06*	*10.43*	*0.08*[f] *(0.78)*
	Reference	Schroeder & Mitchener 1971	Webster 1988	Richardson and others 1974	Cain & others 1983
	Confidence	$+_s +_c$ 2/2		$+_s +_c$ 4/2	
Cobalt	Dose	*20*	*1.2*[f] *(12.0)*	No Avian TRV: Insufficient Data	
	Reference	Mollenhauer & others 1985	Domingo & others 1985		
	Confidence	$+_s +_c$ 2/2			

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ATTAC ENT 1
SAN FRANCISCO BAY REGIONAL TOXICITY REFERENCE VALUES

Contaminant		Regional TRVs - Mammals		Regional TRVs - Birds	
		High TRV (mg/kg-day)	Low TRV (Unadjusted*) (mg/kg-day)	High TRV (mg/kg-day)	Low TRV (Unadjusted*) (mg/kg-day)
Copper	Dose	*631.58*	*2.67[5,6] (26.67)*	*52.26*	*2.3[5,10] (22.99)*
	Reference	Hebert and others 1993	Pocino and others 1991	Jensen and Maurice 1978	Norvell & others 1975
	Confidence	$-_s +_c$ 2/2		$+_s -_c$ 3/2	
Lead	Dose	*240.64*	*0.0015*	*8.75*	*0.014[1] (0.14)*
	Reference	Wise 1981	Krasovskii & others 1979	Edens & Garlich 1983	Edens and others 1976, Edens and Garlich 1983
	Confidence	$+_s +_c$ 2/2		$+_s +_c$ 8/4	
Manganese	Dose	*159.09*	*13.7[1] (135.56)*	*776*	*77.6[1] (776)*
	Reference	Gray & Laskey 1980	Gray & Laskey 1980	Laskey & Edens 1985	Laskey & Edens 1985
	Confidence	$+_s +_c$ 2/2		$+_s -_c$ 2/1	
Mercury[4]	Dose	*4 - rodents* *0.27 - lg mammals*	*0.25 - rodents* *0.027[1] (0.27) - lg mammals*	*0.18*	*0.039[7] (0.078)*
	Reference	EPA-Great Lakes, Fuyuta and others 1978	EPA-Great Lakes, Khera and Tabacova 1973	EPA-Great Lakes, Heinz and Locke 1976	EPA-Great Lakes, Heinz 1974, 1975, 1976, 1979
	Confidence	N/A		N/A	
Molybdenum	Dose	No Mammalian TRV: Insufficient Data		No Avian TRV: Insufficient Data	
	Reference				
	Confidence				
Nickel	Dose	*31.6*	*0.133[1] (1.33)*	*56.26*	*1.38[5] (13.79)*
	Reference	Smith and others 1993	Smith and others 1993	Cain & Pafford 1981	Cain & Pafford 1981
	Confidence	$+_s +_c$ 2/2		$+_s -_c$ 2/2	
Silver	Dose	No Mammalian TRV: Insufficient Data		No Avian TRV: Insufficient Data	
	Reference				
	Confidence				

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SAN FRANCISCO BAY REGIONAL TOXICITY REFERENCE VALUES

Contaminant		Regional TRVs - Mammals		Regional TRVs - Birds	
		High TRV (mg/kg-day)	Low TRV (Unadjusted*) (mg/kg-day)	High TRV (mg/kg-day)	Low TRV (Unadjusted*) (mg/kg-day)
Selenium	Dose	*1.21*	*0.05*	*0.93*	*0.23*
	Reference	Schroeder & Mitchener 1971	Harr & others 1967	Heinz & others 1989	Heinz & others 1989
	Confidence	$^{-}_{s}\,^{+}_{c}$ 2/2		$^{+}_{s}\,^{+}_{c}$ 2/2	
Thallium	Dose	*1.43*	*0.48*	No Avian TRV: Insufficient Data	
	Reference	Downs & others 1960	Downs & others 1960		
	Confidence	$^{-}_{s}\,^{-}_{c}$ 1/1			
Zinc	Dose	*411.43*	*9.60*[1,6] *(96.03)*	*172*	*17.2*[1] *(172)*
	Reference	Shlicker and Cox 1968	Aughey and others 1977	Gasaway and Buss 1972	Gasaway and Buss 1972
	Confidence	$^{+}_{s}\,^{+}_{c}$ 2/2		$^{+}_{s}\,^{+}_{c}$ 3/2	

Notes:

* The unadjusted TRV appears in parentheses. This dose is the TRV without uncertainty factors applied.

See Section 3.4 for an explanation of confidence characterization for TRVs.

[1] Uncertainty factor of 10 for low-effect to no-effect level conversion applied to arrive at low TRV.

[2] EPA's Great Lakes Water Quality Initiative Wildlife Values were used as low TRVs. The low dose was adjusted for subchronic to chronic and LOAEL to NOAEL conversions as applied by EPA. The high dose was selected from data presented in EPA's summary tables. Confidence ratings were not applied to these TRVs.

[3] EPA applied an uncertainty factor of 3 to the dose for low-effect to no-effect level conversion.

[4] Mercury TRVs were selected from data in Great Lakes summary tables. See Section 5.8.2.1 for rationale behind selection of these TRVs. Confidence ratings were not applied to these TRVs.

[5] Uncertainty factor of 10 for subchronic to chronic conversion applied to arrive at a low TRV.

[6] Low TRV was adjusted for or is close to nutritional requirements.

[7] EPA applied to the dose an uncertainty factor of 2 for low-effect to no-effect level conversion.

[8] Dibutyltin and tributyltin databases were combined to arrive at a single TRV for butyltins

[9] The diversity of test organisms in the cadmium data set was limited. The workgroup had high confidence in the TRV for waterfowl, but lower confidence if the TRV is applied to other birds.

[10] The work group considered this TRV to be very conservative for granivorous birds.

[11] Dr. Chernoff (CDFG) suggested that avian TRVs for DDT may be used as surrogate TRVs for the sum of all organochlorine (OC) pesticides. However, the Navy does not recommend this method, as DDT is not functionally equivalent to other OC pesticides.

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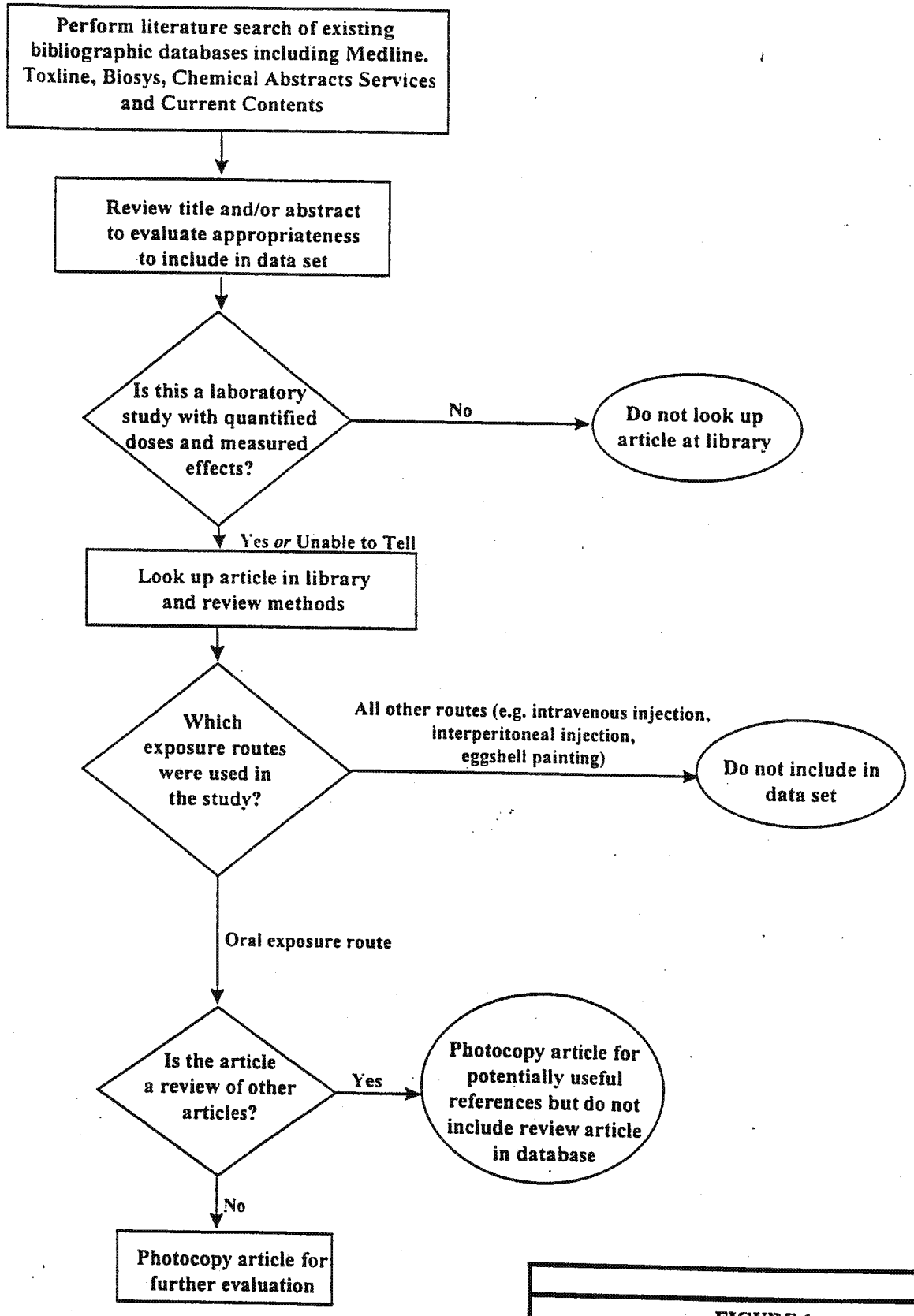
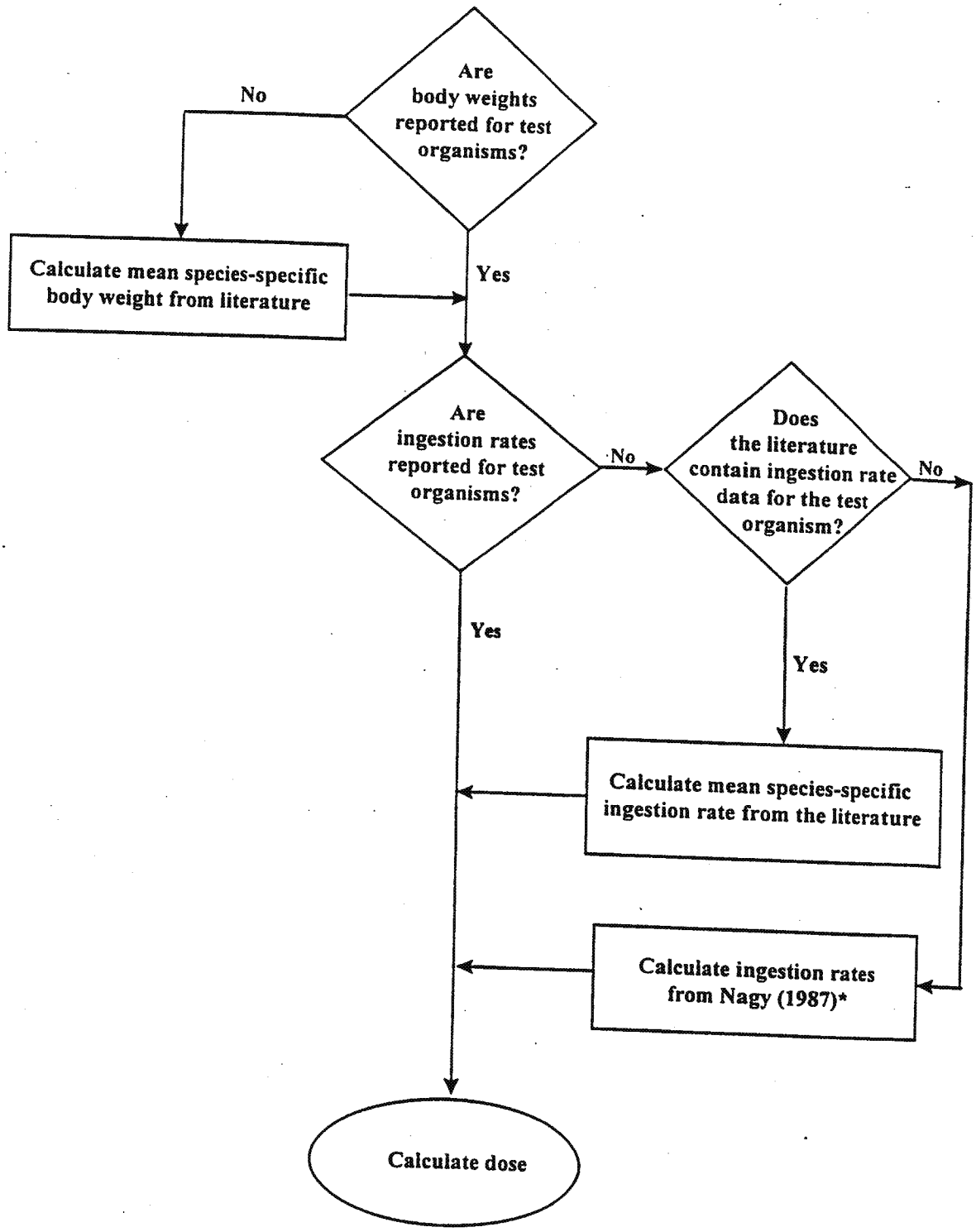


FIGURE 1
Literature Search Decision Tree

PRC ENVIRONMENTAL MANAGEMENT, INC



*Nagy, K.A. (1987) Field metabolic rate and food requirement scaling in mammals and birds. Ecological Monographs 57(2):111-128.

FIGURE 2
Ingestion Rate and Body Weight Decision Tree

PRC ENVIRONMENTAL MANAGEMENT, INC

PLANTS

Dieldrin is taken up by various crops, and most of the dieldrin remains in the roots (ATSDR 1993a). Foliar contamination of soybean plants was found to occur via root sorption and vapor sorption. Bioconcentration is receptor specific. Soybean seeds contained dieldrin in concentrations of about 10 percent of those in soil (Stickel 1968). Peanuts stored two to four times the concentration of aldrin and dieldrin found in the soil (Beck and others 1962, as cited in Stickel 1968).

INVERTEBRATES

Aldrin and dieldrin are toxic ~~against~~ to insects, including corn pests and termites, by contact or ingestion (Hayes 1982, as cited in ATSDR 1993a).

AMPHIBIANS AND REPTILES

Frog embryos treated with dieldrin resulted in accelerated growth and abnormalities in later developmental stages (Brooks 1981, as cited in Power and others 1989). Adverse effects caused by exposure to aldrin and dieldrin include coarse tremors, rigidity, abnormal reactions to stimulation, convulsions, and disorientation (Kaplan and Overpeck 1964, as cited in Power and others 1989). Inhibition of enzyme systems and greater effects from dieldrin than aldrin are reported to occur in reptiles (Phillips and Wells 1974, as cited in Hall 1980).

FISH AND AQUATIC ORGANISMS

Although the toxicities of aldrin and dieldrin are similar in most organisms, in fish, dieldrin is an order of magnitude more toxic than aldrin (Beyer and others 1996). In tests of exploitation rates on guppy populations, populations treated with dieldrin showed reduced growth and reproduction, which would have made them unable to sustain prolonged or high exploitation rates. Such population effects on species that serve as prey to many ecosystem predators could reduce ecosystem productivity and cause nutrient loss (Peterle 1991).

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IRDS

Dieldrin adversely affects reproduction in birds. Eggshell thickness, egg production, and egg fertility decreased in mallards given various doses of dieldrin (Winn 1972, Walker and others 1969, as cited in Beyer and others 1996). The major impact of dieldrin on raptors is reported as being direct mortality, rather than eggshell thinning (Beyer and others 1996).

MAMMALS

The doses at which aldrin is lethal in rats are similar to the lethal doses of dieldren. Decreased survival was seen in rats, dogs, and mice consuming low doses of dieldren or aldrin over long periods (ATSDR 1993a). Adverse effects of dieldren and aldrin exposure include tremors, hyperexcitability, irritability, convulsions, and increases in liver weight and size. Increased postnatal mortality also was seen in mice and rats.

A.2 ARSENIC

Arsenic is a naturally occurring element that is widely distributed in the environment and is used in metallurgy to harden copper, lead, and alloys and in the manufacture of certain types of glass. Historically, some forms of arsenic have been used as pesticides.

Arsenic is present in the environment in both inorganic and organic forms. The bioavailability and toxicity of arsenic are dependent upon the chemical and physical forms of arsenic, the exposure route, and the species of concern. Inorganic arsenic is present in the environment in two major forms, arsenate (As5+) and arsenite (As3+). In the environment, arsenate is more abundant and bioaccumulates more rapidly than arsenite; however, arsenite is the more toxic form (Sadiq 1992). Any environmental conditions that promote an increase in arsenite concentrations will increase the toxicity of arsenic in the environment. The oxidation-reduction environment is the most important environmental parameter that affects the bioavailability of arsenic. Reduced conditions in the environment cause the ratio of arsenite to arsenate to increase, thus increasing the toxicity of arsenic in the environment. In addition to oxidation-reduction, the pH of the aquatic environment influences the toxicity of arsenic. As the pH of the water increases, the toxicity of arsenic decreases as more arsenate is produced (Sadiq 1992).

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Marine organisms accumulate more arsenic than freshwater organisms. Arsenate is more readily bioaccumulated than arsenite (Sadiq 1992). Bioconcentration factors (BCF) experimentally determined for arsenic appear to be relatively low. The methylated species of arsenic are efficiently transferred in the food chain (Eisler 1988a); however, it does not appear to be biomagnified through the food chain (Eisler, 1988a; Callahan and others 1979; EPA 1982a and 1983e, as cited in ATSDR 1993b).

PLANTS

Terrestrial plants may accumulate arsenic by root uptake from the soil or by absorption of airborne arsenic deposited on the leaves. Certain species of plants may accumulate substantial levels of arsenic (Shaw 1990). Soil concentrations of arsenic have been known to reduce crop plant yields (NRCC 1978, as cited in Eisler 1988a). If the roots of the plant absorb excess arsenic, the plant will stop growing and developing (NRCC 1978, as cited in Eisler 1988a). The chemical form of arsenic absorbed by plants will determine the type of toxic effect plants ~~will have when exposed~~. Effects can range from inhibition of light activation, wilting, chlorosis, browning, dehydration, and death (National Academy of Science [NAS] 1977, as cited in Eisler 1988a).

Marine phytoplankton have the ability to bioconcentrate inorganic arsenic to high levels, then transform them to methylated arsenic. The methylated species are efficiently transferred in the food chain (Eisler 1988a); however, it does not appear to be biomagnified through the food chain (Eisler 1988a; Callahan and others 1979; EPA 1982a and 1983e, as cited in ATSDR 1993b).

INVERTEBRATES

Arsenic has been used as a pesticide in the past. Arsenic may reduce growth and metabolism of soil microbiota, reduce numbers of bacteria and protozoans, and may adversely affect earthworms to reduce their numbers in the soil (NRCC 1978, as cited in Eisler 1988a).

AMPHIBIANS AND REPTILES

Very little information was available on the effects of arsenic on amphibians and reptiles. One report states, however, that developing toad embryos exposed to arsenic concentrations observed that 50 percent of developing embryos died or were malformed (Eisler 1988a).

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FISH AND AQUATIC ORGANISMS

Arsenic can produce both carcinogenic and mutagenic effects in aquatic organisms (Eisler 1988a). Toxic effects of arsenic in fish include impaired behavior, reduced growth, lack of appetite, and failure to metabolize food (Eisler 1988a). The chemical form of arsenic, the type of organism, and the organism's life stage all influence the organism's susceptibility to arsenic compounds. In general, the earlier life stages and smaller organisms are more sensitive to arsenic concentrations (Sadiq 1992).

Some species are more susceptible to arsenic toxicity because of their environment and feeding habits.

~~In addition to the stage of development of an organism, the toxic effect of arsenic is influenced by the type organism~~. Marine organisms accumulate more arsenic than freshwater organisms. Bioaccumulation of arsenic in marine organisms is influenced by the amount of arsenic in sea water and is further influenced by the marine organism's feeding habits. Bottom feeders appear to be more sensitive to arsenic concentrations than other types of fish (Sadiq 1992). This is because bottom feeders filter the water column and the fine particulate matter in the water for food. Arsenic in the fine particular matter is incidentally ingested during this search for food. As a result, bottom feeders, such as molluscs, accumulate more arsenic in their soft tissue than fish (Sadiq 1992). Fish on the other hand do not have to filter the water column for food, and as a result, the main route of uptake occurs when they filter the water column for oxygen with their gills. This filtering process occurring in the fish gill tissue is the main route of uptake of arsenic for these types of aquatic organisms (Sadiq 1992).

BIRDS

Some species of birds are more sensitive to arsenic exposure, while others appear to be more tolerant of arsenic exposure (Eisler 1988a). The acute oral exposure of inorganic arsenic destroys the blood vessel lining in the gut, which can result in lower blood pressure (Nystrom 1984, as cited in Eisler 1988a). The acute oral exposure of arsenite in birds was observed to cause hepatocyte damage by arsenic inhibition of the sodium pump in cells (Nystrom 1984, as cited in Eisler 1988a). Acute effects of arsenite in birds include, muscular incoordination, debility, slowness, jerkiness, falling, hyperactivity, fluffed feathers, drooped eyelids, huddled position, unkempt appearance, loss of righting reflex, immobility, and seizures (Eisler 1988a). Chronic effects include systemic, growth, behavioral, and reproductive problems (Stanley and others 1994; Whitworth and others 1991; Camardese and others 1990).

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MAMMALS

Arsenic is a carcinogen, teratogen, and a possible mutagen. Adverse effects produced by arsenic are highly dose-dependent. At low levels, arsenic may be an essential nutrient and substitute for phosphorous in biochemical reactions (ATSDR 1993b). At high levels, however, arsenic is recognized as an effective poison. Chronic exposure to low levels of arsenic can produce malaise and fatigue, gastrointestinal distress, anemia and basophilic stippling, neuropathy, and skin lesions, which can develop into skin cancer. Water-soluble arsenic is efficiently absorbed from the gastrointestinal tract and circulated throughout the body. Trivalent arsenic is detoxified in the liver by conversion to methylarsenic acid and dimethylarsenic acid, which are the principal forms excreted in the urine. The body burden of arsenic can reach considerable levels because it can be sequestered in nails, hair, bones, teeth, skin, liver, kidneys, and lungs (ATSDR 1993b). In mammalian species, arsenic is a teratogen that can pass the placental barrier and produce fetal death and malformations consisting of exencephaly, eye defects, and renal and gonadal agenesis (Eisler 1988a; ATSDR 1993b; Domingo 1994).

A.3 BARIUM

Barium is an alkaline earth metal that is widely distributed in the environment and is used to produce alloys, paints, soap, paper, rubber, ceramics, and glass. Barium is naturally present in plant and animal tissue and may be an essential element in trace amounts.

The solubility of barium compounds influences the adsorption and toxicity of these compounds. The more soluble barium compounds are more easily adsorbed by organisms and may be accumulated in the skeleton (Amdur and others 1991).

Barium is found mainly in inorganic complexes and is stable in the +2 valence state. Environmental conditions such as pH, Eh, cation exchange capacity, and calcium carbonate levels in soil will affect the movement of barium in the environment (ATSDR 1990a). In an aquatic environment, barium will most likely precipitate out of solution as a $BaSO_4$ or $BaCO_3$ insoluble salt, or the barium ion will absorb to particulate matter (ATSDR 1990a).

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Barium can bioaccumulate in terrestrial and aquatic organisms (ATSDR 1990a). Marine plants can bioconcentrate barium by a factor of 1,000 times the concentration found in the water. Marine animals, plankton, and brown algae have reported BCFs of 100, 120, and 260, respectively (Bowen 1966; Schroeder 1970, as cited in ATSDR 1990a). Terrestrial plants bioconcentrate low levels of barium from the soil (Schroeder 1970, as cited in ATSDR 1990a).

PLANTS

Some plants may accumulate barium from soil. Brazil nuts can accumulate high levels of barium (Amdur 1991; ATSDR 1990a).

INVERTEBRATES

No information was available on the effects of barium on invertebrates.

AMPHIBIANS AND REPTILES

No information was available on the effects of barium on amphibians and reptiles.

FISH AND AQUATIC ORGANISMS

In the aquatic environment, the most likely route of particulate metals into fish is through the gill, gut, or skin (Pulsford and others 1992). Very little information was available on the effects of barium on fish and aquatic organisms. In one study, however, barium was observed to inhibit chlorine absorption in the intestine of winter flounder (Charney and Taglietta 1992).

MAMMALS

In addition to skeletal deposition, ingestion of barium salts can result in gastrointestinal distress, muscular paralysis, lowered pulse rate, muscle stimulation, and irregular cardiac contractions (Amdur and others 1991). Rats exposed to barium concentrations in their diet showed toxic responses. In both acute and chronic oral exposure scenarios increased blood pressure was observed in exposed rat populations (ATSDR 1990a). In other acute exposure studies gastrointestinal effects and respiratory weakness were observed in the exposed populations (ATSDR 1990a). Ovary weight and ovary to brain

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weight ratios both decreased as a result of acute oral exposure to barium in rat populations (Borzelleca and others 1988, as cited in ATSDR 1990a). Published data concerning developmental, reproductive, or carcinogenic effects of barium on mammalian species are very limited (ATSDR 1990a).

A.4 BERYLLIUM

In most types of soil, beryllium is expected to be tightly sorbed onto clay particles (Fishbein 1981, as cited in ATSDR 1993c). Beryllium is expected to have limited mobility in soil, although its mobility may increase as a result of formation of soluble hydroxide complexes in soils of higher pH (Callahan and others 1979, as cited in ATSDR 1993c).

In aquatic environments, most beryllium is usually present sorbed to suspended matter or to sediment, rather than in a dissolved form in the water column. Beryllium may precipitate into sediment as a result of a formation of insoluble complexes and is usually sorbed onto clay particles in sediment. A high percentage of beryllium is expected to be immobile in water as a result of this association with sediment particles, although at a high pH, the formation of water-soluble complexes with hydroxide ions may increase the solubility and mobility of beryllium (Callahan and others 1979, as cited in ATSDR 1993c).

Bioconcentration of beryllium in fish is not likely because of the low absorption of beryllium from the water column by aquatic animals. Significant biomagnification of beryllium within the food chain has not been observed (Fishbein 1981, as cited in ATSDR 1993c).

PLANTS AND INVERTEBRATES

Very little information was available on the effects of beryllium on plants or invertebrates.

AMPHIBIANS AND REPTILES

Very little information was available on the effects of beryllium on amphibians and reptiles. However, in a journal article, Jagoe and others (1993) suggest that the toxic effects of beryllium are similar to those by aluminum. In general, metals induce their toxic effects in the gill surface (skin) of amphibians. Reduced survival of adult populations of frogs and salamanders has been observed when the study organisms were chronically exposed to aluminum in the test water (Horne and Dunson 1995). In

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addition, aluminum exposure was shown to cause a significant increase in embryonic mortality (Horne and Dunson 1995).

FISH AND AQUATIC ORGANISMS

Very little information was available on the effects of beryllium on fish and aquatic organisms. However, in a journal article, Jagoe and others (1993) suggest that the toxic effects of beryllium are similar to those produced by aluminum. In general, metals induce their toxic effects in the gill surface of aquatic organisms. Like other metals, beryllium affects the physiological processes occurring at the gill surface, including ion regulation and gas exchange (Jagoe and others 1993). At low concentrations, beryllium causes gill damage. At higher concentrations effects include development of chloride cell apical crypts, increased mucus production, microridge loss, epithelial hyperplasia, and fusions of primary lamellae (Jagoe and others 1993). Beryllium water concentrations were found to cause gill abnormalities and damage to the fish species studied (Jagoe and others 1993).

BIRDS

Very little information was available on the effects of beryllium on birds.

MAMMALS

The major toxicological effects of beryllium occur when the compound is inhaled from the air, and beryllium is then deposited in the lungs of mammals. The mammals that were studied include mice, rats, rabbits, and monkeys. The toxicological effects of beryllium in the lung include pneumonitis, hypersensitivity, and chronic granulomatous pulmonary disease (Amdur 1991).

A.5 CADMIUM

Cadmium is a naturally occurring element. It is used in the production of nickel-cadmium batteries, metal plating, pigments, plastics, synthetics, and alloys. Cadmium in soils may leach into water, especially under acidic conditions (Callahan and others 1979; Elinder 1985, as cited in ATSDR 1993d), and cadmium-containing soil particles may be distributed into the air or eroded into water (EPA 1985, as cited in ATSDR 1993d). In the aquatic environment, the bioavailability of cadmium is dependent on

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such factors as pH, redox potential, water hardness, and the presence of other complexing agents. The most bioavailable form of cadmium is the Cd^{2+} ion. An increase in temperature or salinity will increase the bioavailable form of cadmium and as a result increase the bioaccumulation and toxicity of cadmium to aquatic organisms. A decrease in pH will increase the amount of cadmium ions in water and increase bioaccumulation in aquatic organisms (Sadiq 1992).

Cadmium has no essential biological function and is highly toxic to plants and animals. It is a carcinogen and teratogen, and a suspected mutagen. Cadmium is associated with severe sublethal effects on reproduction at relatively low environmental concentrations (Eisler 1985a). Aquatic and terrestrial organisms at all trophic levels bioconcentrate and bioaccumulate cadmium (Eisler 1985a). Bioconcentration in fish depends on the pH and the organic content of the water (John and others 1987, as cited in ATSDR 1993d). Although some data suggest that lower trophic levels display biomagnification of cadmium, the data available on biomagnification, especially for animals at the top of the food chain, are inconclusive (Beyer 1986; Gochfeld and Burger 1982, as cited in ATSDR 1993d).

PLANTS

Cadmium is known to be toxic to plants at much lower soil concentrations than other heavy metals. Cadmium is more readily taken up by plants than other metals (EPA 1981), and as a result, some plants can accumulate high levels of cadmium in their developing leaflets (Morishita and Boratynski 1992).

INVERTEBRATES

Some insects can accumulate large quantities of cadmium without observable adverse effects (Jamil and Hussain 1992). Certain insects, such as caddis flies, can accumulate high levels of cadmium in their gill tissue (Sadiq 1992). However, very little information was available concerning the effects of cadmium on invertebrates.

AMPHIBIANS AND REPTILES

Very little information was available concerning the effects of cadmium on amphibians and reptiles.

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FISH AND AQUATIC ORGANISMS

Marine organisms appear more resistant to cadmium than freshwater organisms. Cadmium accumulates in the gill tissue of mussels, the digestive glands of scallops, and the liver and kidney of bony fish and sharks (Loring and Prosi 1986; Bryan and Gibbs 1973; Grimanis and others 1978, as cited in Sadiq 1992). In general, however, cadmium accumulates in the liver and kidney of fish (Sindayigaya and others 1994; Sadiq 1992). Cadmium has been shown to be highly toxic in aquatic environments and has been implicated as the cause of deleterious effects on fish and aquatic organisms, including increased mortality, respiratory disruptions, altered enzyme levels, abnormal muscular contractions, reduced growth, and reduced reproduction (Eisler 1985a). Cadmium concentrations in water caused damage to the reproductive organs of fish, a decrease in the survival rate of fish embryos, and a reduction of growth rates of fry (EPA 1976). Crustaceans appear to be more sensitive to cadmium concentrations, as compared to fish and molluscs (Phillips 1980, as cited in Sadiq 1992), and younger stages of aquatic life appear to be more sensitive to cadmium than adults (Sadiq 1992).

BIRDS

Sublethal effects in birds include growth retardation, nephrotoxicity, anemia, damage to the testicles and absorptive epithelium of the duodenum, reduced egg production, and effects on calcium absorption (Scheuhammer 1987).

MAMMALS

In mammalian species, cadmium concentrates in the liver and kidneys and is excreted in the urine at a very slow rate. The acute toxic effects of cadmium given orally produce nausea, vomiting, salivation, diarrhea, and abdominal cramps. Immediate death may be caused by shock and dehydration; renal and cardiopulmonary failure may cause death a week or so after ingestion. Chronic toxicity effects of cadmium given orally to rats are decreased motor skills, peripheral neuropathy, weakness, and muscle atrophy. When inhaled cadmium is a carcinogen that can produce tumors in the lung, trachea, and bronchus.

Cadmium is a known developmental ~~toxin~~ causing teratogenic and mutagenic effects. Parental doses of cadmium have been shown to decrease testosterone and produce adverse effects on the testes and prostate

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of test animals. Prenatal exposure to cadmium has fetotoxic effects, such as reduced fetal weights (ATSDR 1993d), and can cause adverse effects during the development of the lung, brain, testes, eye, and palate (Domingo 1994). It is believed that small amounts of cadmium could affect embryonic DNA and protein synthesis (Holt and Webb 1987, as cited in Domingo 1994).

A.6 CHLORDANE

Chlordane is a broad-spectrum, organochlorine pesticide consisting of about 45 components. Historically used to control soil invertebrate pests, chlordane also adversely affected nontarget species. Although federal law currently prohibits use of chlordane in the United States, persistent chlordane residues and metabolites from past use continue to pose an ecological threat (Eisler 1990). Chlordane and its metabolites do not degrade to any significant extent either biotically or abiotically in either aquatic or terrestrial ecosystems. Chlordane in water does not undergo considerable hydrolysis, oxidation, or photolysis, and biodegradation is minimal (Gore and others 1971, as cited in HSDB 1994). Because of chlordane's low water solubility, high lipid solubility, low vapor pressure, and strong tendency to adsorb to soil and sediment particles, it persists in soil and sediments for extended periods (EPA 1988, as cited in Eisler 1990). Adsorption of chlordane to sediment is expected to be a major aquatic fate process (Callahan and others 1979, as cited in HSDB 1994).

Based on field tests, soil column leaching tests, and K_{oc} estimation, chlordane is expected to be immobile in soil (Cohen 1986, as cited in HSDB 1994). Surface-applied chlordane usually remains in the top 20 centimeters of most soils. Little biodegradation occurs in soil; chlordane residues have been detected in soils 14 years (EPA 1988, as cited in Eisler 1990) and 20 years (Beeman and Matsumura 1981, as cited in ATSDR 1994a) after application. Volatilization is the most important pathway for chlordane release from the surface of soils (ATSDR 1994a), and its vapor toxicity can be persistent and extreme.

Chlordane is known to bioconcentrate, especially in long-lived carnivorous organisms having large amounts of body lipids (Eisler 1990). Chlordane bioconcentration has been shown to increase with trophic levels from zooplankton to marine mammals in marine ecosystems, causing biomagnification of total chlordanes through the food chain, with residues peaking in marine mammals (Kawano and others 1986). Chlordane biomagnification in carnivorous birds is also considerable.

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PLANTS

Residues of chlordane have been detected in vegetable crops grown in soils treated with chlordane (USDA 1965, as cited in HSDB 1994). Chlordane is taken up by rooted aquatic vascular plants both from water and sediment. Chlordane bioconcentrates in roots and is translocated to shoots (ATSDR 1994a).

INVERTEBRATES

Chlordane is toxic to terrestrial invertebrates. Chlordane was used extensively to control grubs, ants, and snails (Eisler 1990). Earthworms were nontarget soil species that were adversely affected by chlordane. Sediment concentrations of chlordane were fatal to sandworms (*Nereis virens*) in 12 days (McLeese and others 1982, as cited in Eisler 1990). Chlordane effects decreased with increasing soil temperature and organic content (NRCC 1975, as cited in Eisler 1990).

AMPHIBIANS AND REPTILES

Symptoms of chlordane poisoning in frogs include neuromuscular changes, excessive thrashing, and tremors (Kaplan and Overpeck 1964, as cited in Power and others 1989). California newts had greatly elevated chlordane residues in the liver as compared to the stomach and carcass.

FISH AND AQUATIC ORGANISMS

Chlordane adversely affects survival, reproduction, and growth in aquatic invertebrates and fish. Symptoms of poisoning in fish include hyperexcitability, increased respiration rate, erratic swimming, loss of equilibrium, and convulsions (Eisler 1990). Other symptoms recorded were immobilization, impaired reproduction, and histopathology (NRCC 1975, as cited in Eisler 1990).

BIRDS

Lethal effects of chlordane in birds result primarily from chlordane metabolites, most notably oxychlordane and heptachlor epoxide; oxychlordane is the most toxic and persistent of the two (Stickle and others 1983, as cited in Eisler 1990). Reproductive impairment has been documented in waterfowl species from a wetland treated with chlordane. Organisms metabolize chlordane into several isomers, of

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which oxychlordane is the most toxic and persistent, even when compared to its parent chemicals (World Health Organization [WHO] 1984, as cited in Eisler 1990; Kawano and others 1988). These isomers can persist in avian tissues for up to 35.4 years (Eliott and others 1988, as cited in Eisler 1990). Chlordane interacts with other chemicals to cause additive or synergistic effects, especially when combined with other organochlorines, such as endrin, methoxychlor, and aldrin in northern bobwhites (Ludke 1976, as cited in Eisler 1990). Symptoms of poisoning include sluggishness, drooped eyelids, fluffed feathers, reduced food intake, and weight loss (Eisler 1990).

MAMMALS

Warm-blooded animals readily absorb chlordane through dermal contact, ingestion, and inhalation, and once the residues are absorbed, they concentrated in the fat, liver, kidney, brain, and muscle (WHO 1984, as cited in Eisler 1990). Chlordane is a nerve stimulant ~~whose physiological target sites are~~ which have nerve and muscle membranes (Greenhalgh 1986, as cited in Eisler 1990). Chronic dietary chlordane adversely affects physiology, growth, and fertility of laboratory mammals, including enlargement and increased pathology of the liver in rats and mice. It also elevated residues in cow's milk, reduced sexual activity and litter viability in rats, depressed growth and delayed development, decreased immune competence, and decreased viability of offspring in mice (Talamantes and Jang 1977 and WHO 1984, as cited in Eisler 1990). Chlordane interacts with other chemicals to cause additive or synergistic effects, especially when combined with other organochlorines such as endrin, methoxychlor, and aldrin in mice (Klassen and others 1986, as cited in Eisler 1990).

A.7 COBALT

Sources of cobalt in the environment are both natural and anthropogenic. Cobalt is naturally present in soil, freshwater, and seawater. Anthropogenic sources of cobalt include fossil fuel burning, vehicular and aircraft exhaust, processing of cobalt-containing alloys and chemicals, sewage sludge, fertilizers derived from phosphate rocks, and copper and nickel smelting and refining (ATSDR 1992a).

Most of the cobalt emitted into the environment settles into the soil or sediment. Cobalt mobility is dependent on the amount of chelating agents in the soil, the pH, and the redox potential of the soil. Lower pH levels increase the mobility of cobalt in the soil. Metal oxides, crystalline minerals, and

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natural organic matter in the soil decrease the mobility of cobalt. Cobalt is slightly mobilized by normal weathering (pH 5 to 8), moderately mobile in the presence of oxidizing sulfide ore, and immobile in organic-rich environments (Perelman 1967).

In most fresh waters, less than 2 percent of cobalt species are present in the dissolved form in the water column, while the rest is precipitated or adsorbed on suspended solids and sediments. Under acidic conditions and in the presence of excess chloride ions or organic and inorganic chelating agents, some mobilization of cobalt from the sediments may occur (ATSDR 1992a). In these conditions, the formation of cobalt complexes may increase the amount of cobalt in the water column.

Traces of cobalt are accumulated by microorganisms, higher plants, and animals. Although essential, excessive intake results in accumulation and toxicity (Considine 1976). Mollusks, crustaceans, and other bottom feeders have been reported to accumulate large quantities of cobalt (Jenkins 1980). However, a study of organisms in Ottawa River sediments, showed no detectable bioaccumulation of cobalt-60 (Evans and others 1988). Bioaccumulation factors for cobalt on a dry-weight basis were 100 to 4,000 for marine fish and 40 to 1,000 for freshwater fish (Smith and Carson 1981). The concentration of cobalt in normal rat tissues has been shown to range from 0.001 to 0.006 parts per million (ppm) of dry matter (Considine 1976). Cobalt appears not to bioaccumulate significantly in benthic bottom feeders in comparison to its concentration is sediment (ATSDR 1992a).

Plant uptake of cobalt from soil is not appreciable. In highly acidic soils and in some higher plants, however, significant uptake has been observed (ATSDR 1992a). The translocation of cobalt from roots to above-ground parts of plants is not significant in most soils. The soil to plant BCF for cobalt ranges from 0.01 to 0.3 (ATSDR 1992a). Plant uptake of cobalt is enhanced by low soil pH (HSDB 1994) but inhibited by complexes formed by organic complexing agents such as (EDTA) in soil (Killey and others 1984; McLaren and others 1986). There is little biomagnification of cobalt in animals at higher trophic levels (Jenkins 1980).

PLANTS

At elevated levels cobalt is a phytotoxin. However, certain plants are known to develop a mechanism of cobalt tolerance and can grow on serpentinite or ore bodies (Kabata-Pendias and Pendias 1992).

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INVERTEBRATES

Very little information was available on the effects of cobalt on invertebrates.

AMPHIBIANS AND REPTILES

Very little information was available on the effects of cobalt on amphibians and reptiles.

FISH AND AQUATIC ORGANISMS

Very little information was available on the effects of cobalt on fish and aquatic organisms. Due to a lack of toxicological data, the EPA has not determined an ambient water quality criterion for cobalt (Diamond and others 1992).

BIRDS

Very little information was available on the effects of cobalt on birds.

MAMMALS

Cardiomyopathy is the primary adverse effect of cobalt in acutely or chronically exposed animals (ATSDR 1992a). Additional studies on animals suggest that exposure to high amounts of cobalt during pregnancy affect fetal health.

Inhalation of cobalt by animals results in respiratory, cardiovascular, hematological, hepatic, renal, ocular. and body weight effects. Short-term exposure of rats to high levels of cobalt in air results in lung damage and death. Short-term exposure of rats, guinea pigs, hamsters, and pigs to lower levels of cobalt in air results in lung damage and increased red blood cells.

Testicular atrophy was reported in rats and mice exposed to cobalt concentrations in air (ATSDR 1992a). Similarly testicular degeneration and atrophy have been reported in rats exposed to cobalt concentrations in water (ATSDR 1992a).

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Stunted growth and decreased survival of offspring is noted in study rats exposed to cobalt in their diet from the third trimester of gestation through lactation (Domingo and others 1985). Rodent fetal growth and development, however, were not adversely affected by gestation-only exposure to high cobalt levels (Paternian and others 1988; Seidenberg and others 1986), so the stunted growth and decreased survival of offspring may be attributable to cobalt transfer through milk.

The rate of absorption of ingested cobalt is variable, depending on such factors as chemical form, nutritional state of body, and preexisting foods in stomach (ATSDR 1992a). Study rats absorbed 30 to 40 percent of the administered dose (Hollins and McCullogh 1971; Taylor 1962).

A.8 COPPER

Copper is a naturally occurring element that is widely distributed in the environment. Copper is the main component of alloys, which include brass, bronze, and gun metal. Copper is an essential trace mineral nutrient and a toxicant (ATSDR 1990b).

Copper is very mobile under oxidizing and acidic conditions and immobile in organic-rich and reducing environments. Adsorption increases with pH and with higher organic matter content. In aquatic systems, copper binds primarily to organic matter and forms complexes with both organic and inorganic ligands (mainly with calcium carbonate) that settle out in sediments (Kirk-Othmer 1965). Under normal pH and redox conditions, copper tends to be present in sediments in the form of organic complexes and coprecipitates with iron oxides, manganese oxides, and cupric carbonate complexes.

Copper is an essential nutrient, and under homeostatic control, biomagnification is not a significant fate process for copper. Bioaccumulated copper is stored in the liver, kidney, bone marrow, and hair (Hammond and Beliles 1980, as cited in Talmage and Walton 1991). Fish can bioconcentrate copper with BCFs ranging from the tens to the hundreds. Mollusks have BCFs for copper that range up to 30,000 (Perwack and others 1980; Chapman and others 1968; Raymont 1972).

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PLANTS

Based on yield reductions of 14 to 28 percent in agronomic and grassland plants, 100 milligrams per kilogram (mg/kg) of total copper in the soil is considered to be a threshold concentration for toxicity to plants (EPA 1987 and Bengtsson and Tranvik 1989, as cited in International Copper Association [ICA] 1992).

INVERTEBRATES

Based on yield reductions of 14 to 28 percent in agronomic and grassland plants, 100 mg/kg of total copper in the soil is considered to be a threshold concentration for toxicity to soil invertebrates (EPA 1987 and Bengtsson and Tranvik 1989, as cited in ICA 1992). Copper is used as an ingredient in many fungicides and insecticides applied on agricultural crops (Meister 1995).

AMPHIBIANS AND REPTILES

Copper is highly toxic to amphibians. Environmental conditions, including pH and water hardness, and the life stage of the amphibian exposed both affect the organism's sensitivity and adverse response to exposure to metal concentrations in water. Although the information concerning amphibians and metal toxicity is limited, it is believed that the primary mechanism of action of metal-induced toxicity and low pH environments is body loss of sodium across the gill surface (MacDonald and Wood 1993, as cited in Horne and Dunson 1995). Tadpoles were adversely affected when exposed to aqueous copper concentrations (Bayliss 1924, as cited in Owen 1981). Copper is toxic to certain types of frogs and salamanders during both acute and chronic exposure studies, causing embryonic curling, body loss of sodium, and mortality (Horne and Dunson 1995). Copper induced mortality more quickly in high pH and low water hardness environments (Horne and Dunson 1995). The earlier life stages of amphibians appear to be more sensitive to copper toxicity (Horne and Dunson 1995).

No data were found on the effects of copper on reptiles.

FISH AND AQUATIC ORGANISMS

Copper is highly toxic in aquatic environments and is a priority pollutant (EPA 1992). Copper is toxic to many fish and aquatic organisms, including mussels, stripped bass, bluegill, and carp. The gill is the

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primary organ for concentrating copper in aquatic organisms. Copper is mainly accumulated in the gill, liver, filaments, stomach, and intestine (Harvey 1978, as cited in Owen 1981). Copper concentrations can significantly affect the hatchability of fish eggs and reduce the growth of fry (EPA 1976). The species of the organism and the organism's age influence the toxicity characteristics of copper. In general, younger organisms are affected at lower concentration levels.

BIRDS

Copper can have toxic effects on birds. Diets containing elevated copper levels can slow the growth rate, diminish egg production, and cause developmental abnormalities in different avian species (Owen 1981).

MAMMALS

The toxic effects of copper have been studied on many animals, including cats, dogs, cattle, sheep, rats, mice, horses, guinea pigs, pigs, and monkeys. Different species of animals display varying levels of sensitivity to copper. However, the main organ affected by exposure to copper is the liver where copper primarily accumulates in the subcellular organelles causing liver cirrhosis. In addition to liver cirrhosis, copper exposure can cause necrotic kidney tubules and brain damage (Owen 1981). The acute toxic effects of copper given orally include gastrointestinal irritation, vomiting (including blood), low blood pressure, jaundice due to liver necrosis, and coma. Chronic exposure to copper can cause accumulation of copper in the body leading to lesions in the liver, brain, and eye and hemolytic anemia.

A.9 DDT

Historically, DDT and related organochlorine insecticides were used world-wide in pest control. In 1972, DDT was banned in the United States because DDT was highly toxic to non-target species. DDT generally occurs as a constituent of a mixture of chlorinated organic compounds, two of the most important being DDE and DDD. DDE and DDD are also metabolites of DDT. All three have similar fate and transport properties. DDT, like many organochlorine contaminants, is characterized by its persistence in the environment; potential for volatilization and transport to unaffected areas; lipophilic nature; toxicity of metabolites; and variability of species responses to chronic exposure of DDT and its metabolites (Peterle 1991). DDT, DDE, and DDD are only slightly soluble in water and adhere to soil and sediment particles (Thibodeaux 1979). DDT and related organochlorine chemicals are slowly

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biodegraded in soil and in aquatic ecosystems (Alexander 1965, as cited in Forsyth and others 1983). These chlorinated hydrocarbons tend to be highly persistent in soil, and often have half-life estimates of greater than 15 years (Lichtenstein and others 1959; Stewart and others 1971, as cited in ATSDR 1992b).

In addition to their relatively long half-life, organochlorine chemicals like DDT are highly lipophilic, and as a result, DDT and similar chemicals have very high BCFs. Biomagnification has also been observed for DDT and its metabolites (Bevenue 1976, as cited in Forsyth and others 1983). The biomagnification of DDT (and related organochlorine pesticides) has been well documented (Hoffman and others 1995), and the deleterious effects associated with trophic-level transfer in both aquatic and terrestrial food chains remains as a concern (EPA 1995). DDT is most widely known for its reproductive effects on birds, primarily piscivorous species, and for its toxicity to aquatic fish and invertebrates.

PLANTS

Terrestrial plants can accumulate elevated levels of DDT (Forsyth and others 1983). DDT can reduce photosynthesis in plants and reduce the ability of the plant to withstand environmental changes. In addition, DDT can decrease the amount of oxygen produced by aquatic plants (EPA 1975).

INVERTEBRATES

DDT was once used as an insecticide. Once invertebrates have adapted to DDT they can accumulate it at high levels (Forsyth and others 1983). DDT can cause immobilization, reproductive impairment, embryo deformation, reduced growth, and mortality in both terrestrial and aquatic invertebrates (EPA 1975).

AMPHIBIANS AND REPTILES

DDT has been observed to cause developmental deformities and hyperactivity in tadpoles (Osborn and others 1981). DDT causes developmental deformities by disrupting the organization of epithelial cells into glands. This can cause blunt snouts and deformed brains in the exposed tadpoles (Osborn and others 1981).

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FISH AND AQUATIC ORGANISMS

DDT is very toxic to fish and aquatic organisms. Even at very low concentrations, DDT can cause mortality (EPA 1975). In fish, DDT inhibits ATPase activity in cellular synthesis and osmoregulation (EPA 1975). DDT affects thyroid activity, alters behavior and activity, affects learning processes, causes developmental defects, and disrupts cellular energy use in fish (EPA 1975). DDT also adversely affects the reproductive success of fish due to its chemical characteristics that allow DDT to become concentrated in the egg yolk. When this happens, the developing fry feed on the DDT-containing yolk, eventually causing increased fry mortality once they are born (EPA 1975).

BIRDS

Reproductive effects of DDT and its metabolites on birds have been well characterized. Organochlorines, including DDT, have been implicated in the thinning of eggshells of at least 54 species of 10 orders of birds (Stickel 1975, as cited in Peterle 1991). DDT is believed to affect the calcium transport and deposition from the female to the egg, resulting in eggshell thinning. In addition to egg shell thinning other birds treated with DDE showed delayed egg laying, reduced hatchability, and alteration of egg size, weight, and content (Vangilder and Peterle 1980, 1981, 1983, as cited in Peterle 1991).

MAMMALS

Low levels of exposure to DDT and organochlorines have caused reproductive effects in mink, bats, shrews, and sea lions (Peterle 1991). In several animal species, acute oral exposure to high doses of DDT has been associated with DDT-induced tremors or myoclonus (abrupt, involuntary contractions of skeletal muscles), hyperexcitability, convulsions, and reduced fertility (EPA 1975). Chronic exposure of experimental animals to DDT is associated with tremors and hyperirritability. DDT-induced developmental effects include decreased fetal body weight, decreased fetal brain and kidney weight, embryotoxicity, fetotoxicity, and neonatal mortality. Reproductive effects of chronic exposure produced abortions, stillbirths, increased maternal and fetal mortality, delayed estrus, a reduction in male libido, and a lack of mammary gland development.

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A.10 HEPTACHLOR

Heptachlor is a persistent insecticide that is nonphytotoxic at insecticidal concentrations. Heptachlor was used extensively from 1953 to 1974 as a soil and seed treatment protecting a variety of crops from pests and was also used to control termites and household insects. EPA proposed cancellation of nearly all registered uses of heptachlor in 1974 because of its potential cancer risk, its persistence, and potential to bioaccumulate and biomagnify throughout the food chain. In the United States, heptachlor use was stopped in 1983 (Beyer and others 1996). The only commercial use of heptachlor products still permitted today is fire ant control in power transformers. Heptachlor epoxide is a breakdown product of heptachlor. Heptachlor epoxide is produced by bacteria in the environment and is also made by animals and people when heptachlor enters their bodies.

INVERTEBRATES

Heptachlor was used as an insecticide to control soil pests (Fairchild 1976, as cited in Beyer and others 1996).

AMPHIBIANS AND REPTILES

In amphibians, heptachlor was observed to be moderately toxic to tadpoles (Sanders 1970, as cited in Power and others 1989).

In reptiles, heptachlor has been observed to cause mortality in snakes, aquatic turtles, box turtles, and lizards (DeWitt and George 1960, and Matschke 1961, as cited in Hall 1980).

FISH AND AQUATIC ORGANISMS

Low levels of heptachlor affect carbohydrate metabolism, osmoregulation, and haemostatic mechanisms in fish (Srivastava and Mishra 1987).

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BIRDS

The effects of heptachlor have been documented on several species of birds, including Canada geese, American kestrels, and Japanese quail. Heptachlor has been known to decrease reproductive success in birds and decrease chick survival rates (Blus and others 1984, Henny and others 1983; Grolleau and Froux 1973, as cited in Beyer and others 1996).

MAMMALS

Heptachlor is absorbed from the gastrointestinal tract of animals, as indicated by the presence of heptachlor or its metabolites in serum, fat, liver, kidney, and muscle after oral exposure. Animal studies have shown that heptachlor undergoes epoxidation, producing heptachlor epoxide, which is more toxic than its parent compound. Hyperexcitability, incoordination, paralysis of the hind legs, difficulty in walking or standing, loss of the righting reflex, whole-body tremors, and self-mutilation are some of the reactions observed in a variety of animals after ingesting heptachlor. Ingestion of heptachlor also seemed to cause a severe decrease in the pregnancy rate of rats. There is evidence of transplacental as well as lactational transfer to human fetuses. The majority of the heptachlor and its metabolites are eliminated via the bile and into the feces (ATSDR 1993e).

A.11 LEAD

Lead has been characterized as a poison for centuries, and environmental pollution from lead is well documented (Eisler 1988b). Lead has been used in the production of solder, pipes, paint, ceramics, roofing materials, caulking, and ammunition and a gasoline additive. From a geochemical perspective, lead is ubiquitous and occurs in rocks, soils, water, plants, animals, and air. Lead is neither essential nor beneficial to living organisms, and all data show that its metabolic effects are adverse. Lead is a mutagen and a teratogen. When it is absorbed in excessive amounts, lead also is carcinogenic or cocarcinogenic, impairs reproduction, adversely impairs liver and thyroid functions, and interferes with resistance to infectious disease (EPA 1979, as cited in Eisler 1988b). In general, lead is toxic in most of its chemical forms and can be incorporated into the body via inhalation, ingestion, dermal absorption, and placental transfer. Lead is a poison that accumulates in the body, and once the amount in the body reaches a certain level, it starts to affect behavior as well as the hematopoietic, vascular, nervous, renal, and reproductive systems (Eisler 1988b).

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The biological availability and fate of lead in soil is affected by such factors as soil pH, organic content, ion-exchange characteristics, and the amount of lead in the soil (NSF 1977, as cited in ATSDR 1993f). Plants and animals may bioconcentrate and bioaccumulate lead; however, biomagnification has not been well documented. Several studies have shown that invertebrates can accumulate lead in their tissues; however, the variability in the extent of lead bioaccumulation suggests much interspecies variation in the mechanisms of lead uptake. Organolead compounds, such as trialkyl and tetraalkyl lead compounds, are more toxic than inorganic forms and have been shown to bioconcentrate in aquatic organisms, as do inorganic lead compounds. High accumulations of lead from ambient sea water by marine plants are well documented. Although lead is bioconcentrated from water, little evidence suggests that it is transferred through the food chain (Wong and others 1978, Branica and Konrad 1980; Settle and Patterson 1980, as cited in Eisler 1988b). Lead concentrations tend to decrease with increasing trophic level in both detrital and grazing food chains in freshwater and marine habitats (Wong and others 1978; Stewart and Schulz-Baldes 1976, as cited in Eisler 1988b).

PLANTS

Lead is not essential for plants, and excessive amounts can cause growth inhibition as well as reduced photosynthesis, mitosis, and water absorption (Demayo and others 1982, as cited in Eisler 1988b).

INVERTEBRATES

A concentration of 12,800 mg/kg of lead in soil is associated with reductions in natural populations of decomposers, such as fungi, earthworms, and arthropods (Beyer and Anderson 1985, as cited in Eisler 1988b).

AMPHIBIANS AND REPTILES

Environmental conditions, including pH and water hardness, and the life stage of the amphibian exposed, affect the organism's sensitivity and adverse response to exposure to metal concentrations in water. Although the information concerning amphibians and metal toxicity is limited, the primary mechanism of action of metal-induced toxicity and low pH environments is believed to be body loss of sodium across the gill surface (MacDonald and Wood 1993, as cited in Horne and Dunson 1995). Very little evidence

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has been published on the effects of lead and amphibians; however, lead may be important as a toxicant to developing embryos (Horne and Dunson 1995).

FISH AND AQUATIC ORGANISMS

Lead is toxic to most aquatic organisms; however, the adverse effects are modified by environmental conditions. Fish continuously exposed to toxic concentrations of waterborne lead show various signs of lead poisoning, including spinal curvature, anemia, degeneration of the caudal fin, destruction of spinal neurons, reduced ability to swim against a current, destruction of the respiratory epithelium, muscular atrophy, paralysis, renal pathology, growth inhibition, retardation of sexual maturity, testicular and ovarian histopathology, decreased survival rate of fry, and death (Eisler 1988b; EPA 1976).

BIRDS

Absorbed lead produces a variety of effects in avian species, including damage to the nervous system, muscular paralysis, inhibition of heme synthesis, damage to kidneys, damage to the liver, and death (Mudge 1983, as cited in Eisler 1988b). Sublethal lead exposure may also have adverse effects of reproduction in some avian species by decreasing plasma calcium, inhibition of growth, and reduced hatchability of chicks.

MAMMALS

Lead can have multiple effects in mammalian species. Lead may cause damage to the nervous system, hematological effects, kidney disfunction, sterility, abortion, neonatal mortality, growth retardation, delays in maturation, and reduced body weight (Amdur and others 1991; Eisler 1988b). Younger mammals may have greater sensitivity to lead toxicity due to their developing blood brain barrier. Developing capillaries in the brain allow lead levels in the blood to be transported to newly formed components of the brain (Amdur and others 1991).

A.12 LINDANE

Lindane, also known as gamma-BHC, is a hexachlorocyclohexane organochlorine insecticide commonly used in vaporizers for insect control (Peterle 1991). Although lindane is very persistent, like most

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organochlorines, its environmental partitioning differs from other insecticides, like DDT. In aquatic systems, lindane's sorption to suspended sediment and biota is not extensive (Callahan and others 1979).

The fate of lindane in aquatic systems is controlled by the availability of biotransformation processes. Lindane transformation will be favored in biologically rich, anaerobic environments (Callahan and others 1979). Hydrolysis and oxidation do not appear to be important fate processes for lindane, and the data on photolysis of lindane are inconclusive. Volatilization from aquatic media is not significant (Spacie and others 1977, as cited in Callahan and others 1979).

Lindane is only slightly bioaccumulated in organisms (Callahan and others 1979). An exception is amphibians, where the high water solubility of lindane and diffusion through skin allow it to be readily accumulated (Kaiser and Dunham 1972, as cited in Power and others 1989).

PLANTS

No data were found on the effects of lindane on plants.

INVERTEBRATES

Lindane has been used as an insecticide to control various pests (Peterle 1991).

AMPHIBIANS AND REPTILES

Chronic exposure of frog eggs resulted in lower hatching success at all tested concentrations of lindane (Marchal-Segault and Ramade 1981, as cited in Power and others 1989). Tadpoles exposed to lindane showed morphological deformities, including lateral deviation of body axis, dorsal lump on cranial area, and darkening of pigmentation. Adult frogs showed some damage to skeletal muscle (Publicover and others 1979, as cited in Power and others 1989).

FISH AND AQUATIC ORGANISMS

Sublethal exposure of fish to lindane produced lesions in the liver and damage to the kidneys (Johnson 1980).

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BIRDS

Lindane is readily metabolized and excreted by birds and is minimally accumulated in tissues (Blus and others 1984, as cited in Beyer and others 1996). The hatchability of eggs from ring-necked pheasants was unaffected by lindane (Ash and Taylor 1964, as cited in Beyer and others 1996).

MAMMALS

Responses to lindane include neurological and behavioral effects and adverse effects on hepatic and kidney functions (Heath and others 1976, Joy 1982, and Dikshith and others 1978, as cited in Cooper and others 1989). Disruption to reproductive development and functions in rats has also been reported (Naishtein and Leibovitch 1971, Lahire and others 1985, and Uphouse 1987, as cited in Cooper and others 1989).

A.13 MANGANESE

Manganese is a naturally occurring substance found in many types of soil. Manganese is an essential trace mineral with many oxidation states. Although its primary use is in iron and copper alloys, it is also used in dry cells, matches and pyrotechnics, fossil fuels, and a variety of chemical processes.

Manganese metal has four different oxidation states (2+, 3+, 4+, and 7+). The specific chemical form is determined by environmental factors such as pH, Eh, microbial activity, and available anions (ATSDR 1992b). The most common form of manganese is present in the divalent form (Mn2+) (EPA 1984a, as cited in ATSDR 1992b). The ability of manganese to adsorb to soil and sediment depends on the organic content present in the soil or sediment and the ion exchange capacity of that medium (Curtin and others 1980, Hemstock and Low 1953, Kabata-Pendias and Pendias 1984, McBride 1979, and Schnitzer 1969, as cited in ATSDR 1992b). As a result soil adsorption values range from 0.2 to 10,000 milliliters per gram (mL/g).

Manganese that is present in water may be bioconcentrated by lower trophic levels (ATSDR 1992b). Manganese BCFs have been reported as 2,500 to 6,300 for phytoplankton, 300 to 5,500 for marine algae, 800 to 830 for intertidal mussels, and 35 to 930 for coastal fish (Folsom and others 1963, as cited in ATSDR 1992b). In another study, BCFs were similarly reported as 10,000 to 20,000 for marine and

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freshwater plants, 10,000 to 40,000 for invertebrates, and 100 to 600 for fish (Thompson and others 1972, as cited in ATSDR 1992b). Although bioconcentration occurs in lower trophic levels, in higher trophic level receptors, homeostasis is reached, and as a result, biomagnification of manganese in the food chain is believed to be insignificant (EPA 1984a, as cited in ATSDR 1992b).

PLANTS

Manganese concentrations were found to be higher in the sprout stage than in the adult stage of *Spartina alterniflora* (Williams and Murdoch 1969). However, manganese concentrations increased to the highest levels after death. These concentrations and related concentration factors were similar to those found in terrestrial monocots, marine algae, and submerged grasses (Williams and Murdoch 1969).

INVERTEBRATES

No data were found on the effects of manganese on terrestrial invertebrates.

AMPHIBIANS AND REPTILES

Very little information was available on the effects of manganese on amphibians and reptiles. In one study, however, manganese has been observed to alter membrane sodium permeability in amphibians (Arhem 1980, as cited in Power and others 1989). In adult frogs, the highest concentration of manganese was found to be in the skin (Baudo 1976, as cited in Power and others 1989).

FISH AND AQUATIC ORGANISMS

Reproductive effects, such as a decrease in spermatogenic activity and injury to testis, have been recorded in fish treated with $MnSO_4$ (Srivastava and Agrawal 1983, as cited in Joardan and Sharma 1990).

BIRDS

Manganese levels in birds were higher in bones, livers, and kidneys than in the brain, heart, or muscle (Mahoney 1978). High levels of manganese caused decreased hemoglobin and liver iron levels, mild

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anemia, and depressed growth in chicks (Southern and Baker 1983). Reproductive effects were minimal in birds fed 90 times the normal dietary level of manganese (Laskey and Edens 1985).

MAMMALS

Symptoms that were observed in rats that ingested elevated levels of manganese included a decrease in weight gain, increase in physical activity, alterations of brain chemicals, slight irritation of the stomach, and delayed testicular development (ATSDR 1992b). In addition, pregnant rats that drank water containing levels of manganese were observed to have litters that weighed less than normal (ATSDR 1992b). Monkeys that drank water containing elevated levels of manganese became weak, and their muscles became rigid (ATSDR 1992b).

Rats and monkeys that inhaled elevated concentrations of manganese dust developed irritation and swelling in the lungs (ATSDR 1992b). Monkeys also developed chemical alterations in the brain as a result of manganese inhalation (ATSDR 1992b). Mice that were exposed to elevated concentrations of manganese in the air were more likely to catch pneumonia and develop behavioral changes (ATSDR 1992b). The parents who inhaled air concentrations of manganese had increased behavioral malformations and smaller offspring than those of the control group (ATSDR 1992b).

A.14 MERCURY

Inorganic and organic forms of mercury are relatively well characterized within an ecotoxicological context. Methyl-mercury and other organomercurical compounds (including ethyl- and phenyl-mercuricals) are among the most toxic organometals in the environment and bioaccumulate through the food chain (Fimreite 1979). The chemical form of mercury influences its distribution in the body, and the comparative toxicity data suggest that the organic species (ethyl- , methyl-, and phenyl-mercury) of the metal are far more toxic than inorganic mercury (Peterle 1991). In general, methyl-mercury as well as its metallic (Hg^0), mercurous (Hg^+), and mercuric (Hg^{--}) form are nonessential and exert their toxicity at the biochemical level as inhibitors of enzyme-catalyzed reactions and protein synthesis.

Mercury is a known mutagen, teratogen, and carcinogen. Its toxicity and environmental effects vary with its form, dose, and route of ingestion and with the species, sex, age, and general condition of the

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organism (Eisler 1987a, Fimreite 1979). Depending on the pH, salt content, and composition of the soil, mercury usually forms various complexes with chloride and hydroxide ions in the soil (Alloway 1990). Biotransformation is an important fate process in the environmental partitioning of mercury. Under favorable conditions, microorganisms in soil and sediment can convert various forms of mercury to methyl-mercury, which is more available for uptake by various organisms and for transport in the food chain and more mobile than inorganic forms (Peterle 1991).

Mercury, particularly in the methylated form, has a high potential for bioaccumulation and biomagnification (Eisler 1987a). Biomagnification of methyl-mercury has been documented for both aquatic and terrestrial food chains (Eisler 1987a). Concentrations of methyl-mercury in higher trophic-level fish have been biomagnified reportedly on the order of 10,000 to 100,000 times those concentrations found in ambient waters (Callahan and others 1979). The accumulation of mercury by aquatic organisms is enhanced at elevated water temperatures, reduced water salinity or hardness, reduced water pH, increased age of the organism, and reduced organic matter in the medium. Mercury transfer and biomagnification through mammalian food chains is well documented.

PLANTS

Plants take up mercury from the soil in relatively insignificant amounts because roots appear to act as a barrier. However, mercury compounds applied to other parts of plants appear to be readily absorbed and translocated (Adriano 1986).

INVERTEBRATES

Some types of invertebrates can accumulate mercury through the food chain with little or no observable effects (Jamil and Hussain 1992). In certain types of flies, however, methyl-mercury can alter chromosomes, causing abnormalities in offspring (NAS 1978 and Khera 1979, as cited in Eisler 1987a). Mercury concentrations in soil have been observed to cause reduced segment regeneration in worms, and at elevated levels, cause mortality (Abbasi and Soni 1983, as cited in Eisler 1987a). For marine invertebrates, mercury was observed to inhibit reproduction (Eisler 1987a).

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estimated to be stored in fat at only 0.01 to 0.1 times its chronic intake, and the half-life of stored methoxychlor in rats is one to two weeks, as compared to an estimated value of six months to one year for DDT (Casarett and Doull's Toxicology 1986, as cited in HSDB 1994). The bioaccumulation ability of methoxychlor is very low (Beyer and others 1996).

INVERTEBRATES

Methoxychlor is an insecticide that has been used to control many insects (Gardner and Bailey 1975, as cited in Beyer and others 1996).

AMPHIBIANS AND REPTILES

Methoxychlor was observed to be moderately toxic to tadpoles (Sanders 1970), as cited in Power and others 1989). Changes in organ weights, feeding, behavior, and survival were not observed in amphibians exposed to methoxychlor (Hall and Swineford 1979, as cited in Power and others 1989). In amphibians, methoxychlor is more readily accumulated through dermal exposure than through ingestion and, as a result, is readily bioconcentrated and not readily biomagnified. Residue levels in amphibians were not related to the exposure duration, which could indicate that methoxychlor is rapidly equilibrated in the body (Power and others 1989).

FISH AND AQUATIC ORGANISMS

Methoxychlor has been observed to cause a variety of responses in exposed fish populations. Behavioral changes, including slow movement and slow response to stimuli, have been observed in exposed salmon fry (Dean and others 1977). In addition to behavioral alterations, methoxychlor has caused reproductive impairment in exposed fish. Reproductive effects caused by methoxychlor exposure include decreased egg production, decreased hatchability, and increased abnormalities in offspring (Holdway and Dixon 1986).

BIRDS

Birds metabolize methoxychlor relatively easily, and as a result, methoxychlor is not accumulated to elevated levels (Gardner and Bailey 1975, as cited in Beyer and others 1996). No evidence has been found regarding methoxychlor residues in relation to increased mortality rates (Beyer and others 1996).

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Methoxychlor has caused feminization in male gull chick embryos. Methoxychlor was injected into developing gull eggs, which resulted in abnormal development of ovarian tissue in male hatchlings (Fry and Toone 1981, as cited in Peterle 1991).

MAMMALS

Methoxychlor is an organochlorine, so its toxic effects are similar to those caused by other organochlorines such as DDT. The primary sites of toxic action are the sensory and motor nerve fibers and the motor cortex in the brain. Symptoms of poisoning include dizziness, disturbed equilibrium, tremors, and convulsions. Liver damage may also occur in mammals exposed to high levels of methoxychlor (Amdur and others 1991).

A.16 MOLYBDENUM

Molybdenum is found in all living organisms and is considered to be an essential or beneficial nutrient. This element is primarily used in the production of steel alloys, which are used in building aircraft and weapons. Fossil fuel combustion, smelting, mining, and milling operations have all contributed to molybdenum contamination in the environment. Molybdenum chemistry is complex and not adequately understood. In water at a pH of more than seven, molybdenum exists primarily as the molybdate ion; at a pH of less than seven, various polymeric compounds are formed, including the paramolybdate ion (Busev 1969, as cited in Eisler 1989a). In soils molybdate is sorbed most readily to alkaline. high calcium, and high chloride soils. Retention is lowest in low pH, low sulfate soils (Smith and others 1987, as cited in Eisler 1989a).

Molybdenum interacts toxicologically with other trace elements, especially copper and inorganic sulfates. In mammals, molybdenum can protect against poisoning by copper, mercury, and probably other metals and may have anti-carcinogenic properties. However, ruminants are sensitive to molybdenum poisoning, especially when accompanied by a deficiency in copper or inorganic sulfates (Eisler 1989a).

Very little information on the bioaccumulative potential of molybdenum was found.

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PLANTS

Plants readily accumulate molybdate, except in soils with low pH, high sulfate, low phosphate, and high organic matter content (Gupta and Lipsett 1981, as cited in Eisler 1989a). No toxicity of molybdenum to field-grown crops has been observed (Soon and Bates 1985, as cited in Eisler 1989a).

INVERTEBRATES

Molybdenum compounds have been used in baits to control termites. These molybdenum baits were fatal to the termite population; however, the other species of insects including fire ants, beetles, and cockroaches were unaffected by the bait (Brill and others 1987, as cited in Eisler 1989a).

AMPHIBIANS AND REPTILES

Very little information was available on the effects of molybdenum on amphibians and reptiles.

FISH AND AQUATIC ORGANISMS

Freshwater and marine fish appear to be relatively resistant to molybdenum exposure (Eisler 1989a). However, rainbow trout eggs exposure to molybdenum for 28 days through day 4 post-hatch caused mortality at elevated levels. Very little information was available on the effects of molybdenum on aquatic invertebrates and fish.

BIRDS

Data are scarce on the effects of molybdenum on avian wildlife under controlled conditions. All studies on birds have been restricted to domestic poultry, which appear to be relatively resistant to molybdenum exposure. At elevated levels, however, molybdenum has been observed to decrease the growth rate of chicks and turkey poults, reduce egg production, and decrease hatchability (Friberg and others 1975, as cited in Eisler 1989a).

MAMMALS

Molybdenum is essential in mammalian diets, can protect against poisoning by copper or mercury, and may be useful in controlling cancer. Almost all studies conducted to date on the effects of molybdenum

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under controlled conditions have been on livestock, especially cattle and sheep. Molybdenum poisoning in ruminants has been observed in livestock (Eisler 1989a). In certain areas of England, cattle and sheep that grazed in fields that had high levels of molybdenum and low levels of copper and inorganic sulfate developed molybdenosis (Underwood 1979, as cited in Eisler 1989a). ~~Symptoms of~~ molybdenosis ~~include:~~ weight loss, diarrhea, and death in extreme cases. Data on the effects of molybdenum on mammalian wildlife are scarce. All evidence indicates that other mammals besides cattle and sheep are comparatively tolerant of high dietary intakes of molybdenum (Underwood 1971, Buck 1978, Chappell and others 1979, and Friberg and Lener 1986; as cited in Eisler 1989a).

A.17 NICKEL

Nickel is a naturally occurring metal. Nickel is mined for use in electroplating, iron and steel processing, nickel-cadmium batteries, fuel combustion, and a variety of other applications.

Nickel has many oxidation states: -1, 0, +1, +2, +3, and +4. Ni^{2+}, however, is the most common form present in the environment (Environment Canada 1994a). Nickel is strongly adsorbed by soil, although to a lesser degree than lead, copper, and zinc (Rai and Zachara 1984; Alloway 1990). Many forms of nickel are found in soil, and many factors affect the extent to which these different forms of nickel are adsorbed, making nickel adsorption highly site-specific. Amorphous oxides of iron, manganese, and clay minerals are the most important adsorbents of nickel in soil. In alkaline soils, adsorption may be irreversible, thus limiting nickel's availability and mobility in these soils. Cations, such as calcium and magnesium, reportedly reduce adsorption as a result of competition for binding sites, whereas anions, like sulfate, reduce adsorption because of complexation. Nickel adsorption depends strongly on pH (Rai and Zachara 1984; Alloway 1990). In an aquatic environment, environmental factors, such as pH, redox potential, and organic matter content, can affect the fate, transport, and biological availability of nickel (Environment Canada 1994a).

BCFs for nickel have been reported between 120 and 550 for submerged lichens; 770 and 1,500 for submerged mosses; 2,000 and 4,500 for *Daphnia;* 200 to 1,000 for clams, zooplankton, and benthos; and 230 and 330 for fish (Dietz 1973, Cowgill 1976, Mathis and Cummings 1973, and Hutchinson and others 1976, as cited in Environment Canada 1994a). Recent studies of nickel levels in voles and rabbits living on sludge-amended land did not indicate any accumulation of nickel in these herbivores or in the plants

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on which they fed (Alberici and others 1989, and Dressler and others 1986, as cited in ATSDR 1995a). Animals appear to be able to regulate the amount of nickel that is accumulated in the body, and as a result, biomagnification in upper trophic levels is believed to be insignificant (Environment Canada 1994a).

PLANTS

Nickel tends to be less available in soils than zinc or cadmium but is generally more available to plants than copper (Alloway 1990). The soil chemistry of nickel is relatively simple and is largely based on its occurrence as the divalent Ni^{2+}. Nickel becomes more soluble with decreasing pH, allowing more nickel to be bioavailable to plants. The clay content and texture of the soil will also influence the bioavailabiltiy of nickel to plants. Depending upon these edaphic factors and on nickel's biological role as a ultra-trace element, nickel is bioconcentrated by plants; the greatest bioconcentration occurs in soils that have naturally high levels of nickel where some plants are classified as "hyperaccumulators" (Alloway 1990). Similar patterns of nickel bioconcentration also occur in highly contaminated soils (for example, near nickel and copper smelters).

The effects of nickel toxicity on plants include reduced growth of roots and shoots, poor branching, deformation of plant parts, decreased dry matter production, leaf spotting, abnormal flower shape, mitotic root tip disturbance, germination inhibition, and chlorosis (Mishra and Kar 1974, Rauser 1978, McIlveen and Negusanti in press, as cited in Environment Canada 1994a).

INVERTEBRATES

Very little information was available on the effects of nickel on invertebrates. However, microorganism growth and survival were reduced as a result of elevated nickel exposure (Babich and Stotzky 1982, as cited in Environment Canada 1994a).

AMPHIBIANS AND REPTILES

Nickel exposure in amphibians has been observed to slow down the response time of the potassium system in myelinated nerve fibers (Arhem 1980, as cited in Power and others 1989). In addition, nickel

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has also been observed to alter sodium permeability across cell membranes in amphibians (Arhem 1980, as cited in Power and others 1989).

FISH AND AQUATIC ORGANISMS

Nickel is both a carcinogen and a mutagen in the aquatic environment (EPA 1992). The observed effects of nickel exposure in an aquatic environment to fish and invertebrates include tissue damage, genotoxicity, and decreased growth (EIFAC 1984, and IPCS 1991, as cited in Environment Canada 1994a). Molluscs and crustaceans appear to be more sensitive to nickel exposure than other aquatic organisms (Hall 1978, as cited in Environment Canada 1994a).

BIRDS

Elevated dietary concentrations of nickel caused growth inhibition in poultry. The expression of nickel toxicity is influenced by the age, reproductive status, nutritional content of the diet, and exposure duration in test organisms. This information should be considered in the interpretation of the risk posed by nickel to terrestrial wildlife (NAS 1980).

No effects were observed on adult mallards exposed to nickel in their diet. No effects to adult mallards were observed regarding body weight, histological changes in liver and kidneys, tissue damage, blood chemistry, egg-laying ability, hatchability percentages, and hatchling survival to 14 days of age (Eastin and O'Shea 1981, as cited in Environment Canada 1994a). However, mallard ducklings fed diets containing elevated nickel concentrations up to 90 days were observed to develop tremors and ataxia (Cain and Pafford 1981, as cited in Environment Canada 1994a). Newly hatched chickens were also observed to have slower growth rates as a result of diets containing elevated nickel concentrations (Ling and Leach 1979, as cited in Environment Canada 1994a).

MAMMALS

Growth inhibition was the primary effect to domestic livestock fed elevated levels of nickel in their diet. The expression of nickel toxicity was observed to be influenced by the age, reproductive status, nutritional content of the diet, and exposure duration in test organisms. This information should be considered in the interpretation of the risk posed by nickel to terrestrial wildlife (NAS 1980).

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Rats in a subchronic gavage study of nickel chloride in water experienced lethargy, ataxia, irregular breathing, reduced body temperature, and discolored extremities (EPA 1994). Inhalation of nickel subsulfide in rats increased the incidence of lung tumors (ATSDR 1995a). The central nervous system appears to be the target organ for nickel oral toxicity, while the lung is the target organ for inhalation exposure.

A.18 ORGANOTINS

Organotins are a group of compounds characterized by at least one tin-carbon bond. Mono- and diorganotins are used as polyvinyl chloride (PVC) stabilizers in the plastics industry. Triorganotins are used in agriculture as fungicides, acaricides, and molluscicides and are used in ship paints as antifoulants (Ema and others 1996). Sources of organotins in the environment include leaching from organotin-stabilized pipes, ship paints, and organotin manufacturing processes (Environment Canada 1993).

Organotins have low mobility in the environment due to low aqueous solubility, low vapor pressure, and high affinity for soils and sediments (Blunden and Chapman 1986, as cited in Eisler 1989b). Butyltin compounds do not volatilize significantly from water. Butyltins do not persist in aquatic ecosystems with half-lives estimated to be less than a few months at 20 °C. Organotin persistence in the environment is also limited by elevated temperatures, increased sunlight intensity, and aerobic conditions. Degradation of tributyltin to di- and monobutyltins occurs in water and sediment with half-lives ranging from days to weeks in water and longer in sediment (Bryan and Gibbs 1991).

Organotins accumulate in lipid-rich layers of water and in biota. Bioconcentration of organotins by marine organisms, especially algae, is high (Eisler 1989b). However, food chain biomagnification is limited because upper-trophic-level consumers have the ability to reduce organotins into less toxic metabolites, which are then easily excreted.

PLANTS

Small plants (*Fucus vesiculosus*) took up tributyltin from solution with a bioaccumulation factor of 1,500 (Bryan and Gibbs 1991). Eelgrass decomposes tributyltin to dibutyltin and then to monobutyltin, which is diffused into the surrounding water.

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INVERTEBRATES

Populations of spider mites have developed resistance to organotin acaricides (cyhexatin and fenbutatin) (Eisler 1989b).

AMPHIBIANS AND REPTILES

Frog embryos treated with tributyltin for five days showed decreased weights at concentrations that caused 40 to 50 percent mortality (Laughlin and Linden 1982, as cited in Power and others 1989).

FISH AND AQUATIC ORGANISMS

Of the organotins, tributyltin is especially toxic to aquatic organisms. Some adverse affects of tributyltin on fish include sluggishness, loss of appetite, altered body pigmentation, air gulping and damaged gills, damaged cornea, and damaged bile duct (Chliamovitch and Kuhn 1977, and Thompson and others 1985, as cited in Eisler 1989b). Reduction in egg deposition occurs in marine gastropods and bivalve mollusks exposed to tributyltin. Mollusks are the most sensitive marine organisms to organotins (Bryan and Gibbs 1991). An adverse effect of organotin on mollusks is shell thickening.

BIRDS

Triorganotins (especially trimethyltins and triethyltins) are the most toxic organotins to birds (Eisler 1989b). Tremors, ataxia, and lethargy are some effects observed in mallard ducklings exposed to lethal concentrations of trimethyltin. Sublethal effects include low body weight, enlarged livers, and elevated kidney weight. Tributyltin and dibutyltin have caused growth retardation and general depression of metabolic activity in chickens (Guta-Socaciu and others 1989).

MAMMALS

Tributyltins are highly toxic to mammals, causing central nervous system dysfunction in rabbits and skin irritation, impaired growth, kidney damage, and reduced thymus growth in rats (Eisler 1989b). Rats exposed to dibutyltins have shown lethargy and significant decreases in body weight gain (Khaliq and others 1991). Monoorganotins are reported to be relatively inert to mammals (Pellikan and Cerny 1970, as cited in Ueno and others 1994).

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A.19 POLYNUCLEAR AROMATIC HYDROCARBONS

Polynuclear aromatic hydrocarbons (PAHs) range from low molecular weight PAHs composed of two aromatic rings, including naphthalene, to high molecular weight PAHs bearing three or more aromatic rings, including phenanthrene and benzo(a)pyrene. There are thousands of PAH compounds, each differing in the number and position of the aromatic rings and the amount of substitutions in their basic structure. These substitutions may include methyl groups, oxygen groups, or other elemental groups. PAH solubility decreases with increasing molecular weight and increasing log K_{ow} values (Eisler 1987b).

In aquatic environments, PAHs may evaporate, disperse in the water column, become incorporated into bottom sediments, concentrate in aquatic biota, or experience photodegradation, chemical oxidation, or biodegradation (Suess 1976, as cited in Eisler 1987b). Depending upon the physicochemical characteristics of the individual compound, the compound will primarily adsorb to suspended sediment or colloids, while only about 30 to 35 percent will dissolve into the water column (Lee and Grant 1981, as cited in Eisler 1987b). PAHs in aquatic sediments degrade very slowly in the absence of penetrating radiation (Suess 1976, as cited in Eisler 1987b) and may persist for long time periods in oxygen-poor basins or in anoxic sediments (Neff 1979, as cited in Eisler 1987b).

PAHs cause a wide variety of adverse biological effects in numerous organisms under laboratory conditions, including effects on survival, growth, metabolism, and tumor formation. Inter- and intraspecies responses to PAHs are quite variable and are modified by interaction with other inorganic and organic compounds, including other PAHs (Eisler 1987b). PAHs have also been observed to enhance the cytochrome P_{450} levels in the liver. Cytochrome P_{450} and mixed function oxidases are primarily responsible for detoxifying chemicals in the liver, and when these chemicals are altered, the toxicity of other compounds that the organisms encounter may be greater than they would be otherwise. In this way, PAHs lower the organism's resistance to other toxins (Amdur and others 1991). The higher molecular weight PAHs are known to be carcinogenic, mutagenic, and teratogenic to a wide variety of organisms, including aquatic life, amphibians, birds, and mammals. The lower molecular weight PAHs are generally not carcinogenic but are more acutely toxic than their higher molecular weight relatives (Eisler 1987b). Lower molecular weight PAHs show little tendency to biomagnify in food chains and are relatively rapidly metabolized in vertebrates, provided toxicity is not expressed.

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Many species of aquatic organisms rapidly bioconcentrate and bioaccumulate PAHs from low concentrations in freshwater or marine settings. The ability of PAHs to bioconcentrate and bioaccumulate is chemical-specific. The molecular weight, the position of the aromatic rings, and the type of substitutions all influence the ability of a compound to bioconcentrate and bioaccumulate in ecological receptors. BCFs tend to increase with increasing molecular weight and increasing log K_{ow} values. Species-specific characteristics are also critical in evaluating the bioconcentration potential of PAHs; organisms with relatively high lipid contents tend to bioconcentrate PAHs to greater levels than others (Eisler 1987b).

What about impact of photo-activated PAHs?

PLANTS

The biological fate of PAHs in soils is poorly unde[illegible] ilable information suggests that plants, fungi, and soil bacteria absorb [illegible] rom soils. These materials may be available for uptake from the rhizosphere [illegible] 95). In general, phytotoxic effects caused by PAH exposure have not been observed; however, very little data have been published on this subject (Eisler 1987b). One study observed that PAH concentrations inhibited algae growth (Bastian and Toetz 1982, as cited in Environment Canada 1994b).

INVERTEBRATES

Very little information was available on the effects of PAHs on invertebrates.

AMPHIBIANS AND REPTILES

Very little information was available concerning the effects of PAHs on amphibians and reptiles. One study, however, observed that air concentrations of benzene and toluene can inhibit blood cell maturation in amphibians (Garavini and Seren 1978, as cited in Power and others 1989). The degree of inhibition was dependent on the frequency of exposure (Garavini and Seren 1978, as cited in Power and others 1989). In addition, aromatic hydrocarbon exposure can lead to increased incidences of cancer in amphibians.

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FISH AND AQUATIC ORGANISMS

PAHs vary substantially in their toxicity to aquatic organisms. Toxicity of PAHs tends to increase with increasing molecular weight, especially increasing alkyl substitution. PAHs have been linked to various liver tumors in fish (Environment Canada 1994b), and increased mortality has been observed in water fleas, nymphs, and mayflies exposed to PAHs (Krantzberg and Boyd 1992, and Murphy and others 1993, as cited in Environment Canada 1994b). Sediment PAH concentrations have been observed to cause liver lesions in flatfish and in brown bullheads (Eisler 1987b). PAHs and their metabolites also suppress the immune system in aquatic organisms.

BIRDS

For birds, several investigations have suggested that the presence of PAHs in petroleum cause embryo toxicity in avian species (Hoffman and Gay 1981, and Albers 1983, as cited in Eisler 1987b). Embryo effects include reduced embryo growth, incomplete skeletal ossification, and defects in the eye, brain, liver, and bill.

MAMMALS

PAH compounds are distinct in their ability to produce tumors in skin and in most epithelial tissues of mammals. Some PAHs have been linked to increased occurrence of leukemia, lung adenoma, and stomach tumors in mice. PAHs have resulted in altered hematopoietic function as well as development of pathological conditions in lymphoid tissues. Impaired reproduction is frequently observed in chronic exposures where ovotoxicity and antispermatogonic effects have been noted. Other systemic effects include adrenal necrosis as well as changes in the intestinal and respiratory epithelia. Many PAHs induce biotransforming enzymes, including the mixed-function oxidases present in the liver. Some PAHs and their metabolites also suppress the immune system. Immunosuppression results in decreased responsiveness to mitogens and an increased susceptibility to disease. The majority of available information on the toxicological properties of PAHs is focused on their carcinogenicity to mammals (EPA 1980, and Lee and Grant 1981, as cited in Eisler 1987b).

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A.20 POLYCHLORINATED BIPHENYLS

Polychlorinated biphenyls (PCBs), or Aroclors, are among the most persistent man-made compounds in the environment, resisting degradation for years. This family of compounds contains 209 individual isomers. PCBs have been widely used as coolants and lubricants because of their insulating and nonflammable properties. The manufacture of PCBs was halted in 1977 because of their ability to bioaccumulate in the environment and adversely affect wildlife.

PCBs remain in the environment for long periods of time. The physiochemical properties of PCB compounds allow them to resist environmental degradation processes. The degree of chlorination and the position of chlorine substituents of a PCB compound influences the ability of environmental processes to break down the compound. In general, the more chlorinated PCB compounds resist environmental break down reactions and thus remain in the environment for longer periods of time. Due to their physicochemical characteristics, PCBs bind tightly to soil and sediment particles and organic matter. Depending on the particular isomer of PCB, K_{oc}s range from 510 to 13,300,000. As a general rule, most K_{oc}s for PCB mixtures are greater than 5,000 (Sklarew and others 1987, as cited in HSDB 1994).

The environmental persistence of PCBs combined with their lipophilic nature allow them to bioconcentrate, bioaccumulate, and biomagnify significantly in the environment. The physicochemical properties of the PCBs influence the extent of uptake and the metabolic fate of PCBs in the body. The ability of animals to metabolize PCBs tends to increase in the following order: fish< birds< mammals (Matthews and others 1984, as cited in HSDB 1994). PCBs are absorbed from the stomach, skin, and lungs. PCBs initially concentrate in the liver, blood, and muscle; however, they soon are sequestered into fat tissue, where they have a long half-life. PCBs that are poorly metabolized tend to become concentrated in the fatty tissue.

In general, bioaccumulation of PCBs is rapid, and depuration is slow, and diet appears to be an important route of PCB accumulation. PCB body burdens in marine organisms, especially benthic organisms, appear directly related to log PCB concentrations in sediments (Shaw and Connell 1982, as cited in Eisler 1986). In terrestrial or semi-aquatic vertebrates, PCBs tend to bioaccumulate to their highest

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concentrations in the livers of fish-eating birds followed by species that feed on small birds and mammals, worms and insects (NAS 1979, as cited in Eisler 1986). In studies of marine food chains, concentrations of PCBs rapidly biomagnify in higher trophic level carnivores. In these food chains, piscivores, such as gulls and pelicans, often have the highest level of PCBs in their body tissues.

PLANTS

Soil algae exhibit depressed photosynthesis and growth inhibition when exposed to concentrations of PCBs (Eisler 1986). In other studies, algae exposed to PCB concentrations had an increased mortality rate, decreased reproduction, and impaired growth (Beyer and others 1996).

INVERTEBRATES

Very little information was available on the effects of PCBs on terrestrial invertebrates.

AMPHIBIANS AND REPTILES

Very little information was available on the effects of PCBs on amphibians and reptiles.

FISH AND AQUATIC ORGANISMS

Adverse effects associated with exposure to PCBs in aquatic organisms include decreased growth, reproductive toxicity, mutagenicity, histopathology, and a variety of biochemical perturbations (Eisler 1986; Beyer and others 1996). Reproductive toxicity has been reported for several aquatic species, and the effects include reduced survival of developing eggs, increased mortality in eggs and fry, and reduced fertilization success (Eisler 1986).

BIRDS

Birds exposed to PCB concentrations have shown the following effects: disruptions in normal patterns of growth, reproduction, metabolism, and behavior (Peakall and others 1972, as cited in Eisler 1986). PCBs can damage the liver, kidney, spleen, and thyroid in birds (Beyer and others 1996). However, reproductive impairment is the most sensitive endpoint for birds exposed to PCBs. Reproductive effects

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caused by PCB exposure include embryo mortality, teratogenic effects, decreased hatching success, and reduced eggshell thickness (Beyer and others 1996).

MAMMALS

PCB exposures in mammals are associated with adverse effects, including reproductive impairment and failure, ~~physiological effects,~~ altered behavior, mutagenic, carcinogenic, and teratogenic effects (Eisler 1986; Beyer and others 1996). In mammals, the most consistent pathological changes occur in liver. In females, ~~however,~~ PCBs are transferred through lactation and placenta from adult to offspring; hence, in utero effects and fetotoxicity may be expressed.

A.21 SELENIUM

Selenium is an essential trace element but is harmful at concentrations only slightly higher than the nutritional requirement (Eisler 1985b). Results of laboratory studies and field investigations with fish, mammals, and birds have led to general agreement that elevated concentrations of selenium in diet or water are associated with reproductive abnormalities and growth retardation. Not as extensively documented are reports of selenium-induced chromosomal aberrations, intestinal lesions, shifts in species composition of freshwater algal communities, swimming impairment of protozoans, and behavioral modifications (Eisler 1985b).

In aerobic waters, selenium is present in the selenite (H_2SeO_3, $HSeO_3^{-1}$, SeO_3^{-2}) or selenate (H_2SeO_4, $HSeO_4^{-}$, SeO_4^{-2}) quadravalent or hexavalent oxidation states. These chemical species are very soluble, and most of the selenium discharged into the aquatic environment is transported in these forms to the ocean. Selenium has a sorptive affinity for hydrous metals oxides, clays, and organic materials. Sorption by sediments or suspended solids can result in enrichment of selenium concentrations in sediment beds. Sorption or precipitation with hydrous iron oxides is probably the major control on mobility of selenium in aerobic waters. Selenium can be methylated by a variety of organisms, including benthic microflora. In a reducing environment, hydrogen selenide may be formed. Both the methylated forms and hydrogen selenide are volatile and may escape to the atmosphere. Formation of volatile selenium compounds in the sediments can remobilize sorbed selenium (Eisler 1985b).

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The current understanding of selenium toxicology indicates that ecological effects are primarily caused by selenium in the food chain, rather than selenium dissolved in the water column (Philips 1988, and Luoma and others 1992, as cited in Taylor and others 1992). Once in the water column, selenium enters the food chain through bioconcentration by phytoplankton, which are then consumed in large quantities by crustaceans and bivalves. Crustaceans and bivalves are, in turn, eaten by fish and waterfowl. Bioconcentration, bioaccumulation, and biomagnification of selenium can increase selenium levels more than 1,000 fold from water to fish and animals (Saiki and Lowe 1987, as cited in Taylor and others 1992). The greatest step increase occurs between water and phytoplankton and other aquatic plants; subsequent steps in the food chain typically increase selenium concentrations by a factor of 2 to 6 (Lemly and Smith 1987, as cited in Taylor and other 1992). BCFs for various species of marine algae range from 16,000 to 337,000, depending on the species and the water column levels (Zhang and others 1990, as cited in Taylor 1992).

PLANTS

Selenium has been observed to cause growth retardation in freshwater green algae (Hutchinson and Stokes 1975, Klaverkamp and others 1983, as cited Eisler 1985b).

INVERTEBRATES

Very little information was available on the adverse effects of selenium on invertebrates.

AMPHIBIANS AND REPTILES

Very little information was available on the effects of selenium on amphibians and reptiles. One report, however, states that during frog development, cranial and vertebral deformities and lower survival were documented when exposed to selenium concentrations (Browne and Dumont 1979, as cited in Eisler 1995).

FISH AND AQUATIC ORGANISMS

In general, selenite is more toxic to earlier life stages, and the degree of the effect is increased with increasing temperatures (Klaverkamp and others 1983, as cited in Eisler 1985b). Selenium is teratogenic, and its toxicity depends greatly on its chemical form (Eisler 1985b). It has been suggested that selenite is

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more toxic than selenate and is preferentially concentrated over selenate by mussels (EPA 1990, as cited in Eisler 1985b). Signs of selenium poisoning include loss of equilibrium, lethargy, loss of coordination, muscle spasms, protruding eyes, swollen abdomen, liver degeneration and swelling, reduced blood hemoglobin levels, increased white blood cell numbers, swollen gill lamella with extensive cellular vacuolization, and necrotic and degenerating ovarian follicles (Ellis and others 1937, Sorensen 1984, as cited in Eisler 1985b). Elevated concentrations of selenium were observed to cause reproductive failure, anemia, reduced hatch, reduced growth, reduced swimming rate, and chromosomal aberrations in aquatic organisms (Hodson and others 1980, Adams 1976, Bovee and O'Brien 1982, Krishnaja and Rege 1982, as cited in Eisler 1985b).

BIRDS

Selenium exposure in the diet or drinking water of avian species is associated with reproductive abnormalities, congenital malformations, selective bioaccumulation, and growth retardation (Eisler 1985b). Selenium has been observed to cause reduced hatching of eggs, decreased egg weight, decreased egg production, anemia, and embryo deformation, including deformed eyes, beaks, wings, and feet (Ort and Latshaw 1978, and Harr 1979, as cited in Eisler 1985b).

MAMMALS

Chronic effects of selenium on mammals include reproductive abnormalities such as congenital malformations; reduced numbers of young in litters; high mortality of young; infertility among surviving young in rats, mice, swine, and cattle; and intestinal lesions (Harr 1978, and NRC 1983, as cited in Eisler 1985b).

Chronic exposure of selenium, known as alkali disease, has been observed in cattle, hogs, and horses that graze on feed containing elevated levels of selenium. Adverse effects include deformed hooves, hair loss, lassitude, articular cartilage erosion, reduced conception, increased reabsorption of fetuses, and heart, kidney, and liver degeneration (Eisler 1985b).

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A.22 SILVER

Silver occurs naturally in the environment in the form of silver nitrate, silver chloride, silver sulfide, or silver oxide (USPHS 1990). Some industrial discharges can introduce silver compounds into the environment. It tends to form complexes with inorganic chemicals and humic substances in soils. Consequently, the mobility of silver in soils is affected by drainage and erosion potential, the presence of soil organic matter, oxidation-reduction potential, and pH conditions. Silver tends to be mobile in well-drained soils. Organic matter complexes with silver and causes it to become immobile. Because silver is toxic to soil microorganisms and inhibits bacterial enzymes, biotransformation is not expected to be a significant process (Domsch 1984, as cited in ATSDR 1990c).

The transport and partitioning of silver in surface waters and soils are influenced by the particular form of the compound. The major forms of silver in water include the monovalent ion as sulfate, bicarbonate, or sulfate salts; more complex ions with chlorides and sulfates; and as an integral part of, or adsorbed onto, particulate matter and aquatic biota (Boyle 1968, as cited in ATSDR 1990c). Sorption is the dominant process leading to the partitioning of silver in sediments (Callahan and others 1979, as cited in ATSDR 1990c), and pH and oxidation-reduction conditions affect sorption (Anderson and others 1973, as cited in ATSDR 1990c). When decaying animal and plant material is abundant, silver strongly precipitates as the sulfide form or combines with humic materials (Smith and Carson 1977, as cited in ATSDR 1990c).

Silver is bioaccumulated by marine organisms (Nelson and others 1983). There is no evidence that silver is biomagnified in terrestrial animals, although this may occur in some aquatic invertebrates (Adriano 1986).

PLANTS

Silver is not considered to be highly phytotoxic; even high concentrations in soil appear to have little or no effect on plant growth.

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INVERTEBRATES

Very little information was available on the effects of silver on invertebrates.

AMPHIBIANS AND REPTILES

Very little information was available on the effects of silver on amphibians and reptiles.

FISH AND AQUATIC ORGANISMS

Silver is one of the most hazardous trace elements to aquatic species (EPA 1992). The younger life stages of development appear to be the most sensitive to silver concentrations (Klein-MacPhee and others 1984). Silver concentrations have been observed to cause increased larvae mortality, physical abnormalities in developing larvae, reduced hatch, and reduced growth in winter flounder larvae (Klein-MacPhee and others 1984). Juvenile mussels exposed to silver concentrations exhibited growth inhibition (Calabrese and others 1984). Silver also has been observed to effect reproductive behavior and reduce larvae releases from gastropods (Nelson and others 1983).

BIRDS

Very little information was available on the effects of silver on birds.

MAMMALS

Inhalation studies have shown that silver can be absorbed in the lungs, while ingestion studies have shown that silver can be absorbed in the gastrointestinal tract (Amdur and others 1991). Once in the body, silver can accumulate in the liver, while only a small amount is excreted (Amdur and others 1991). A decrease in weight gain was observed in rats exposed to silver in drinking water (Matuk and others 1989, as cited in ATSDR 1990c). Intravenous doses of silver to experimental animals caused pulmonary edema, congestion, and eventual death (Amdur and others 1991).

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A.23 THALLIUM

Thallium naturally occurs in the environment. As a trace metal, thallium co-occurs with other metals and coal; its release to the environment is frequently coincidental with industrial activities using these raw materials. Compounds that contain thallium are generally highly soluble in water; hence, thallium may be biologically active in aqueous solution. When in solution, thallium generally occurs as a monovalent cation. In soil and sediments thallium is generally adsorbed to particulates within the physical matrix. The biotic and abiotic processes that influence the cycling of thallium in the environment are poorly understood; however, the biological fate and effects of thallium have been described sufficiently to evaluate its potential risks in aquatic and terrestrial habitats.

Low levels of thallium may be bioconcentrated in an aquatic environment. Experimental thallium BCFs have been determined for aquatic vertebrates and invertebrates, and values range between 10 and 1,500. The majority of these BCFs are reported at less than 100 (Zitko and Carson 1975, Zitko 1975, Barrows and others 1978, as reported in ATSDR 1992c). The relatively large range probably represents species and body size differences in experimental conditions. In terrestrial habitats, plants take up thallium from the rhizosphere; hence, the potential for its entry into terrestrial food chains exists (Ewer 1988, Sharma and others 1986, Cataldo and Wildung 1983, as cited in ATSDR 1992c).

PLANTS

When present in the soil in sufficient quantities, terrestrial vascular plants may bioaccumulate thallium (Ewers 1988; Sharma and Singh 1986). Published information on the effects of thallium on terrestrial microorganisms, plants, and animals is limited (ATSDR 1992c).

INVERTEBRATES

Various forms of thallium have been used as insecticides. Thallium acetate and thallium sulfate were used as ant poisons (Travis 1943).

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AMPHIBIANS AND REPTILES

Very little information was available concerning the effects of thallium on amphibians and reptiles; however, in the aquatic environment, study results indicate that thallium is as acutely toxic as copper on a weight basis (Zitko and others 1975).

FISH AND AQUATIC ORGANISMS

Very little information was available concerning the effects of thallium on fish and aquatic organisms; however, in the aquatic environment, study results indicate that thallium is as acutely toxic as copper on a weight basis (Zitko and others 1975). In one study, thallium concentrations reduced the percent embryo hatchability, reduced the growth of fish larvae, and caused mortality in the fish species studied (LeBlanc and Dean 1984).

BIRDS

Very little information was available concerning the effects of thallium on birds. Thallium has been used as a poison to control predators and rodents. Birds, such as eagles, hawks, magpies, and turkey vultures, were accidentally poisoned by these baits (Robinson 1948). In one acute toxicity test, eagles were given a single LD_{50} dose. Effects included loss of muscular coordination, loss of balance, reluctance to move, loss of appetite, belligerence, fear-threat displays, falling, debilitation, loss of righting reflex, distress, breathing complications, and immobility (Bean and Hudson 1976).

MAMMALS

Thallium is very toxic to mammals, and various forms of thallium were once used to control pest populations in the United States. Species that were poisoned by the pesticide include coyotes, dogs, bobcats, rodents, and other animals (Robinson 1948).

In mammals thallium can affect the heart, lung, liver, kidney, nervous system, and reproductive organs (ATSDR 1992c). In rats, exposure to large amounts of thallium for a short period of time can cause heart malfunctions and death. Rats that drank water containing smaller amounts of thallium were observed to have damage to their testes and nervous system (ATSDR 1992c).

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A.24 ZINC

Zinc is an essential trace element for all living organisms, and zinc deficiency can be a problem for both plants and animals. Zinc is primarily used as a protective coating for metals and used in the production of alloys such as bronze and brass. The adverse effects of zinc exposure to animals include growth retardation, testicular atrophy, skin changes, and poor appetite (Prasad 1979, as cited in Eisler 1993).

Most of the zinc introduced into aquatic environments is eventually partitioned into sediment. Zinc released from sediment is enhanced under conditions of high dissolved oxygen, low salinity, and low pH. Dissolved zinc usually consists of the hydrated zinc ion and various organic and inorganic complexes. In reducing conditions, organically bound zinc typically forms insoluble sulfides (MacDonald 1993).

BCFs vary widely between and within species of aquatic organisms (Eisler 1993). In marine environments, the most effective zinc accumulators included red and brown algae, ostreid and crassotreid oysters, and scallops. Invertebrates can bioaccumulate large quantities of zinc (Jamil 1992), which could potentially be passed on to higher trophic level consumers. Studies show that bony structures can act as long-term repositories for zinc (Macapinlac and others 1966). Zinc concentrations have been shown to increase with increasing trophic levels from phytoplankton to zooplankton, but not to fish (Balasubramanian 1995).

PLANTS

Zinc is an essential nutrient for plant growth in small amounts but is toxic to plants at elevated levels. Zinc can cause significant adverse effects on growth, survival, and reproduction in representative sensitive species of aquatic plants (Eisler 1993). Elevated levels of zinc in soil can cause mortality in some terrestrial plants and inhibit photosynthesis in others (Eisler 1993).

INVERTEBRATES

Certain terrestrial and aquatic invertebrates are sensitive to zinc. Reduced growth, inhibited reproduction, and reduced survival are effects that zinc can have on both terrestrial and aquatic invertebrates (Eisler 1993).

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AMPHIBIANS AND REPTILES

Environmental conditions, including pH and water hardness, and the life stage of the amphibian exposed both affect the organism's sensitivity and adverse response to exposure to metal concentrations in water. Although the information concerning amphibians and metal toxicity is limited, the primary mechanism of action of metal induced toxicity and low pH environments is believed to be body loss of sodium across the gill surface (MacDonald and Wood 1993, as cited in Horne and Dunson 1995). In one study there were no significant effects of acute and chronic exposures of frogs and salamanders and their larvae to zinc (Horne and Dunson 1995). In addition, the pH of the aquatic environment had no effect on the toxicity of zinc unlike the other metals that were studied (Horne and Dunson 1995).

However, another study observed that zinc caused significant adverse effects on growth. survival, and reproduction in representative sensitive species of amphibians (Eisler 1993). In this study, zinc was shown to cause teratogenic effects to frog embryos (Eisler 1993).

FISH AND AQUATIC ORGANISMS

The gill epithelium is the primary route of zinc entry into the body of fish (Eisler 1993). Zinc can cause significant adverse effects on growth, survival, and reproduction in representative sensitive species of protozoans, sponges, molluscs, crustaceans, echinoderms, and fish (Eisler 1993). Zinc has been shown to cause teratogenic effects to fish embryos (Eisler 1993).

BIRDS

Different species of birds have varying sensitivities to zinc exposure. Acute effects of zinc in ducks caused mortality and pancreatic degradation (Eisler 1993). Reduced growth and death were observed in poultry chicks fed diets containing elevated zinc levels. Younger stages of life appear to be more sensitive to zinc exposure. The pancreas and bone are primary target organs of zinc in birds (Eisler 1993). Decreased weight gain was observed in Japanese quail, chickens, and turkeys fed diets containing zinc (NAS 1980).

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MAMMALS

Zinc is relatively nontoxic in mammals; however, excessive zinc intake adversely affects survival of all tested mammals and produces a wide variety of neurological, hematological, immunological, hepatic, renal, cardiovascular, developmental, and genotoxic effects (PHS 1989, as cited in Eisler 1993). The pancreas and bone are primary target organs of zinc exposure in mammals (Eisler 1993). Toxic effects of zinc can be observed in many domestic animals, including dogs, cats, ferrets, cattle, sheep, and horses, as a result of ingesting zinc-containing objects (Eisler 1993). Zinc concentrations in the diet of pregnant rats and sheep caused increased incidence of hypocuprosis, still births, and fetal resorptions (Ketchenson and others 1969, and Campbell and Mill 1979, as cited in Domingo 1994).

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APPENDIX C

DATABASE SEARCH AND RESULTS

TABLE C-1

REPRESENTATIVE LIST OF DATABASES SEARCHED

Oceanic Abstracts (OCA)	1974-date (m)
Official Patent Gazette (PAT)	1970-date (w)
Oncology Abstracts (LSC)	1979-date (m)
Organic Chemistry Sections (CAS)	1968-date (sm)
kaging Science &Technology Abstracts (PST)	1982-date (bm)
PAIS Indexes (PAS)	1972-date (m)
Paper and Board Industries (PIR)	1975-date (sm)
PaperChem (IPC)	1968-date (m)
Patent Abstracts of Japan (PAJ)	1976-date (m)
Patent Assignment File (PAF)	Current (q)
Patent Registry (PAT)	1970-date (w)
PCT Int'l Applications (PCT)	1986-date (w)
Pharmaceutical News Index (PNI)	1974-date (m)
Physical, Inorganic, Analyl. Chem. Sec (CAS)	1968-date (sm)
Physics Abstracts (INS)	1969-date (w)
Pollution Abstracts (PAB)	1970-date (m)
PROMT (PMT)	1979-date (w)
Printing Abstracts (PIR)	1975-date (bw)
PsycINFO (PSY)	1984-date (m)
Pumps &Fluids Machinery Abstracts (FLD)	1973-date (m)
Registry of Toxic Effects of Chem. Substances (RTC)	1971-date (q)
Reports in Education (ERC)	1968-date (q)
Rubber & Plastics Research Abstracts (RPA)	1973-date (bw)
Scientific &Technical Aerospace Reports (USG)	1970-date (sm)
System for Information on Grey Lit. in Europe (SGL)	1985-date (m)
Society of Automotive Engineers (SAE)	1965-date (q)
Society of Manufacturing Engineers (SME)	1974-date (q)
SoftBase Database (BSD)	1988-date (m)
Solid-Liquid Flow Abstracts (FLD)	1973-date (m)
Standards Database (STD)	Current (r)
ıe of Contents (TOC)	1994-date (d)
Textile Technology Database (TTD)	1978-date (m)
Thomas Register of American Manufacturers (TRM)	Current (sa)
Toxicology Abstracts (LSC)	1979-date (m)
Trade & Industry Database (TNG)	1994-date (w)
Upcoming Conferences (UCF)	Current (m)
U.S. Trademark File (TMK)	1884-date (w)
Virology Abstracts (LSC)	1979-date (m)
Vocational and Technical Education Abstracts (ERC)	1968-date (q)
Ward's Business Directory (WRD)	Current (sa)
Water Resources Abstracts (WRA)	1977-date (m)
Weldasearch (WLD)	1967-date (m)
Who's Who in Technology (WHO)	Current (a)
World Ceramics Abstracts (WCA)	1978-date(bm)
World Surface Coatings Abstracts (WSC)	1982-date (m)
World Business Directory (WBD)	Current (sa)
World Textiles Abstracts (WTA)	1978-date (m)
World Translations Index (WTI)	1977-date (m)

Legend for Database Updates

d = daily	w = weekly
m = monthly	q = quarterly
a = annually	r = randomly
bm = one issue every two months	(bimonthly)
sm = two issues every month	(semi-monthly)
sa = two issues every year	(semi-annually)
sf = special file or one issue type	
bw = one issue every two weeks	(bi-weekly)

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A Representative List

Additional Resources Are Accessed When Appropriate and Available.

Abstracted Business Information (INF)	1980-date (m)
Aerospace Database (AEO)	1962-date (sm)
.erospace/Defense Markets & Technology (DMT)	1984-date (w)
Agricultural Abstracts (AGR)	1972-date (m)
Algology, Mycology & Protozoology Abstracts (LSC)	1979-date (m)
Alloys Index (ASM)	1966-date (m)
Aluminum Industry Abstracts (AIA)	1972-date (m)
Amino Acid, Peptide & Protein Abstracts (LSC)	1979-date (m)
Animal Behaviour Abstracts (LSC)	1979-date (m)
Analytical Abstracts (AAN)	1991-date (m)
Applied Chemistry & Chemical Engineering (CAS)	1968-date (sm)
Applied Ecology Abstracts (LSC)	1979-date (m)
Applied Federal Technology (AFT)	1970-date (sm)
Aquatic Sciences & Fisheries Abstracts (LSC)	1979-date (bm)
Bacteriology Abstracts (LSC)	1979-date (m)
BioBusiness (BIO)	1978-date (w)
Biochemistry Sections (CAS)	1968-date (sm)
Bioengineering Abstracts (EIX)	1970-date (w)
Biological Abstracts (BIO)	1972-date (bw)
Biological Abstracts/RRM (BIO)	1972-date (bw)
Biological Membrane Abstracts (LSC)	1979-date (m)
BioResearch Index (BIO)	1972-date (bw)
Biosis Previews (BIO)	1972-date (sm)
Books in Print (BOK)	Current
Books Out of Print (BOK)	1500s-date
Business & Industry (BNI)	1995-date (d)
Business Dateline (BDL)	1985-date (w)
CA Search (CAS)	1968-date (sm)
AB Abstracts (CAB)	1984-date (m)
Calcified Tissue Abstracts (LSC)	1979-date (m)
Ceramics Abstracts (CER)	1980-1993 (sf)
Chemical Abstracts Condensates (CAS)	1968-date (sm)
Chemical Business NewsBase (CBN)	1992-date (w)
Chemical Engineering Abstracts (CEA)	1983-date (m)
Chemical Safety NewsBase (CSN)	1995-date (m)
Chemoreception Abstracts (LSC)	1979-date (m)
Civil Engineering Hydraulics Abstracts (FLD)	1973-date (m)
Coal Abstracts (EDB)	1976-date (sm)
Commerce Business Daily (CBD)	1991-date (d)
Computer Controls Abstracts (INS)	1969-date (w)
Computer Database (CDB)	1983-date (bw)
Conference Papers Index (CPI)	1973-date (d)
Corporate Technology Database (CRT)	Current (sa)
Dissertation Abstracts (DIS)	1861-date (m)
DTIC (DOD)	1996-date (m)
Dun's Market Identifiers (DMI)	Current (r)
Dun's International Market Identifiers (DME)	Current (r)
Ei Compendex*Plus (EIX)	1970-date (w)
Electrical and Electronics Abstracts (INS)	1969-date (w)
Electronic Publishing Abstracts (PIR)	1975-date (sm)
Energy Information File (EDB)	1976-date (sm)
Engineered Materials Abstracts (EMA)	1986-date (m)
Engineering Index (EIX)	1970-date (w)
Engineering & Industrial Software Directory (ESD)	1985-date (a)
.tomology Abstracts (LSC)	1979-date (m)
European Patents - Applications (EPA)	1978-date (w)
European Patents - Granted (EPB)	1978-date (w)
Federal Computer Products (FCP)	1970-date (sm)
Federal Register Database (FDR)	1994-date (d)
Federal Research in Progress (FRP)	Current (r)
Feeding, Weight & Obesity Abstracts (LSC)	1979-date (m)
FINDEX (FDX)	Current (r)
Firedoc (FRD)	1985-date (r)
Fluid Flow Measurements Abstracts (FLD)	1973-date (m)
Fluid Power Abstracts (FLD)	1973-date (m)
Fluid Sealing Abstracts (FLD)	1973-date (m)
Fluidex (FLD)	1973-date (m)
Fluidics Feedback Abstracts (FLD)	1973-date (m)
Foods Adlibra (FAL)	1986-date (m)
Food Science & Technology Abstracts (FST)	1972-date (m)
Freedonia Industry Analysis (FIA)	Current (r)
Frost & Sullivan Market Reports (FNS)	1982-date (r)
Funk & Scott Index (PFS)	1985-date (w)
Furniture Industry Research Association (FIR)	1979-date (m)
Genetics Abstracts (LSC)	1979-date (m)
GeoRef (GEO)	1978-date (sm)
GLASSFILE (GLS)	1970-date (q)
Global*base* (GBS)	1994-date (w)
Global Mobility Database (SAE)	1965-date (q)
Global Products Database (GLO)	Current (r)
Government Reports Abstracts (USG)	1970-date (sm)
Health Effects of Environmental Pollutants (BIO)	1972-date (bw)
Imaging Abstracts (IMA)	1977-date (sa)
Immunology Abstracts (LSC)	1979-date (m)
Industrial Aerodynamics Abstracts (FLD)	1973-date (m)
Industrial and Applied Microbiology (LSC)	1979-date (m)
Inform (INF)	1980-date (m)
Information Technology Focus (INS)	1969-date (w)
Inside Conferences (CON)	1994-date (d)
Inspec (INS)	1969-date (w)
International Aerospace Abstracts (AEO)	1962-date (sm)
International Dredging Abstracts (FLD)	1973-date (m)
International Packaging Abstracts (PIR)	1975-date (sm)
International Pharmaceutical Abstracts (IPA)	1992-date (m)
Investext Citations (INV)	1995-date (d)
ISMEC (ISM)	1973-date (bm)
Journals in Education (ERC)	1968-date (q)
Kosmet (KOS)	1977-date (m)
Library and Information Science Abstracts (LIS)	1978-date (m)
Macromolecular Sections (CAS)	1968-date (sm)
Magazine Index (MGI)	1994-date (w)
Management Contents (MNC)	1978-date (w)
Management and Marketing Abstracts (MMA)	1975-date (sm)
Marketing & Advertising Reference Service (MAR)	1985-date (w)
MarkIntel (MKI)	Current (d)
Materials Business File (MDB)	1985-date (m)
Mechanical Engineering Information (ISMEC)	1973-date (bm)
Medline (MED)	1966-date (w)
Metals Abstracts (ASM)	1966-date (m)
Microcomputer Abstracts (MCA)	1981-date (m)
New Product Announcements (NPA)	1985-date (w)
Newsletter Index (NWL)	1997-date (w)
NIOSHTIC (NIO)	1950-date (q)
Nonwoven Abstracts (PIR)	1975-date (sm)
Nucleic Acids Abstracts (LSC)	1979-date (m)
Occupational Safety and Health (NIO)	1950-date (q)

TABLE C-2

SUMMARY OF SEARCH RESULTS

Chemical	Receptor	Database	Number of Citations
Aldrin	rodents	NERAC	35
	rodents	miscellaneous[1]	3
	birds	NERAC	2
Antimony*	rodents	Toxline	68
	birds	Toxline	12
	several	Agricola	4
	several	Ecotox	1
	several	Current Contents	147
	several	TtEMI Library[2]	14
	several	miscellaneous	5
Arsenic	rodents	Toxline	408
	rodents	Agricola	13
	rodents	Enviroline	11
	rodents	Current Contents	20
	rodents	miscellaneous	6
	birds	Toxline	128
	birds	Enviroline	34
	birds	Ecotox	1
	birds	Agricola	35
	several	TtEMI Library	67
	several	Current Contents	190
Barium*	rodents	NERAC	32
	birds	NERAC	43
Benzo(a)pyrene	rodents	NERAC	206
	rodents	Toxline	198
	rodents	miscellaneous	15
	birds	NERAC	4
	birds	Toxline	126
	birds	miscellaneous	5
	several	Current Contents	20
Beryllium*	rodents	NERAC	62
	birds	NERAC	4
Cadmium	mammals[3]	NERAC	165
	rodents	Toxline	419
	birds	Toxline	491
	birds	Agricola	13
	birds	Ecotox	10
	several	TtEMI Library	188
	several	miscellaneous	36
	several	Current Contents	43
Chlordane*	rodents	Toxline	213
	rodents	Agricola	23
	rodents	Medline	204

	rodents	Biosis	31
	birds	Toxline	80
	birds	Agricola	12
	birds	Enviroline	29
	birds	Biosis	19
	several	TtEMI Library	157
	several	miscellaneous	4
	several	Current Contents	82
Chromium*	rodents	NERAC	194
	rodents	Toxline	411
	rodents	Agricola	14
	birds	NERAC	43
	birds	Toxline	119
	birds	Agricola	2
	birds	Ecotox	1
	several	TtEMI Library	42
	several	Agricola	194
	several	Current Contents	27
	several	miscellaneous	22
Cobalt	rodents	NERAC	44
	rodents	miscellaneous	1
	birds	NERAC	37
Copper	mammals[3]	NERAC	57
	rodents	Toxline	136
	rodents	Agricola	88
	birds	Toxline	92
	birds	Agricola	15
	birds	Ecotox	2
	several	TtEMI Library	42
	several	Current Contents	84
	several	miscellaneous	12
DDD	rodents	Toxline	108
	rodents	Enviroline	22
	rodents	Agricola	17
	birds	Toxline	63
	birds	Enviroline	25
	birds	Agricola	7
DDE	rodents	Toxline	111
	rodents	Agricola	36
	birds	Toxline	69
	birds	Enviroline	228
	birds	Agricola	66
	several	TtEMI library	102
	several	Current Contents	9
DDT	mammals[3]	NERAC	69
	rats	Toxline	86
	mice	Toxline	80
	rodents	Agricola	203
	birds	Toxline	94

	birds	Agricola	178
	birds	miscellaneous	27
	several	Current Contents	35
	several	Enviroline	697
Dibutyltin	rodents	NERAC	10
	birds	NERAC	22
Endosulfan*	rodents	Toxline	71
	rodents	Agricola	65
	birds	Toxline	36
	birds	Agricola	15
	several	TtEMI Library	33
	several	Enviroline	44
	several	Current Contents	156
Endrin*	rodents	Toxline	271
	rodents	Agricola	40
	birds	Toxline	38
	birds	Agricola	16
	several	Enviroline	41
	several	TtEMI Library	33
Heptachlor	rodents	NERAC	30
	rodents	miscellaneous	5
	birds	NERAC	9
	birds	miscellaneous	2
Lead	mammals[3]	NERAC	206
	rodents	Toxline	378
	rodents	Agricola	72
	rodents	miscellaneous	20
	birds	Toxline	160
	birds	Ecotox	12
	birds	Agricola	57
	birds	miscellaneous	14
	several	TtEMI library	133
	several	Current Contents	46
Lindane	rodents	NERAC	8
	rodents	Toxline	757
	rodents	Enviroline	70
	rodents	Agricola	274
	birds	NERAC	6
	birds	Toxline	156
	birds	Enviroline	14
	birds	Agricola	25
	several	TtEMI Library	25
	several	Current Contents	56
Manganese	rodents	NERAC	250
	rodents	Toxline	84
	rodents	Agricola	25
	birds	NERAC	3
	birds	Toxline	114
	birds	Agricola	7

	several	Agricola	453
	several	TtEMI Library	32
	several	Current Contents	24
Mercury	mammals[3]	NERAC	40
	rodents	Toxline	226
	rodents	Agricola	14
	rodents	Biosis	125
	rodents	Medline	432
	rodents	Current Contents	90
	birds	Toxline	155
	birds	Agricola	29
	birds	Ecotox	28
	birds	Biosis	116
	birds	Medline	198
	birds	Current Contents	12
	several	Current Contents	23
	several	HSDB	12
	several	IRIS	76
	several	miscellaneous	28
Methoxychlor	rodents	NERAC	27
	rodents	miscellaneous	13
	birds	NERAC	2
Molybdenum*	rodents	NERAC	35
	birds	NERAC	36
Naphthalene	rodents	NERAC	97
	rodents	Toxline	176
	birds	NERAC	20
	birds	Toxline	42
Nickel	rodents	NERAC	247
	rodents	Toxline	111
	rodents	Agricola	7
	birds	NERAC	29
	birds	Toxline	100
	several	TtEMI library	23
	several	Agricola	175
	several	Current Contents	58
Selenium	mammals[3]	NERAC	75
	rodents	Toxline	177
	rodents	Agricola	64
	birds	Toxline	151
	birds	Agricola	27
	birds	Ecotox	4
	several	TtEMI library	64
	several	Current Contents	23
	several	EPA reference list	18
	several	miscellaneous	16
Silver*	rodents	NERAC	109
	rodents	Toxline	228
	birds	NERAC	33

	birds	Toxline	60
	birds	Agricola	6
	several	TtEMI Library	21
	several	Agricola	76
	several	Current Contents	28
Thallium	rodents	NERAC	127
	rodents	Toxline	34
	rodents	Current Contents	4
	birds	NERAC	6
	birds	Toxline	37
	several	TtEMI library	23
	several	Agricola	27
Tributyltin (TBT)	rodents	NERAC	29
	birds	NERAC	22
Zinc	mammals[3]	NERAC	130
	rodents	Toxline	289
	rodents	Agricola	133
	rodents	miscellaneous	10
	birds	Toxline	99
	birds	Agricola	23
	several	TtEMI library	49
	several	Current Contents	68
	several	EPA reference list	18

Note: A title may be cited in more than one search.

* Searches were performed for chemicals marked with an asterisk, but papers were not reviewed for derivation of TRVs during this project. Search results are provided here for purposes of completeness.

[1] Miscellaneous searches include papers located incidentally during the project, including through reference lists included in other articles, recommendations from colleagues, and other methods.

[2] The TtEMI library contains papers collected over several years for many projects, and is searched via an electronic bibliographic database.

[3] Mammal refers to the following specific search parameters: "small mammals," "*Lutra canadensis*," and "*Urocyon cinereoargenteus*."

APPENDIX D

MEETING MINUTES
FOR TOXICITY REFERENCE VALUE WORK GROUP MEETINGS

CONTENTS

Meeting Minutes **Page**

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MINUTES FOR AUGUST 20, 1996 TRV WORKING MEETING D-39

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MINUTES FOR OCTOBER 3, 1996 TRV WORKING MEETING D-69

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SAN FRANCISCO BAY
REGIONAL TOXICITY REFERENCE VALUES
WORKING MEETING
JULY 19, 1996

Date: July 19, 1996
Time: 9:30 a.m.
Location: Regional Water Quality Control Board Office, Oakland, California

Participant	Organization
Eugenia McNaughton	U.S. Environmental Protection Agency (EPA)
Barbara Smith	EPA
Susan Gladstone	Regional Water Quality Control Board (RWQCB)
Laurie Sullivan	National Oceanic and Atmospheric Administration (NOAA)
William Van Peeters	Engineering Field Activity West (EFA West)
Roy Santana	EFA West
Martha Burford	PRC Environmental Management, Inc. (PRC)
Garry Donaldson	PRC
Mary Gleason	PRC
Cooper Heins	PRC
Greg Linder	PRC
June Mire	PRC
Emily Pimentel	PRC

INTRODUCTION

This was the first working meeting of the Biological Technical Advisory Group's (BTAG) toxicity reference value (TRV) work group to develop regional TRVs for the San Francisco Bay. The main objective of the Navy, Regulatory, and Trustee agencies is to reach consensus on regional TRVs in order to assess risk to higher trophic level receptors from site contaminants at Naval installations. The meeting included members of the TRV development team representing the Navy, the EPA Region 9 BTAG and the Naval Weapons Station (WPNSTA) Concord ecological assessment team.

The contaminant and receptor lists for regional TRVs were prioritized in previous working meetings, and TRVs needed for the qualitative ecological assessment at the WPNSTA Concord Litigation Area were

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developed first, so that they could be included in the WPNSTA Concord ecological assessment. The purpose of this meeting was to evaluate proposed high and low TRVs for four metals at the Litigation Area (cadmium, copper, arsenic, and zinc) for both birds and mammals. Attachment A contains the agenda for the meeting, and Attachment B contains a list of handouts for the meeting.

Dr. Mire (PRC) discussed how the process of deriving regional TRVs relates to those TRVs that were developed by PRC for Moffett Federal Airfield (Moffett). As agreed during the Moffett TRV development process, Moffett TRVs were considered specific only to Moffett, and were revised to arrive at regional TRVs. The revision process involved searching for any new or additional research papers for each chemical, updating and expanding the ingestion rate/body weight database for test and receptor organisms, subsequent entering of new data, and performing a final quality control (QC) check. Also, in cases where default numbers were used for the Moffett effort, full TRV development was completed to arrive at regional TRVs.

The group discussed how to include work group members not in attendance at this meeting so that the TRVs could represent consensus on the part of the regulatory and trustee agencies. It was decided that meeting minutes would be prepared before the next meeting. The meeting minutes will contain action items and summarize decisions and relevant discussions. Ms. Heins (PRC) will distribute the meeting minutes to those not in attendance and solicit input from them. Ms. Heins will summarize input and concerns expressed by those not in attendance in the first hour of the next meeting; time will be made available for a brief discussion of any unresolved issues.

Dr. Linder (PRC) expressed concern that some of the Moffett TRVs may not be revised in time to meet certain report deadlines, specifically the WPNSTA Concord Inland Area remedial investigation report. The group agreed that, under those circumstances, it would be appropriate to use Moffett TRVs until regional TRVs can be developed.

METHODOLOGY

The methodology for deriving TRVs is documented and available through PRC. Ms. Heins summarized these methods:

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- Literature searches: To conduct bibliographic database searches, PRC is currently using NERAC, a private company that specializes in technical and scientific bibliographic database searches. Comparisons with manual database searches resulted in high confidence that all relevant citations are retrieved by NERAC. The search results are downloaded by PRC and all titles and abstracts are read. Only the most obviously inappropriate citations are eliminated from the list at this point. A list of papers to be retrieved is compiled. Search results are retained for future reference.

- Library work: Papers are retrieved from the University of California (UC) Berkeley and UC Davis libraries. At the library, abstracts and methods sections of the papers are read to confirm ecologically relevant exposure routes such as oral exposures through diet or water. Only studies using clearly inappropriate exposure routes such as injection or exposure through the eggshell (eggshell painting) are not copied. This process provides a collection of papers dealing with exposure routes that are as close to field exposure routes as possible.

- Reading: Papers are read and considered to be of acceptable quality when quantified doses and measured effects are reported, when the researchers use appropriate statistics and report statistical significance, when the exposure duration is chronic or subchronic, when sample sizes are adequate, and when treatments are compared to appropriate controls.

- Data extraction: Data are then extracted from the papers. Types of data extracted include: reported concentrations, duration of exposure, body weights, age, species, doses, and ingestion rates. When doses are not reported in milligrams per kilogram of body weight per day (mg/kg-day), the data spreadsheet being developed uses the reported concentration in the diet, body weights, and ingestion rates to calculate a dose in mg/kg-day. If body weights and ingestion rates are not reported in the paper, they are estimated using means of literature values.

- Dose figures: Spreadsheet doses are plotted to yield a visual representation of the range of effect and no effect levels. No effect levels are represented in the figures by open symbols; effect levels are represented by closed symbols. In most cases, log scales have been used to accommodate broad ranges of data. Circled numbers in the figures represent record numbers that correspond to spreadsheet records. Data are grouped along the x axis of the plots into types of effects such as systemic or reproductive.

- High/low TRV: The low TRV represents a chronic, no effect level equivalent. It is intended to represent a dose at which adverse effects are not expected. The high TRV represents a dose at which adverse effects are almost certain and are generally chosen from the middle of the range of effects. Proposed TRVs are discussed with the TRV working group, at which time final high and low TRVs are selected. TRVs are then allometrically converted. Allometric conversion is a body scaling calculation that adjusts for extrapolation from the test organism to the receptor species of interest.

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SAN FRANCISCO BAY REGIONAL TRVS

Data spreadsheets, dose figures with proposed TRVs, and critical papers were mailed to participants in advance of the meeting. Proposed low TRVs were highlighted yellow and proposed high TRVs were highlighted blue.

The group discussed the issue of selecting values falling between data points. It was agreed that TRVs should always be based on a dose associated with a specific paper. This method of selecting TRVs provides a means to support decisions and limits subjectivity.

The group discussed proposed TRVs for all contaminant/receptor pairs on the agenda.

Cadmium/birds

Ms. Heins pointed out that a mistake had been made on the data spreadsheet. At dose 0.19 mg/kg-day in the bottom of the reproductive column, a closed symbol had mistakenly been placed where an open symbol should be. This correction changed the effect level (EL) at that dose to a no effect level (NEL).

For the low TRV, PRC proposed using a study by Cain and others (1983) in which a dose of 1.07 mg/kg-day resulted in no degenerative effects on specific organs and tissues, and no effect on blood chemistry in mallard ducklings. The group discussed choosing a TRV lower than the proposed low TRV because at 1.06 mg/kg-day, Leach and others (1978) reported decreased egg production in white leghorn chickens. This paper was reviewed; however, the group decided that the proposed low TRV at 1.07 mg/kg-day was preferable because the study used mallard ducklings rather than adult chickens. The group agreed that studies using mallards were preferable because they more closely resemble the wildlife species of concern than do chickens. It was pointed out that most research on chickens is conducted to increase efficiency in poultry production.

In choosing the low TRV, sample size was also considered. The study by Leach and others (1978), reported a sample size of 5 chickens. The study by Cain and others (1983) reported a sample size of 10 ducklings per experiment. This study also reported mild to moderately severe kidney degeneration in

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4 out of 12 ducklings at this dose, but statistical significance was not reported for this effect. The group concluded that the low TRV should be 1.07 mg/kg-day.

PRC proposed a dose of 19.08 mg/kg-day for the high TRV based on a study by White and others (1978), in which reproductive and kidney effects were observed. The proposed high TRV was acceptable to the group.

Cadmium/rodents

PRC proposed a low TRV based on a study by Valois and Webster (1989), in which a dose of 0.19 mg/kg-day had no effect on choroid epithelial cells in mice. The group discussed changing the low TRV to 0.06 mg/kg-day. At this dose, Webster (1978) treated female mice for 6 weeks plus 18 days of gestation and observed no effect on fetal weight. The group agreed that 0.06 mg/kg-day was a more appropriate low TRV because it represents a reproductive no effect level and is, therefore, more ecologically relevant than the effects studied by Valois and Webster (1989).

PRC proposed using a study by Schroeder and Mitchener (1971) to derive the high TRV. In this multigenerational study, a dose of 2.64 mg/kg-day resulted in increased mice pup deaths, increased runts in F_1 and F_2 generations, and failure to breed in the F_2B generation. The group agreed with the proposed high TRV of 2.64 mg/kg-day.

Copper/birds

For the low TRV, PRC proposed a dose of 22.99 mg/kg-day from a study by Norvell and others (1974). This dose did not affect weight gain in broiler chicks. Effects were observed at a lower dose (22.36 mg/kg-day from a study by Bakalli and others 1995); however, the effects at this dose were positive effects from a breeder experiment that investigated methods to create low-cholesterol chickens. The group agreed that the low TRV should be 22.99 mg/kg-day.

PRC proposed to base the high TRV on a study by Jensen and Maurice (1978), in which a dose of 52.26 mg/kg-day resulted in increased gizzard erosion, feed to weight gain ratio, and gizzard and proventriculus weights. This dose was selected because the only reproductive effects in the data set were

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observed at 200 mg/kg-day (Shivanandappa and others 1983), which fell above a dose that resulted in increased mortality 149.16 mg/kg-day from a study by Van Vleet and others 1981). Additionally, gizzard erosion was considered ecologically relevant because it affects a bird's ability to eat. The group agreed with the proposed high TRV of 52.26 mg/kg-day.

Copper/rodents

PRC proposed a low TRV of 26.62 mg/kg-day. At this level, Pocino and others (1991) reported no effects on ingestion rate, body weight, number of thymus cells, or mortality. Ms. Heins explained that the effect levels falling below this dose are immune response experiments in which antigens such as sheep red blood cells (SRBC) are injected into the test organism and immune response is measured. These effects are considered of questionable ecological relevance because their correlation to immunity involving diseases that mice may contract in the field has not been demonstrated.

Another effect level falling below the proposed low TRV was 1.45 mg/kg-day from a study by Massie and Aiello (1984), which reported a decrease in the mean life span survival curve at this dose. This dose was not selected because the authors report low confidence in this effect level. In their discussion, the authors state that they believe little or no change in the rate of senescence occurs below 36.23 mg/kg-day. They state that all survival curves in mice should be regarded with suspicion. For this reason, the paper by Massie and Aiello (1984) was not considered suitable as a basis for a TRV. The group agreed that the low TRV should be 26.62 mg/kg-day.

For the high TRV, PRC proposed a dose of 631.58 mg/kg-day from a study by Hebert and others (1993). The group agreed with the proposed high TRV at this dose.

Arsenic/birds

PRC proposed a low TRV of 5.5 mg/kg-day from a study by Stanley Jr. and others (1994). In this multigenerational study, no effects on egg weight, days to first egg, duckling production, duckling body weight, growth, liver weight, growth, or glycogen depletion were observed at this dose. At a lower dose of 4.02 mg/kg-day in a study by Camardese and others (1990), enzyme and hematological effects were observed. The proposed low TRV was not based on these effects because they were of questionable

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ecological relevance. Dr. Linder explained that these effects are considered biomarkers of exposure, not adverse effects, and that they may be interpreted as healthy responses to contaminant exposure. Ms. Heins stated that effects of questionable ecological relevance are included in the data sets to signify that the papers have been reviewed and considered.

A dose of 22.01 mg/kg-day from a study by Stanley Jr. and others (1994) was proposed as the high TRV. This dose is the lowest observed adverse effects level (LOAEL) that corresponds to the no observed adverse effects level (NOAEL) that was the proposed low TRV. The group agreed that the study on which the proposed low and high TRVs were based was particularly suitable because it examined reproductive, developmental, and systemic effects and was a multigenerational study. The group agreed that the low TRV should be 5.5 mg/kg-day and the high TRV should be 22.01 mg/kg-day.

Arsenic/rodents

For the low TRV for arsenic, PRC proposed using a study by Schroeder and others (1968), in which a dose of 0.32 mg/kg-day resulted in no effects on growth rates, survival, glycosuria, proteinuria, blood pressure, tumors, or heart weight. The group considered the proximity of the proposed low TRV to an effect level for decreased longevity of 0.35 mg/kg-day from a study by Schroeder and Balassa (1967). The length of the Schroeder and Balassa (1967) laboratory study was 3 years. The group agreed that this study is not representative of field conditions because wild mice are normally preyed upon within the first year of life. A reproductive no effect level at 0.01 mg/kg-day from a study by Schroeder and Mitchener (1971) was not selected because the study was considered to be relatively lower in quality than the study by Schroeder and others (1968). The group agreed that the low TRV should be 0.32 mg/kg-day.

PRC proposed a high TRV of 4.70 mg/kg-day based on a study by Brown and others (1976). In this study, a dose of 4.70 mg/kg-day resulted in decreased water intake, changes in cellular respiratory parameters, and decreased kidney to body weight ratio. The group discussed whether the proposed high TRV may be too low for a risk manager to feel comfortable that adverse effects would undoubtedly occur at this level. The group agreed that an examination of acute effects or the concentration lethal to 50 percent of a test group (LC_{50}) would help to put the range of effects in better perspective. The group

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agreed to postpone a decision on the high TRV until other data could be found and used for comparison. Ms. Heins agreed to research and present LC_{50} values at the next meeting.

Zinc/birds

For the avian low TRV for zinc, PRC proposed using a study by Lu and Combs (1988), in which a dose of 11.36 mg/kg-day resulted in no effect on alpha-tocopherol levels in the liver and pancreas, and no effect on pancreatic amylase levels in leghorn chicks. The majority of the group considered this dose to be too low and difficult to justify in terms of ecological relevance. The reproductive no effect level at 126.5 mg/kg-day was suggested. This dose is from a multigenerational study by Stahl and others (1990), in which the authors reported no effects on several reproductive parameters. Effect levels below this value were discussed, but rejected as low TRVs because they are enzymatic and not necessarily adverse effects (see arsenic/bird discussion). Laurie Sullivan (NOAA) expressed concern over raising the low TRV so dramatically, but acknowledged that she could not justify her hesitation. The group tentatively agreed on the revised low TRV of 126.5 mg/kg-day.

The proposed high TRV of 138.45 mg/kg-day (Lu and Combs 1988) was considered too low relative to the revised low TRV. Instead, 344.10 mg/kg-day was proposed as the new high TRV. At this dose, Gasaway and Buss (1972) reported decreases in body weight and testes to body weight ratios in mallards. The dose was considered appropriate because the study on which it is based examined reproductive effects, the test organism is the mallard, and the dose is below concentrations that caused mortality. The group decided that the high TRV should be 344.10 mg/kg-day.

Zinc/rodents

PRC proposed a low TRV of 39.13 mg/kg-day based on a study by Uriu-Hare and others (1989), in which no effects on several reproductive parameters were observed in rodents. Alternatively, a dose of 205.71 mg/kg-day was suggested as the low TRV, since there are no definite ecologically relevant adverse effects from 39.13 mg/kg-day to 205.71 mg/kg-day. There was general agreement that selection of 205.71 mg/kg-day was more consistent with the logic used to select low TRVs in the past. The group agreed that the low TRV should be 205.71 mg/kg-day.

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The proposed high TRV of 411.43 mg/kg-day, based on a study by Schlicker and Cox (1968), was accepted by the group. At this dose, fetal resorption was observed in rats.

SELENIUM AND LEAD TRVS

The data spreadsheet, figures with proposed TRVs, and critical papers were handed out. It was agreed that TRVs for the selenium and lead spreadsheets would be discussed at the August 2, 1996 meeting.

TRVS FOR MERCURY, DDT, AND PCBS

PRC proposed using wildlife criteria from the EPA Great Lakes Water Quality Initiative documents (EPA 1995) as TRVs for mercury and DDT. Copies of sections of these documents were handed out.

Ms. Heins explained that the methods employed by PRC for deriving TRVs were, in part, based on the approach EPA used as part of the Great Lakes Water Quality Initiative (EPA 1995). The Great Lakes documents and the work used in developing them are generally considered thorough and of high quality. For this reason, using these numbers would eliminate duplication of work and save substantial resources. The resource savings would allow PRC to focus its efforts on the next set of regional TRVs to be developed. The members of the group agreed to review the Great Lakes documents and be prepared to discuss this proposal at the meeting on August 2.

TRVS FOR LARGER MAMMALS

Ms. Heins stated that bibliographic database searches had been completed for arsenic, cadmium, copper, lead, selenium, and zinc for the otter and gray fox (receptors important at WPNSTA Concord) and a wide variety of mammals. With the exception of lead, the search results were very limited. Ms. Heins asked the group to consider options for these contaminant/receptor pairs in preparation for discussion at the next meeting.

In order for the next set of TRVs to be included in the Naval Station Treasure Island remedial investigation report, a meeting to discuss these TRVs was scheduled for August 12, 1996 at 9:30 a.m., at the RWQCB office in Oakland, California.

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ATTACHMENT A

AGENDA

AGENDA

SAN FRANCISCO BAY REGIONAL TRV

WORKING MEETING

JULY 19, 1996

I. Objectives: Regional TRVs for Naval Facilities
Initial focus on Naval Weapons Station Concord receptors and contaminants

II. Brief Overview of Methodology

III. Cadmium

A. Birds
B. Rodents

IV. Copper

A. Birds
B. Rodents

Lunch (12:00 - 1:00)

V. Zinc

A. Birds
B. Rodents

VI. Arsenic

A. Birds
B. Mammals

VII. Preview of Selenium, Lead, and PCBs

VIII. Preview of Mercury and DDT (EPA Great Lakes documents)

Reminder: The next meeting of the TRV work group is scheduled for August 2, 1996 at 9:30 a.m.

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ATTACHMENT B

LIST OF HANDOUTS

LIST OF HANDOUTS

- San Francisco Bay Regional Approach: Derivation of TRVs
- San Francisco Bay Regional Approach: Addressing Uncertainty
- Spreadsheets and Figures for: Arsenic/Mice, Lead/Birds
- EPA Great Lakes Water Quality Initiative Document Sections
- Bibliography on salt marsh harvest mouse, black rail, and clapper rail (for WPNSTA Concord project team)

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SAN FRANCISCO BAY
REGIONAL TOXICITY REFERENCE VALUES
WORKING MEETING
AUGUST 2, 1996

Date: August 2, 1996
Time: 9:30 a.m.
Location: Regional Water Quality Control Board Office, Oakland, California

Participant	Organization
Clarence Callahan	U.S. Environmental Protection Agency (EPA)
Barbara Smith	EPA
Eugenia McNaughton	EPA
James Haas	U.S. Fish and Wildlife Service (FWS)
Laura Valoppi	Department of Toxic Substances Control (DTSC)
Gerald Chernoff	DTSC
Susan Gladstone	Regional Water Quality Control Board RWQCB)
Susan Ellis	California Department of Fish and Game (DFG)
William Van Peeters	Engineering Field Activity West (EFA WEST)
Cooper Heins	PRC Environmental Management Inc.(PRC)
Greg Linder	PRC
Mary Gleason	PRC

INTRODUCTION AND OBJECTIVES

This was the second working meeting of the work group to develop TRVs for use in ecological assessments at Navy installations in the San Francisco Bay Area. The overall objective of these working meetings is to develop TRVs to assess risk to higher trophic level receptors from site contaminants at Naval installations; the goal is to obtain consensus from regional regulatory and trustee agencies and the Navy on the TRVs selected.

The specific objectives of today's meeting were to: 1) review the discussion and selection of TRVs from the last meeting on July 19, 1996 for those individuals who did not attend, 2) select TRVs for selenium and lead, 3) discuss the use of TRVs based on rats and mice in the development of TRVs for larger mammals, and 4) discuss the use of the EPA Water Quality Initiative Wildlife Criteria (EPA 1995) for mercury and DDT, and 5) select TRVs for PCBs. Objectives 1 and 2 were mostly completed; objectives 3,4, and 5 were deferred until the next meeting on August 12, 1996.

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Corrections: Two errors in the minutes from the July 19, 1996 meeting were noted and PRC agreed to revise the meeting minutes. These two errors were:

1) Gerald Chernoff (DTSC) pointed out that the draft minutes from the August 2 minutes (page 5) stated that a neurotoxicological endpoint was selected over a reproductive endpoint because the target effect of arsenic is neurotoxicological. This statement could be interpreted to mean that arsenic does not cause adverse reproductive effects or that they are not important. PRC agreed to reword the sentence.

2) Dr. Chernoff pointed out an error on page 6, where the word mallard should be replaced by rats in the discussion of zinc effects on rodents.

BRIEF REVIEW OF METHODOLOGY

Ms. Heins (PRC) briefly reviewed the methodology used in the derivation of TRVs. This lead to a general discussion of various aspects of the methodology. Dr. Callahan (EPA) asked how TRVs relate to the use of bioassays and whether the Navy will still use bioassays. Mr. Van Peters (EFA WEST) assured the group that bioassays are still considered an important tool in assessing risk. Ms. Valoppi (DTSC) asked whether studies using exposure routes such as eggshell painting with PAHs could be used in the identification of TRVs. Ms. Heins responded that the derivation of TRVs requires quantified ingested doses representative of field exposure. She stated that risk assessors may wish to incorporate eggshell painting in a qualitative evaluation of risk. Multigenerational studies with reproductive or other ecologically significant effects are considered the best types of studies. Mr. Haas (FWS) informed the group about work on reproductive effects of selenium on birds done by Joe Skorupa and agreed to provide the group with more information.

Ms. Valoppi expressed a general concern about variation in sensitivity among species and whether uncertainty factors (UF) related to interguild conversions would be applied. For example, for some contaminants, the only studies available were conducted on chickens or mallards and it is not known whether the effects noted can be directly related to similar effects in other types of birds in other feeding guilds. Ms. Heins stated that the hazard quotient methodology was specifically designed to avoid using UFs, whenever possible. PRC is accounting for uncertainty usually involved in deriving TRVs by performing extensive primary literature searches to account for the maximum amount of available data, by calculating low and high TRVs to account for the distribution of data in the TRV data set, by allometrically converting doses from test organism to receptor, by calculating low and high site-specific

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doses, and by applying a confidence rating to each TRV that reflects the level of confidence associated with applying that number to a specific feeding guild. She stated that UFs make it difficult for the risk manager to know what the number means in terms of effects. The group expressed concern about the fact that numbers tend to get used without adequate attention to qualifiers or any measure of uncertainty in the number. Ms. Valoppi stated that the low TRV is supposed to be "safe" and that if good data and poor data are used in a similar fashion without uncertainty factors to derive TRVs then there is no way to distinguish between a good, safe TRV and a poor TRV that may not actually be safe. Ms. Valoppi recommended using interguild UFs and then providing a qualifier so that it is clear which numbers the group has a lot of confidence in. Dr. Smith (EPA) stated that, historically, UFs were applied very liberally. Dr. Linder (PRC) reminded the group that using several UFs, often set arbitrarily at 10, results in numbers that are so low as to be useless in screening sites. He suggested that, if the group decides to use UFs, serious attention be paid to the values used in accounting for uncertainty. Dr. Smith said this was a technical point of basic disagreement in the group that may need to be revisited. Dr. Callahan agreed to review strategies for minimizing interspecies or interguild uncertainty.

REVIEW OF RESULTS OF THE LAST MEETING:

Arsenic/Rodents

At the last meeting, the group agreed upon a low TRV of 0.32 mg/kg-day based on a study by Schroeder and others (1968). There was more concern at the last meeting about the high dose for the high TRV, as the data presented did not appear to represent an upper bound to adverse effects, and no mortality was seen at the doses included on the spreadsheet. At the last meeting Ms. Heins agreed to review the Agency for Toxic Substances and Disease Registry (ATSDR) toxicity profiles to determine at what higher doses effects were observed. Ms. Heins reported that the ATSDR data indicated LC_{50}s for mice and rats were in the range of 8-10 mg/kg-day. The group decided that the dose at 4.7 mg/kg-day based on a study by Brown and others (1976) was still an appropriate high TRV.

Arsenic/Birds

At the last meeting, the group agreed on a low TRV of 5.5 mg/kg-day based on a study by Stanley, Jr. and others (1994) and a high TRV of 22.01 mg/kg-day based on the same study. Ms. Valoppi pointed out

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that this was a good example of little variability in study organisms, as all relevant studies were based on mallards. She said that these numbers may be appropriate for waterfowl, but may not be appropriate for other types of birds. Ms. Valoppi also pointed out that decreased growth in females was observed at 30 ppm in the study by Stanley, Jr. and others (1994) and that this was not reflected in the spreadsheet. The group agreed that 5.5 and 22.01 mg/kg-day should be the low and high TRVs but that these values should be footnoted to indicate uncertainty in using these values for other guilds of birds.

Cadmium/Rodents

At the last meeting, the group agreed that a dose of 0.06 mg/kg-day, based on a study by Webster (1978) was an appropriate low TRV and a dose of 2.64 mg/kg-day based on a study by Schroeder and Mitchener (1971) was an appropriate high TRV. There was additional discussion of these values; however, there were no dissenting opinions.

Cadmium/Birds

At the last meeting, the group proposed a low dose of 1.07 mg/kg-day (Cain and others 1983) and a high dose of 19.08 mg/kg-day (White and others 1978) for the low and high TRVs respectively. Ms. Valoppi pointed out that the doses on the spreadsheet for several data points were based on nominal doses, even though measured doses were given. She emphasized that measured doses should be used when they are provided. For example, the dose indicated in record number 14 in the spreadsheet (Cain and others 1983) should be based on a measured quantity in the food of 14.6 parts per million (ppm) and a dose of 0.78 mg/kg-day. Record number 3 (White and others 1978) should have a food concentration of 1.6 ppm and a calculated dose of 0.15 mg/kg-day. Record number 4 (White and others 1978) had a measured concentration of 210 ppm resulting in a calculated dose of 20 mg/kg-day, while record number 5 had a measured dose of 15.2 ppm resulting in a calculated dose of 1.45 mg/kg-day. Ms. Valoppi also pointed out that effects were observed in the study by Cain and others 1983.

In reference to the cadmium TRVs, Ms. Valoppi stated that her main concerns were that 1) there were only data on egg production for chickens and only data on effects on testes and kidneys for mallards; 2) suitable NOAELs for both types of effects were not available; 3)Records 3 through 7 include only studies of less than 90 days and were subchronic. She also pointed out that the open circle indicating no

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effects at 1.91 mg/kg-day (White and others 1978) on the data spreadsheet showed effects on spermatogenesis and should be filled in to reflect an effect: the group agreed. The group suggested that the high TRV be retained at 19.08 mg/kg-day. At Ms. Valoppi's request, the group agreed to defer the decision on the low TRV until she had an opportunity to review studies by Leach and others (1979).

Copper/Rodents

At the last meeting, a low dose of 26.62 mg/kg-day, based on a study by Pocino and others (1991), and a high dose of 631.58 mg/kg-day based on a study be Hebert and others (1993) were proposed for the low and high TRVs. There was additional brief discussion by the group with the consensus that these numbers were appropriate.[1]

Copper/Birds

At the last meeting, a low dose of 22.99 mg/kg-day (Norvell and others 1974) and a high dose of 52.26 mg/kg-day (Jensen and Maurice 1978) were selected for the low and high TRVs. Ms. Valoppi pointed out that the study by Norvell and others (1974) was only 8 weeks in duration and asked if a UF would be applied to go from subchronic to chronic. Dr. Linder (PRC) reminded the group that the lower bounds of a low TRV needed to be at or above the essential nutritional level. For quail, this level is about 1.1 mg/kg-day; Dr. Linder agreed to investigate what this level might be for chickens. Ms. Valoppi proposed using the dose at 22.99 divided by a UF of 10 for the sub-chronic to chronic conversion: this would lead to a low TRV of 2.299 mg/kg-day.

Dr. Gleason suggested that this would be a conservative number for chickens (or granivorous birds) and asked if this number could also be marked with a notation that it was very conservative. The group agreed on a tentative low TRV of 2.299 with a notation that it is considered very conservative for granivorous birds. The group agreed to revisit this number if nutritional levels of copper for birds were found to be in the same range as 2.3 mg/kg-day. The group accepted the high TRV of 52.26 mg/kg-day.

[1] In a telephone conversation on September 9, 1996 between Dr. Chernoff and Ms. Heins, Dr. Chernoff pointed out that the TRV was based on a subchronic study. He recommended applying a UF of 10, but pointed out that the resulting TRV would be close to the nutritional requirements of 2.5 and this should be indicated.

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Zinc/Rodents

Dr. Chernoff asked why there weren't more data on rodents as the spreadsheets did not seem to reflect data found in the ATSDR toxicity profiles. Ms. Heins explained that only primary literature is reflected in the data spreadsheets. and that NERAC searches are date-limited and do not retrieve older citations. She stated that these factors may have contributed to the lack of overlap between PRC and ATSDR data sets. Ms. Heins agreed to look into why the NERAC search did not retrieve many of the same records as in the ATSDR. Dr. Chernoff agreed to look for additional studies on zinc effects in mice. The group agreed that until both data sets were reviewed, it was better not to select rodent TRVs for zinc. The group agreed to discuss this at the next meeting.

Zinc/Birds

At the last meeting, the group proposed a tentative low dose of 126.5 mg/kg-day (Stahl and others 1990) and a high TRV of 411.43 (Shickler and Cox 1968). Ms. Valoppi pointed out that, from the spreadsheet, it appeared that ducks were more sensitive than chickens and that she was not comfortable with the low of 126.5 mg/kg-day. Most of the effect values less than 126.5 mg/kg-day were studies looking at enzymatic activity. Dr. Linder stated that these effects may reflect normal responses to exposure to a chemical and may not indicate adverse ecological effects. Ms. Valoppi stated that injury includes things other than reproductive effects; emphasizing that she felt pancreatic effects may be relevant. Ms. Valoppi agreed to research this issue and propose a low and high TRV for zinc at the next meeting.

Lead/Rodents

PRC proposed a low dose of 0.88 mg/kg-day based on a study by Draski and others (1989) that showed no effects on pup birth weight. This was a multigenerational study; no studies with lower no-effects values were available. Dr. Chernoff pointed out that the TRV used at Moffett was 0.002 mg/kg-day based on a study with rats and asked why rat data were not included in this spreadsheet. Dr. Smith stated that the work group originally decided at some point in the process to limit their data to mice under the assumption that mice are generally more sensitive to toxicants than rats. She explained that rat data were used when the quantity of mouse data were insufficient. Dr. Chernoff stated that the proposed TRVs are

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fficient provided that the low TRV is only going to be applied to mice. If these numbers will be applied to larger mammals, then data on rat sensitivity should be included. Ms. Heins explained that data sets for rodents were originally compiled under the assumption that separate TRVs would be derived for larger mammals. The issue of TRVs for larger mammals was on the agenda for discussion later in the day. The group agreed to select the low TRV of 0.88 mg/kg-day but to "star" this number indicating that it is only relevant to mice[2].

PRC proposed a high dose of 680.56 mg/kg-day based on a study by Rasil e (1995) showing increased sterility in F1 and F2 mice and decreased litter viability. This study represented the mid-range of effects presented in the spreadsheet. Ms. Valoppi and Dr. Chernoff expressed concern about the data gaps between 14 mg/kg-day and 280 mg/kg-day and pointed out that adverse effects (including mortality) were seen at 4.62 mg/kg-day in the study by Schroeder and Mitchener (1971). This was a multigeneration study but included only one dose level. The group agreed that lead effects could be seen across generations and multigenerational studies were preferred. Decreased body weight and behavioral effects were noted at 14.6 mg/kg-day (Draski and others 1989). Ms. Heins pointed out that the objective in selecting a high TRV is to use the spreadsheets to look at the full range of effects and to select a value that represents a mid-range where adverse effects are expected; if this number is based on an effect level that is too low and not supported by the other data in the data set, it will not be possible to screen sites.

Dr. Smith pointed out that at 4.62 mg/kg-day there are effects on survivorship and that in general, the group had agreed to pick numbers below mortality levels. The group discussed the possibility of selecting 4.62 mg/kg-day as the high TRV, but to star (*) this number as being very low and acknowledging the data gaps that limited choices. Dr. Callahan, Ms. Heins and Mr. Van Peeters indicated that they thought this number was too low to be an effective screening tool. Dr. Chernoff agreed to review the data in the ATSDR to determine whether there were data available to support selecting a value between PRC's proposed high and 4.62 mg/kg-day in the study by Schroeder and Mitchener (1971). The group agreed to postpone selection of the high TRV until the next meeting, when Dr. Chernoff would present his findings.

[2] The group eventually decided to include available rat data from ATSDR for consideration in cases where rats were not included in the original data set. After reviewing the rat data, Dr. Chernoff recommended a TRV of 0.0015 mg/kg-day based on a study by Krasovskii and others (1997). This value was selected as the low TRV.

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:ad/Birds

PRC proposed a low TRV of 0.13 mg/kg-day based on a study by Edens and Garlich (1983) that showed no effect on egg production. From the same study, PRC proposed a high TRV of 8.75 mg/kg-day that showed a decrease in egg production. Ms. Valoppi acknowledged that the spreadsheet included data from a variety of types of birds, but expressed concern that there were no multigenerational studies or studies addressing developmental effects. Mr. Haas (FWS) pointed out that lead is transferred to the egg. Ms. Valoppi was concerned that the study by Edens and Garlich (1983)showed no effect but the chick was dosed at 6 weeks of age; the study by Edens and others (1976) showed adverse effects at 0.14 mg/kg-day when hatchlings were dosed. The group agreed that Ms. Valoppi would review these papers and suggest low and high TRVs at the next meeting.

Selenium/Rodents

DTSC asked to defer this topic until the next meeting as Dr. Chernoff (DTSC), who was responsible for reviewing these papers, had to leave the meeting early. The group agreed.

Selenium/Birds

PRC proposed a low TRV of 0.23 mg/kg-day based on a study by Heinz and others (1989) that showed no effects on embryos or hatchlings. PRC proposed a high TRV of 0.93 mg/kg-day based on the same study that resulted in decreased hatching success and hatchling weight. Ms. Valoppi suggested that data based on the various forms of selenium be separated on the spreadsheets or at least considered differently. Selenomethionine is generally the form likely to be found in wetlands and is more toxic than selenite. She also pointed out that the spreadsheet indicates that the study by Stanley and others (1996) is multigenerational, but that it only looks at parent and F_1 generations. Ms. Valoppi said that many of the studies used diets with at least 10% water (in chow) and that doses may need to be altered. Dr. Smith said that she had contacted Purina and that most pelletized chow had about 10% water which results in reported doses 10% lower than actual doses. She agreed to call and find out how chow and mash differ in water content and discuss this at the next meeting. Ms. Heins stated that she recalled this issue being

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discussed during the Moffett TRV development and that the group agreed that adjusting all doses for water content would be too time-consuming and would result in only minor changes.[3]

Ms. Valoppi said that she thought earred grebes were more sensitive to selenium than mallards and she was concerned about interspecies sensitivity. Mr. Haas told the group that Joe Skorupa had reviewed selenium effects on birds; Mr. Haas agreed to provide the group with the review.

Ms. Valoppi proposed a low dose of 0.19 mg/kg-day based on the study by Stanley and others (1996), in which ducklings received the same dose as adults; the study by Heinz and others (1989) did not have similar dosing of young. She pointed out that selenium has a narrow range between a safe and toxic dose as indicated by studies at Kesterson Reservoir. She proposed a high dose of 0.47 mg/kg-day based on a study by Heinz and others (1989) that showed teratogenic effects and decreased hatching success. Ms. Heins indicated that she did not think this dose was in the mid-range of effects, but was at the low end of the range of effects. The study at 0.55 mg/kg-day from a study by Stanley and others (1994), was more in the mid-range of effects and used selenomethionine as the form of selenium; this study showed decreased duckling production and increased teratogenesis. The group agreed to have a low TRV of 0.19 and a high TRV of 0.47 mg/kg-day with a notation indicating low confidence in the low TRV for birds other than waterfowl[4].

Schedule

Dr. Gleason (PRC) reminded the group that ecological assessment reports from several installations are due in August, some of them very soon, and that it was important for the group to decide which TRVs would be used in these reports. The group agreed that the process of developing regional TRVs was very important and that it was necessary to make progress on these numbers this month. The group scheduled additional meetings on August 20 and 29, 1996 to continue the process. Dr. Smith also said that she thought that correct technical conclusions based on good benchmark numbers were important,

[3] The issue of the water content of feeds was never revisited by the group and the doses were not adjusted.
[4] At the meeting on August 20, 1997, Ms. Valoppi indicated that she had received more information on the effects of selenium on birds. For this reason, the selenium TRVs for birds were revisited at that time. Refer to the August 20 meeting minutes for details.

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and that the schedule of deliverables may need to be adjusted so that reports and conclusions did not need to get rewritten once final TRVs were developed. Mr. Van Peeters agreed to check with RPMs in the Navy to determine what schedule adjustments may be necessary.

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ATTACHMENT

AGENDA

AGENDA

SAN FRANCISCO BAY REGIONAL TRV

WORKING MEETING

AUGUST 2, 1996

Meeting Time: 9:30 a.m.
Location: Regional Water Quality Control Board
Suite 500, Room 4A
2101 Webster St., Oakland, California

I. Introductions/Meeting Objectives

II. Brief Review of Methodology

III. Discussion of Results of Last Meeting (arsenic, cadmium, copper, zinc)

IV. Lead

V. Selenium

Lunch

VI. TRVs for Larger Mammals (otter and fox)

VII. DDTs (Great Lakes)

VIII. Mercury (Great Lakes)

IX. PCBs

Reminder: The next meeting of the TRV work group is scheduled for August 12, 1996 at 9:30 a.m.

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SAN FRANCISCO BAY REGIONAL TOXICITY REFERENCE VALUES
WORKING MEETING
AUGUST 12, 1996

Date: August 12, 1996
Time: 9:30 a.m.
Location: Regional Water Quality Control Board Office, Oakland, CA

Participant	Organization
Ned Black	U.S. Environmental Protection Agency (EPA)
Barbara Smith	EPA
James Haas	U.S. Fish and Wildlife Service (FWS)
Gerald Chernoff	Department of Toxic Substance Control (DTSC)
Susan Gladstone	Regional Water Quality Control Board (RWQCB)
Susan Ellis	California Department of Fish and Game (DFG)
Cooper Heins	PRC Environmental Management Inc. (PRC)
June Mire	PRC
Martha Burford	PRC

INTRODUCTION

This was the third working meeting of the work group to develop regional toxicity reference values (TRV). The main objective of the series of meetings is for the Navy and regulatory and trustee agencies to reach consensus on regional TRVs in order to assess risk to higher trophic level receptors from site contaminants at Naval installations.

The objectives of the meeting were to: 1) discuss the use of mercury and DDT wildlife criteria developed as part of the Great Lakes Water Quality Initiative (EPA 1995); 2) review and select the following TRVs deferred from the previous meeting on Aug. 2, 1996: cadmium/bird low TRV, zinc/mice TRVs, zinc/bird TRVs, lead/mice high TRVs, lead/bird TRVs, and selenium/mice TRVs; 3) discuss the method for selecting TRVs for larger mammals, and 4) select TRVs for PCBs. Objectives 1. 3. and 4 were completed; objective 2 was partially completed. Previously deferred TRVs for birds were postponed as requested by DTSC. The lead/mice high TRV was also deferred so that additional papers could be reviewed by Dr. Chernoff (DTSC).

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EPA GREAT LAKES VALUES FOR DDT AND MERCURY

General Discussion:

Ms. Heins (PRC) reminded the group that the methods employed by PRC for deriving TRVs were based on the approach EPA used as part of the Great Lakes Water Quality Initiative (EPA 1995). The Great Lakes documents and the work used in developing them are considered thorough and of high quality. For this reason, using these numbers would eliminate duplication of work already done. Ms. Heins (PRC) proposed using EPA's benchmark values for the low TRV and selecting the high TRV from the summary tables in the Great Lakes document. She added that, in some cases, EPA had applied uncertainty factors (UF) between 1 and 10 for low-effect to no-effect and subchronic to chronic conversions. This is different from the work group method of applying default UFs of 10 only. She proposed using the UFs that EPA proposed. Another difference in methods is that EPA applied interspecies UFs, but did not perform allometric conversions. Ms. Heins proposed continuing to use allometric conversions without interspecies UFs.

Dr. Smith (EPA) expressed concern over whether EPA performed dose calculations using the same methods as those used by PRC. Ms. Heins explained that the EPA used reported body weights and ingestion rates whenever possible, and when body weights and ingestion rates were not reported, they used a summary table supplied in the technical support document. This was similar to the protocol used at PRC. Dr. Mire (PRC) reported that when doses from papers in Great Lakes data set were put through PRC calculations the results were similar. Ms. Heins explained that body weights and ingestion rates used by PRC also included body weights and ingestion rates found in the Great Lakes summary tables. Dr. Smith stated that the group should clearly indicate that PRC's methods were the same as those used by EPA, and that the work group is considering the Great Lakes documents published work since the documents were peer reviewed.

DDT/Birds

PRC proposed for the low TRV EPA's benchmark dose of 0.027 mg/kg-day which was divided by a UF of 3, to convert the lowest observed adverse effect level (LOAEL) to a no observed adverse effect level (NOAEL) equivalent. The resulting low TRV would be 0.009 mg/kg-day. The dose was based on a

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pelican study by Anderson and others (1975). The study was of long duration and was the most sensitive bird in the data set. Concerns were raised as to whether or not the group should choose separate values for terrestrial and aquatic birds to derive regional TRVs. Ms. Heins explained that the most sensitive bird was picked to derive the low TRV to be protective of all avian guilds. The group accepted for the proposed low TRV 0.009 mg/kg-day.

PRC proposed for the high TRV a dose of 1.5 mg/kg-day from a study by Heath and others (1969) showing adverse effects on reproductive success in a two year mallard study. This was a long term study in the mid-range of effects in the data set presented in table 1-6 of the Great Lakes document (EPA 1995). There was a discussion of the numbers used for the ecological assessment at Moffett Federal Airfield (Moffett). Ms. Heins reported that for the Moffett TRV effort PRC used EPA's avian wildlife value. This value was adjusted by uncertainty factors used by EPA. The adjusted value was used as the low TRV and the unadjusted value was used as the high TRV.

The group discussed the toxicity of DDT and DDE and whether it was appropriate to have separate TRVs for each. Dr. Mire pointed out that most of the data collected on sites is mixed or total DDTs. The group agreed to use the data available; if the data set included separate numbers for DDE and DDT, perhaps separate numbers could be selected. The group decided that since the toxic levels of DDT and DDE were different, and since separate doses were reported in the Great Lakes summary table, selecting separate numbers for DDE and DDT for the high TRV would be appropriate. Mr. Haas (FWS) explained that site assessors could use the numbers in a ratio when the ratio of DDT/DDE on the site was known; if the ratio was not known for a specific site the assessor could either fall back to closest site ratio or take the more conservative value. Ms. Heins pointed out that for DDT, the 1.5 mg/kg-day was in the mid-range of effects in table 1-6 below most of the mortality levels. Dr. Smith pointed out that the DDE egg cracking effect at 0.60 mg/kg-day from the same study should be considered. The group agreed that the high would be 1.5 mg/kg-day for DDT and 0.60 mg/kg-day DDE. Both were from the from the Heath and others (1969) study.

DDT/Mammals

EPA's mammalian wildlife value was based on a NOAEL of 0.8 mg/kg-day in a two year rat study on reproductive success (Fitzhugh 1948). The group accepted the low TRV of 0.8 mg/kg-day. PRC

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proposed for the high TRV a dose of 16 mg/kg-day in a six month rat study, in which effects on offspring growth were observed (Clement and Okey 1974). The group accepted the dose for the high TRV.

Mercury/Birds

EPA's avian wildlife value for mercury was based on several studies by Heinz (1974,1975,1976a,1976b, 1979). EPA selected a dose of 0.078 mg/kg-day divided by a UF of 2, for a LOAEL to NOAEL conversion, resulting in a dose of 0.039 mg/kg-day. This study was a three generation mallard study showing adverse effects on reproduction. The group agreed on the proposed low TRV of 0.039 mg/kg-day.

For the high TRV, PRC proposed a dose of 0.18 mg/kg-day from a 1.5 year mallard study by Heinz and Locke (1976). Ned Black (EPA) asked about using the 0.25 mg/kg-day dose, from a pheasant study of similar length (Spann and others 1972). Dr. Black explained that using this study was consistent with the method of choosing a mid-range effect and that, by using this study, more than one species of bird would be used. Dr. Smith indicted that the dose of 0.25 mg/kg-day was an unbounded LOAEL, but that the 0.18 mg/kg-day dose was bounded. She also explained that Heinz studies were high quality and looked at several different types of endpoints. There was some concern about organomercury compared to inorganic mercury compounds and how that might reflect the data collected at the sites. Dr. Mire stated that most of the mercury data collected was from sediment, soil, or invertebrates and that the labs analyze for total mercury. The mercury in soil is mostly inorganic mercury; however, the form taken up by animals has usually been converted to organomercury compounds. The numbers chosen from the Great Lakes document were reflective of organomercury compounds. Since organic forms represent only a portion of total mercury, selecting numbers based on organic compounds is considered to be conservative. The group accepted the dose of 0.18 mg/kg-day for the high TRV.

Mercury/Mammals

EPA's mammalian wildlife value was based on mink study by Wobeser and others (1976), in which a dose of 0.27 mg/kg-day resulted in adverse effects. EPA divided the dose by a UF of 10, for sub-chronic to chronic conversion, resulting in an adjusted dose of 0.027 mg/kg-day. The study was conducted over a 93 day period, and measured effects on anorexia, ataxia, and mortality. Dr. Chernoff stated that a low

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TRV of 0.027 mg/kg-day, while protective for mink, may be too conservative for rodents. Dr. Smith suggested using the mink data for larger mammals since data on rodents was also available in the Great Lakes document. The group agreed to use the dose of 0.027 mg/kg-day as the low TRV dose for larger mammals only. Dr. Chernoff recommended basing the low TRV for rodents on the study by Khera and Tabacova (1973) study because it was a high quality rat study of long duration with a NOAEL on reproductive development. The group agreed on a dose of 0.25 mg/kg-day (Khera and Tabacova 1973) for the low TRV for rodents and 0.027 mg/kg-day (Wobeser and others 1976) for the low TRV for larger mammals.

PRC proposed for the high TRV a dose of 4 mg/kg-day from a rat study on development (Fuyuta and others 1978). The group accepted the proposed high TRV dose. The group also decided that the high TRV dose for the larger mammals would be the unadjusted 0.27 mg/kg-day from Wobeser and others (1976).

DISCUSSION OF ARMY/NAVY DERIVED TRVS

Dr. Black gave the group background information on the Army TRV effort for the Presidio. He explained that the agencies had invited the Army contractor to these meetings and were met with a negative response. Mr. Haas indicated that in some cases, there is an order of magnitude of difference between the Navy numbers and Army numbers. Ms. Gladstone pointed out that the critical difference is that the group was following a consensus approach between the Navy and agencies to derive the Navy TRVs. Dr. Smith, Dr. Black and Mr. Haas indicated that they had much greater confidence in the methods used by PRC and the Navy to derive TRVs than those employed by the Army. Dr. Black stated that he planned to contract the tri-services to inform them of the situation and to discuss an appropriate course of action.

REVIEW OF TRVS DEFFERED FROM AUGUST 2, 1996 MEETING

Zinc/Rodents

The original PRC proposed low TRV was a dose of 39.13 mg/kg-day, based on a study by Uriu-Hare and others (1989), in which no effects on several reproductive parameters were observed in rats. At the July

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19, 1996 meeting a new dose of 205.71 mg/kg-day (Schlicker and Cox 1968) was proposed. The group had agreed that this dose was more consistent with the logic used to select low TRVs in the past.

At the August 2, 1996 meeting there was general concern that 205.71 mg/kg-day was too high, and that there were no data between the 39.13 mg/kg-day and the 205.71 mg/kg-day. Dr. Chernoff had expressed concern that data in the ATSDR were not included in the spreadsheets. Ms. Heins had stated that NERAC searches often do not retrieve very old citations depending on the date limitations of the databases searched. Gray literature is also not used in PRC's data sets. Ms. Heins suggested solving this problem by supplementing PRC's data sheets with ATSDR's tables in order to insure that all available data are considered when selecting TRVs. PRC had retrieved papers cited in ATSDR from the library and given them to Dr. Chernoff to review.

At this meeting (Aug. 12, 1996) Dr. Chernoff reported to the group his findings. Dr. Chernoff said that after reviewing the ATSDR toxicity profile, he felt that two studies were potentially useful and worthy of review. He had reviewed ATSDR record number 33 (Walters and Roe 1965), and record number 42 (Fernandes and others 1979). In the Walters and Roe (1965) study, anemia was found in some of the mice, but the authors only mentioned it in passing and no data were presented. The study by Fernandes and others (1979) was on zinc deficiency and was inappropriate for TRV derivation. Dr. Chernoff stated that based on his findings, he felt that the original dose proposed by PRC was appropriate for the low. The group agreed on 39.13 mg/kg-day from the Uriu-Hare and others (1989) study as the low TRV[5].

The original PRC proposed high from the July 19, 1996 meeting was 411.43 mg/kg-day from a study by Schlicker and Cox (1968). Dr. Chernoff indicated that zinc toxicity varied a lot from study to study depending on differences in carbonate and chloride forms of zinc, but he felt comfortable with 411.43 mg/kg-day from Sc hlicker and Cox (1968). The group agreed on a high TRV of 411.43 mg/kg-day.

[5] In a telephone conversation on September 9, 1996, Dr. Chernoff proposed a revised low TRV of 9.61 mg/kg-day from a study by Aughey and others (1977). In this study, mice were given zinc sulfate in water for 14 months. A dose of 96.08 mg/kg-day resulted in hypertrophy and vacuolation of pancreatic islet cells in the adrenal cortex. A UF of 10 was applied to this dose to adjust the effect level to a no effect level equivalent, resulting in a low TRV of 9.61 mg/kg-day. The TRV was revised to reflect this change.

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Lead/Rodents

The low TRV PRC proposed at the Aug. 2, 1996 meeting was 0.88 mg/kg-day based on a study by Draski and others (1989). PRC had proposed a high TRV of 680.56 mg/kg-day based on a study by Rasile (1995). At the Aug. 2, 1996 meeting, a dose of 4.62 mg/kg-day from a study by Schroeder and Mitchener (1971) was proposed as the high TRV. At that meeting Dr. Callahan (EPA), PRC, and the Navy indicated that they thought this value was too low to be an effective screening tool. Dr. Chernoff had agreed to review the data in the ATSDR to determine whether there were data available to support selecting a value between PRC's proposed high dose and 4.62 mg/kg.

At this meeting, the proposed high TRV was discussed further. Dr. Chernoff had checked the ATSDR profiles for data supporting the low dose of 4.62 mg/kg-day. He reported that the ATSDR wasn't that helpful, and that a lot of the low numbers were nerve conduction or behavioral studies that had little or no ecological relevance. Dr. Chernoff requested that the final decision on the high TRV for lead be deferred until the next meeting so that he could review the studies by Miller and others (1982) from ATSDR record number 43, and Chowdhury and others (1984) from ATSDR record number 59. The group agreed to defer a decision on the high TRV until Aug. 20, 1996.

Selenium/Rodents

PRC proposed a low TRV 0.48 mg/kg-day, based on a study by Nobunaga (1979), in which no effects on fetal success were observed in mice given 0.48 mg/kg-day of selenium. This dose was selected because it was a reproductive endpoint, there were no significant effects below this dose, and there were other no effect levels above this dose. The group agreed on a low TRV of 0.48 mg/kg-day[6].

PRC proposed a high TRV of 1.21 mg/kg-day, based on a study by Schroeder and Mitchener (1971). There was some confusion over numbers in ATSDR that may not have been incorporated into the decision for low and high TRVs. When the group checked the sources they were the same for the PRC spreadsheet and ATSDR. Several of the doses differed between PRC's spreadsheet and ATSDR tables

[6] In a telephone conversation on September 9, 1996, Dr. Chernoff proposed a revised low TRV of 0.05 mg/kg-day based on a study by Harr and others (1967), in which no effects on hepatic lesions were observed at this dose. The TRV was revised to reflect this change.

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even though the same dietary concentrations from the same papers were used. Ms. Heins stated that she would investigate how ATSDR was calculating doses. She indicated that ATSDR probably used standardized body weights and ingestion rates for each of the test organisms, while PRC used age-, species-, and gender-specific body weights and ingestion rates when available. The group agreed on a high TRV of 1.21 mg/kg-day.

TRVS FOR LARGER MAMMALS

Ms Heins stated that the bibliographic database searches had been completed for arsenic, cadmium, copper, lead, selenium, and zinc for a wide variety of mammals including dogs, mink, rabbits, and guinea pigs. The searches resulted in very few citations. PRC read the lead papers and entered the data into spreadsheets; these spreadsheets were distributed to the group. Ms. Heins explained that since very little data on larger animals are available, a decision on whether to use rodent data adjusted by allometric conversions must be made. She proposed using a combination of the rodent spreadsheets, ATSDR toxicological profiles, and spreadsheets comprising any additional data on larger mammals to decide on TRVs for larger mammals at the next meeting. She also pointed out that, since there were discrepancies between PRC's and ATSDR's calculated doses, any doses chosen from ATSDR would have to be re-calculated using PRC's methods.

TRVS FOR PCB

Dr. Chernoff asked whether or not data had been collected at Naval facilities for PCB congeners. Dr. Smith explained that arochlor analysis has typically been done because it is less expensive than congener analysis and because the agencies have not resolved the issue of how to interpret congener data. She also explained that, in choosing TRVs for the Moffett ecological assessment, the most toxic arochlor was chosen for the most sensitive species. Dr. Smith also informed the group that at present, no information on how different congeners affect different organisms is available.

PCB/Birds

DTSC requested that this discussion be deferred to Aug. 20, 1996 because Ms. Valoppi was absent from this meeting. The group agreed.

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PCB/Rodents

PRC proposed a low TRV of 0.36 mg/kg-day from a study by Simmons and McKee (1992), in which mice were given PCB for 21 days, and no effects on enzyme activity or liver weight were observed at this dose. Questions were posed about using an enzyme based study for the low TRV. Ms. Heins explained that the only other low NOAEL a dose of 0.71 mg/kg-day from a study by McCoy and others (1995). In this study a significant reproductive LOAEL at 0.71 mg/kg-day was also reported. The group agreed to a dose of 0.36 mg/kg-day from Simmons and McKee (1992).

PRC proposed a high TRV of 20 mg/kg-day from a study by Johansson (1987). At this dose, a decrease in testes weight were observed in juvenile mice. Mr. Haas pointed out that there was a reproductive multigenerational effect at 1.28 mg/kg-day from a study by Linzey (1987). Ms. Heins also indicated that Mr. Haas proposed change would be appropriate since there were two reproductive studies below the 1.28 mg/kg-day dose. The group agreed on a high TRV of 1.28 mg/kg-day.

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ATTACHMENT A

LIST OF HANDOUTS

LIST OF HANDOUTS

PCB spreadsheet/plot and proposed dose papers
ATSDR summary tables for:
- zinc
- lead
- selenium

Great Lakes Summary Tables:
- Mercury/Birds
- Mercury/Mammals
- DDT/Birds
- DDT/Mammals

Summary of TRV Derivation for NAVSTRA TI
Derivation of Toxicity Reference Values (TRVs) for NAVSTRA Treasure Island
High Quality papers for Nickel and Cobalt
Attachments 1-8
Spreadsheets for:
- Naphthalene/mice
- Naphthalene/birds
- Benzo(a)pyrene/mice
- Silver/birds
- Cobalt/mice
- Nickel/mice

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SAN FRANCISCO BAY REGIONAL TOXICITY REFERENCE VALUES
WORKING MEETING
AUGUST 20, 1996

Date: August 20, 1996
Time: 9:30 a.m.
Location: Department of Toxic Substance Control, Berkeley, CA

Participant	Organization
Ned Black	U.S. Environmental Protection Agency (EPA)
Barbara Smith	EPA
Mary Blevins	EPA
James Haas	U.S. Fish and Wildlife Service (FWS)
Gerald Chernoff	Department of Toxic Substance Control (DTSC)
Laura Valoppi	DTSC
Susan Ellis	California Department of Fish and Game (DFG)
William Van Peeters	EFA West
Cooper Heins	PRC Environmental Management Inc. (PRC)
June Mire	PRC
Greg Linder	PRC
Martha Burford	PRC

INTRODUCTION

This was the fourth working meeting of the work group to develop regional toxicity reference values (TRV). The main objective of these meetings is for the Navy, regulatory, and trustee agencies to reach consensus on regional TRVs in order to assess risk to higher trophic level receptors from site contaminants at Naval installations.

The objectives of this meeting were to: 1) resolve outstanding TRVs including: lead/mice high TRV, lead/birds TRVs, cadmium/bird low TRV, zinc/bird TRVs, selenium/bird TRVs, 2) choose TRVs for PCBs/birds, and 3) discuss TRVs for larger mammals including: arsenic, cadmium, copper, lead, selenium, zinc, and PCBs. Objective 1 was completed for lead/bird TRVs, but other items under that objective were deferred to the Aug. 29, 1996 meeting. Objective 2 was deferred to Aug. 29, 1996 meeting, and objective 3 was mostly completed.

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OUTSTANDING TRVS

Lead/Birds

PRC originally proposed a low TRV of 0.13 mg/kg-day based on a study by Edens and Garlich (1983) that showed no effect on egg production. In the Aug. 2, 1996 meeting, Ms. Valoppi (DTSC) indicated that while the Edens and Garlich (1983) study dosed chicks at 6 weeks of age, the study by Edens and others (1976) showed adverse effects at 0.14 mg/kg-day when hatchlings were dosed. The group had decided to postpone making a decision until Ms. Valoppi had a chance to review the studies and propose a new low TRV.

In this meeting, Ms. Valoppi reported that the unbounded lowest observed adverse effect level (LOAEL) of 0.14 mg/kg-day from the study by Edens and others (1976) was similar to the 0.13 mg/kg-day dose reported in the study by Edens and Garlich (1983). Ms. Valoppi stated that since these two numbers were similar, the low TRV should be 0.14 mg/kg-day with a UF (UF) of 10, for a LOAEL to NOAEL conversion, which would give a low TRV of 0.014 mg/kg-day. She also stated that a reason for not choosing the 0.13 mg/kg-day dose was that the test organisms were dosed when older.

Dr. Linder (PRC) requested that the application of UFs be revisited by the group. He was concerned that the original doses provided in the studies would get lost with the application of UFs. He also pointed out that any number the group chooses must be technically defensible, which means choosing a UF of 10 must be defensible as well. Dr. Linder stressed that he felt uncomfortable with a TRV that was an order of magnitude lower and questioned the usefulness of such a number in the field. Mr. Haas (FWS) pointed out that the group could accept this adjustment and revisit this low TRV once the TRVs have been applied and field tested. He said that the LOAEL for decreased body weight at 0.1 mg/kg-day supports selection of the 0.014 mg/kg-day dose. Ms. Heins (PRC) explained that the original dose from the study and the adjusted number would be on the final summary sheet so that it would always be possible to tell when UFs were applied. The group decided to accept the low TRV of 0.014 mg/kg-day.

PRC proposed for a high TRV a dose of 8.75 mg/kg-day from a study by Edens and Garlich (1983). The group agreed on this dose as the high TRV.

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Selenium/Birds

At the Aug. 2 (1996) meeting Ms. Valoppi had proposed a low TRV of 0.19 mg/kg-day from a study by Stanley and others (1996) and a high TRV of 0.47 mg/kg-day based on a study by Heinz and others (1989). Ms. Heins had pointed out at the Aug. 2, 1996 meeting that the 0.47 mg/kg-day was not in the mid-range of effects, but was at the low end of the range of effects. She proposed a high TRV of 0.55 mg/kg-day, based on a study by Stanley and others (1994). in which a decrease in litter size and increased teratogenesis were observed at this dose. This dose was in the mid-range of effects and used selenomethionine as the form of selenium. The group agreed, at the Aug. 2 meeting, on a low TRV of 0.19 mg/kg-day and a high TRV of 0.47 mg/kg-day with a notation indicating that these numbers are valid for waterfowl, but may not be as suitable for other birds.

At this meeting, Aug. 20, 1996 Ms. Valoppi stated that she had received more information from Joe Skorupa's review of selenium effects on birds. She said that she had not had a chance to review the documents, but that in her brief discussion with Dr. Skorupa, he indicated that 3.6 parts per million (ppm) selenium in the diet resulted in adverse effects in birds. He also found that 2.2 ppm selenium in the diet caused immune system effects in birds, and 2.0 ppm selenium in the diet caused the birds to be more susceptible to infection. Ms. Valoppi agreed to review the Skorupa literature and contact Ms. Heins to propose TRVs for selenium. Ms. Heins stated that she would need specific information about test species age and sex, and a referenced dose in order to perform the TRV dose calculations.

Cadmium/Birds and Zinc/Birds

Ms. Valoppi requested that discussions on avian TRVs for cadmium and zinc be deferred to the August 29, 1996 meeting.

Lead/Rodents

In the last meeting, PRC had agreed to retrieve several papers cited in the Agency for Toxic Substances and Disease Registry (ATSDR) toxicity profile for lead and send copies to Dr. Chernoff (DTSC). At this meeting, Ms. Burford (PRC) reported that several of the papers had not been available at the library and

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that she would attempt to locate them before the next meeting. The group agreed to postpone discussions on rodent TRVs for lead until the Aug. 29, 1996.

Discussion of DDT Speciation

During these discussions the speciation of DDT was revisited. This topic was introduced again when Ms. Valoppi questioned the decision to use both a DDE and DDT high TRV for birds, stating that all DDT degrades to DDE. Dr. Mire (PRC) stated that results of soil and sediment sampling at Naval facilities indicates that DDT was not degrading to DDE at a uniform rate. In fact, aged DDT has been found at many of the sites. The group agreed that it was appropriate to keep the DDT and DDE TRVs for birds. Ms. Heins reminded the group that at the meeting on August 12, 1996, separate TRVs were selected for DDT and DDE in this case because data were available for both in the Great Lakes document. The decision at that time had been to use separate TRVs when the ratio of DDT:DDE at a site was known.

Explanation of Differences between PRC and ATSDR TRV Dose Calculation

Ms. Heins reported that, after investigating how ATSDR was arriving at their dose calculations, she found that prior to the latest unpublished toxicity profiles, ATSDR used a single value for body weights of test organisms (i.e., a single value for all mice and a single value for all rats) and then calculated the ingestion rate as a percentage of that body weight. This was different from PRC's method of calculating doses using species-, strain-, age-, and sex-specific body weights and associated ingestion rates.

TRVS FOR LARGER MAMMALS

In the August 12, 1996 meeting, Ms. Heins had distributed spreadsheets of data resulting from the bibliographic database searches for information on the effects of lead on larger mammals. She had pointed out that the data on the spreadsheets were sparce and generally of poor quality for deriving TRVs. She had recommended that, for each contaminant, TRVs for larger mammals be selected from the rodent spreadsheets, data presented in ATSDR toxicity profiles, and any additional data resulting from bibliographic database searches for larger mammals. The group agreed to attempt to select TRVs for larger mammals using these sources of data.

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Arsenic/Larger Mammals

Ms. Heins reported that a literature search produced no new studies other than those found on PRC arsenic/mice spreadsheet or in ATSDR toxicity profiles. Since very little information on the effects of arsenic on larger mammals was available, she stated that it may be necessary to select the TRV from the rodent data set. Ms Heins explained the effect of using rodent data and allometrically converting it to an equivalent dose for an otter or fox. When a TRV for a small animal is allometrically converted to a dose to a larger mammal, the TRV decreases. Conversely, a TRV for a large animal, allometrically converted to a smaller animal, becomes larger. A dose of 0.48 mg/kg-day, to a mouse, once allometrically converted, would become a dose of 0.012 mg/kg-day for an otter and 0.018 mg/kg-day for a fox.

The group looked at the data found in the ATSDR toxicity profiles. Dr. Chernoff was interested in neurological studies on pigs -- record number 25, 26, and 27 in the ATSDR data tables (ATSDR 1993). Dr. Smith (EPA) pointed out that if dose of 0.32 mg/kg-day, which was the low arsenic TRV for rodents was allometrically converted to an otter it would be approximately 0.08 mg/kg-day. The four fold reduction in conversion between mouse and otter was assumed based on Ms. Heins' example at the beginning of the discussion. Dr. Smith explained that the 0.87 mg/kg-day LOAEL reported for pigs in ATSDR would have to go through a LOAEL to NOAEL conversion which change it to approximately 0.087 mg/kg-day. After this conversion, the value the 0.087 mg/kg-day would have to be allometrically converted from pig to otter which would increase the number. This comparison indicated that allometrically converting rodent data to larger mammals appeared to be more conservative and, when large mammal data sets are sparce, more appropriate.

The group agreed to use the previously selected low and high rodent TRVs for arsenic to derive TRVs for larger mammals. The low TRV was 0.32 mg/kg-day, based on a study by Schroeder and others (1968), and the high TRV was 4.7 mg/kg-day, based on a study by Brown and others (1976). Dr. Linder indicated that he would check on the difference between inorganic and organic forms of arsenic.

Cadmium/Larger Mammals

There was some discussion of data in the ATSDR toxicity profile (ATSDR 1992b), but after applying the different allometric conversions to the test organisms, the doses were in the same range as the-

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allometrically converted rodent TRVs. The group decided to use the rodent low TRV of 0.06 mg/kg-day, based on a study by Webster (1978) the rodent high TRV of 2.64 mg/kg-day, based on a study by Schroeder and Mitchener (1971). The group agreed that these doses would serve as the cadmium TRVs for all mammals.

Copper/Larger Mammals

The group decided that ATSDR record number 34 (ATSDR 1992a), Aulerich and others (1982) should be reviewed before a decision on copper TRVs for larger mammals was made. Ms. Burford agreed to retrieve the paper from the library. Dr. Linder agreed to review the paper in preparation for the next meeting..

Lead/ Larger Mammals

The discussion about the lead TRVs for larger mammals was preceded by a discussion of the August 12, 1996 decision for the low rodent TRV for lead. Ms. Valoppi asked if the intermediate exposure studies (page 68) from ATSDR (ATSDR 1992c) had been reviewed by Dr. Chernoff. Dr. Chernoff explained that he planned to review record number 43, Miller and others (1982), and record number 59, Chowdhury and others (1984) from ATSDR. Ms. Valoppi requested that Dr. Chernoff review ATSDR records 56 (Hilderbrand and others 1973), 58 (Krasovskii and others 1979), and 61 (Barratt and others 1989). Ms. Burford agreed to retrieve these papers from the library and send copies to Dr. Chernoff for his review for the next meeting on Aug. 29, 1996. After reviewing the spreadsheets containing data for larger mammals, the group decided in advance to use the low and high TRV values for rodents for larger mammals as well.

Selenium/Larger Mammals

The group discussed studies from ATSDR (ATSDR 1995) that might be appropriate for large mammal TRVs, but when allometric conversions were applied to the ATSDR doses, the values were similar to rodent data in the PRC spreadsheets. The group decided to use the selenium low and high rodent TRVs for larger mammals as well as rodents. Thus, the agreed upon low TRV for mammals was 0.48 mg/kg-

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day, based on a study Nobunaga (1979).[7] The mammalian high TRV was 1.21 mg/kg-day, based on a study by Schroeder and Mitchener (1971).

Zinc/Larger Mammals

Preceding the discussion of TRVs for larger mammals, Ms. Valoppi and Mr. Van Peeters (EFA WEST)wanted to revisit the low and high TRVs chosen at the Aug. 12, 1996 meeting. Mr. Van Peeters was concerned that the low TRV of 39.13 mg/kg-day, based on a study by Uriu-Hare and others (1989), was too conservative. He suggested that TRV be based on a dose of 205.71 mg/kg-day from a study by Schlicker and Cox (1968). Ms. Heins pointed out that there was an LD_{50} at 86 mg/kg-day that overrode the choice of the 205.71 mg/kg-day dose for the low TRV. The group agreed that the dose of 39.13 mg/kg-day, based on a study by Uriu-Hare and others (1968), was appropriate for the low TRV.[8]

Ms. Valoppi expressed concern with the dose for the high TRV decided at the Aug. 2, 1996 meeting (411.43 mg/kg-day based on a study by Schlicker and Cox 1968). She indicated that in ATSDR record number 47 (ATSDR 1994), serious effects were observed at 200 mg/kg-day. Mr. Haas pointed out that the 200mg/kg-day dose in ATSDR was from the same study (Schlicker and Cox,1968)as the dose of 411.43 mg/kg-day from the PRC spreadsheet. The discrepancy in the dose appeared to be a result of the differences in the way ATSDR and PRC calculated doses. The group reconfirmed that 411.43 mg/kg-day was appropriate for the high TRV as decided at the Aug. 2 (1996) meeting.

The group discussed TRVs for larger mammals. The group agreed that ATSDR record numbers 34, 35, 36, and 59 (ATSDR 1994), Anderson and Dannylchuk (1979), Straub and others (1980), Aulerich and others (1991), and Bleavins and others (1983), respectively, should be reviewed before a final decision was made on larger mammal TRVs. Ms. Burford agreed to retrieve these studies from the library and send them to Ned Black (EPA), Dr. Chernoff, and Dr. Linder for their review.

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[7] In a telephone conversation on September 9, 1996, Dr. Chernoff proposed a revised low TRV of 0.05 mg/kg-day based on a study by Harr and others (1967), in which no effects on hepatic lesions were observed at this dose. The TRV was revised to reflect this change.

[8] In a telephone conversation on September 9, 1996, Dr. Chernoff proposed a revised low TRV of 9.61 mg/kg-day from a study by Aughey and others (1977). In this study, mice were given zinc sulfate in water for 14 months. A dose of 96.08 mg/kg-day resulted in hypertrophy and vacuolation of pancreatic islet cells in the adrenal cortex. A UF of 10 was applied to this dose to adjust the effect level to a no effect level equivalent, resulting in a low TRV of 9.61 mg/kg-day. The TRV was revised to reflect this change.

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PCB/Larger Mammals

The group decided that ATSDR record numbers 92, 98. and 101 (ATSDR 1996), which were Wren and others (1987), Bleavins and others (1980), and Aulerich and Ringer (1977), respectively, should be reviewed. The group also decided to review Aulerich and others (1985) and den Boer (1984) from the Great Lakes document. Ms. Burford agreed to retrieve these studies from the library and send them to Dr. Chernoff for his review.

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ATTACHMENT A

AGENDA

AGENDA
REGIONAL TRVS
WORKING MEETING
AUGUST 20, 1996

Meeting Time: 9:30 a.m.
Location: Department of Toxic Substances Control
Redwood Room
700 Heinz Avenue, Berkeley, CA

I. Introductions/Meeting Objectives

II. Resolve Outstanding Issues

III. Lead/Rodents

IV. Lead/Birds

V. Cadmium/Birds

VI. Zinc/Birds

VII. PCBs/Birds

Lunch

VIII. TRVs for Larger Mammals

a. Arsenic

b. Cadmium

c. Copper

d. Lead

e. Selenium

f. Zinc

g. PCBs

h. DDT

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ATTACHMENT B

LIST OF HANDOUTS

LIST OF HANDOUTS

Agenda

ATSDR summary tables for:

- arsenic
- cadmium
- copper
- lead
- selenium
- zinc
- PCB

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SAN FRANCISCO BAY REGIONAL TOXICITY REFERENCE VALUES
WORKING MEETING
AUGUST 29, 1996

Date: August 29, 1996
Time: 9:30 a.m.
Location: Department of Toxic Substances Control, Berkeley, CA

Participant	Organization
Ned Black	U.S. Environmental Protection Agency (EPA)
Mary Blevins	EPA
James Haas	U.S. Fish and Wildlife Service (FWS)
Gerald Chernoff	Department of Toxic Substances Control (DTSC)
Laura Valoppi	DTSC
Susan Gladstone	Regional Water Quality Control Board (RWQCB)
Susan Ellis	California Department of Fish and Game (DFG)
William Van Peeters	Engineering Field Activity West (EFA WEST)
Cooper Heins	PRC Environmental Management. Inc. (PRC)
Greg Linder	PRC
Kristin Gade	PRC
Garry Donaldson	PRC
Jennifer Holder	Entrix

INTRODUCTION

This was the fifth meeting of the work group to develop regional toxicity reference values (TRV). The main objective of these meetings is for the Navy and regulatory and trustee agencies to reach consensus on regional TRVs in order to assess risk to higher trophic level receptors from site contaminants at Naval installations.

The objectives of the August 29, 1996 meeting were to: 1) discuss and select TRVs for the following metals and PAHs: barium, beryllium, cobalt, molybdenum, nickel, silver, thallium, benzo(a)pyrene, and naphthalene; and 2) review and select the following TRVs deferred from previous meetings: cadmium avian TRVs, copper mammalian TRVs, lead rodent and larger mammal, selenium avian, zinc avian and larger mammal, PCB avian and larger mammal. Ms. Heins (PRC) stated that many TRVs had been deferred at previous meeting, causing delays in the schedule. She stressed these values needed to be selected by the end of the day in order for the TRVs to be used in a remedial investigation report at

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Treasure Island. Objective 1 was completed; objective 2 was partially completed. The PCB TRVs for larger mammals were deferred so that Dr. Chernoff (DTSC) could present information that was not available at the meeting. The avian TRVs for selenium were deferred so that papers could be reviewed by Ms. Valoppi (DTSC).

General Discussion:

Jennifer Holder (Entrix) reminded the group that the spreadsheets and scatter plots for the TRVs to be discussed were distributed at the August 12, 1996 meeting. Dr. Holder explained that at the time that the TRVs proposed in those handouts were derived, Entrix staff had not read the ATSDR papers on which some of the proposed TRVs were based. Subsequent review of the ATSDR papers resulted in some changes to the proposed TRVs. Other proposed TRVs were based on the same studies as the TRVs selected during the Moffett TRV process, but the numbers differ slightly. Ms. Heins explained that these differences are due to the fact that the data used in the Moffett TRV derivation process have been updated using a larger database of body weights and ingestion rates.

Barium/Birds

Dr. Holder stated that searches did not yield any data appropriate for deriving avian TRVs for barium so a TRV cannot be derived. The group agreed that there were insufficient data available to derive an avian TRV for barium.

Barium/Mammals

Dr. Holder stated that NERAC searches yielded only medium quality papers on the effects of barium on rodents. A spreadsheet was not produced because no high quality papers were located. Data summarized in the ATSDR toxicity profiles were discussed. Dr. Holder stated that the ATSDR contained mainly cardiological data and very few chronic studies. Most of the reported effects occurred at about 1 ppm and were not ecologically relevant. She did not feel it was appropriate to determine a TRV based on the limited data available. Dr. Linder (PRC) agreed that there was not enough information to justify deriving a TRV. Ned Black (EPA) stated that even though the available data may not be sufficient for TRV derivation, the available information should be used qualitatively in risk assessments.

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Beryllium/Birds

Dr. Holder stated that searches did not yield any relevant data for beryllium and birds, so a TRV cannot be derived. The group agreed that insufficient data were available to derive an avian TRV for beryllium.

Beryllium/Mammals

Dr. Holder stated that literature searches yielded very little information concerning beryllium and rodents. A spreadsheet was not produced. Data summarized in the ATSDR toxicity profile were discussed. Dr. Holder stated that the proposed TRVs in the handouts had been based on the ATSDR data, but when the papers were read, they were discovered to be of very low quality. She recommended that no TRV be derived, based on the limited data available. The group agreed.

Cobalt/Birds

Dr. Holder stated that searches did not yield any data for cobalt and birds, so a TRV cannot be derived. The group agreed with this assessment.

Cobalt/Mammals

Dr. Holder stated that the literature searches for toxicological information on cobalt had turned up some papers. This information was supplemented with data from the ATSDR. Dr. Holder had proposed a high TRV before looking at the ATSDR papers, but had additional information for the group's consideration since reading the ATSDR papers. Dr. Linder asked whether the data covered radiological or chemical effects of cobalt. Dr. Holder responded that the literature only included chemical effects. She stated that the ATSDR focused mainly on rodent data.

Dr. Holder stated that several studies summarized in ATSDR were human clinical studies resulting from the use of cobalt in beer in the 1960s to stabilize the foam. Heart problems, in some cases resulting in mortality were seen among people drinking 6 to 30 pints of beer per day. The group agreed that there may have been confounding effects in those studies, and that they should be excluded from consideration.

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Dr. Holder stated that she had originally proposed TRVs based on a paper by Krasovskii and Fridlyand (1971), but was uncomfortable with that proposal after reading the paper. The paper focused on neurological effects, but the methods used were not clearly stated. She suggested that it would be more appropriate to base the TRVs on other papers that looked at reproductive effects.

Dr. Holder pointed out that the authors of several papers cited in the ATSDR that focused on reproductive effects actually stated doses in mg/kg-day in the text of the study; however, the doses reported in the ATSDR were much lower. For example, in ATSDR record number 44 (Domingo and others 1985), a LOAEL for stunted pup growth was reported as 5.4 mg/kg-day, when the authors of the paper reported the dose as 12 mg/kg-day. Similarly, in ATSDR records 45 and 47 (Mollenhauer and others 1985 and Pedigo and others 1988), the doses were reported to be 13.25 mg/kg-day and 5.7 mg/kg-day, while the studies' authors reported doses of 19.89 and 23 mg/kg-day. Ms. Heins stated that doses reported in a study in mg/kg-day should always be used; it is only necessary to calculate doses when the chemical concentration is only given as a proportion of the exposure medium – for example, parts per million (ppm) in feed. Ms. Heins stated that the ATSDR doses have consistently been lower than the doses calculated using the methods employed by PRC for calculating doses. She explained that the ATSDR doses are calculated using one average body weight for each type of test organism, regardless of age, strain, or sex, and that the ingestion rate used is a percentage of the body weight. The group reviewed the papers to verify the reported doses.

Dr. Holder recommended basing the low TRV on the study by Domingo and others (1985), in which a dose of 12 mg/kg-day resulted in stunted pup growth. Because this was an effect level, a UF of 10 would be applied to convert the effect level to a no effect level equivalent. She recommended against applying an additional UF for the sub-chronic length of the study because a sensitive life stage was being examined. The group agreed on a low TRV of 1.2 mg/kg-day. The group agreed on this dose as the low TRV.

For the high TRV, Dr. Holder noted that there are three papers in the ATSDR data set in which testicular damage was seen at doses of approximately 20 mg/kg-day. Ms. Heins noted that the reported 20 mg/kg-day dose for Nation and others (1983) would probably be higher if recalculated. A high TRV of

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20 mg/kg-day for cobalt in rodents was approved by the group, based primarily on ATSDR record number 45 (Mollenhauer and others 1985).

Molybdenum/Birds and Mammals

Dr. Holder stated that only medium quality papers for molybdenum were available, and that ATSDR has not issued a toxicity profile on molybdenum. The group agreed that no TRVs would be derived for molybdenum.

Nickel/Birds

PRC proposed an avian low TRV of 13.79 mg/kg-day, based on a study by Cain and Pafford (1981), in which no effects on tremors or edema in joints were observed in ducklings during a 90 day study. Ms. Valoppi mentioned that chickens may be more sensitive to the effects of nickel than ducks, based on the weight loss seen in the study by Weber and Reid (1968). Dr. Chernoff agreed, stating that the Ling and Leach, Jr. (1979) study showed a similar effect. Both were shorter studies (3-4 weeks), but showed significant weight loss.

Ms. Valoppi stated concern with setting a low TRV because there were not many studies in the data set, they are all on either chickens or mallards, and none of the studies were chronic. She proposed applying a UF to address the limitations of the data set. Ms. Heins objected, stating that application of a UF for this reason would be inconsistent with the TRV methodology used to this point. Mr. Haas stated that he favored the use of a UF to address the lack of species diversity on the data set. Ms. Heins explained that species diversity is addressed in the confidence rating for each TRV.

Ms. Valoppi proposed using a UF of less than 10. Dr. Black and Mr. Van Peeters (EFA West) stated that they were not comfortable with using a UF other than 10 in this situation. Ms. Heins suggested that the TRV be annotated in the summary table with a footnote saying that confidence in TRV is higher for certain species of birds than others. She reiterated that the concern seemed to be about lack of species, which, under the stated methodology, is not an appropriate reason to apply an UF. Mr. Haas stated he thought an UF for subchronic to chronic was warranted. There was discussion of how to decide when to apply a subchronic to chronic UF for a study performed on a sensitive life stage. Ms. Heins explained

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that UFs had been applied to low TRVs when the study was subchronic or when the dose was an effect level. In the past, if these two conditions were both present, but the study looked at a sensitive life stage, only one UF was applied, as opposed to two. Ms. Valoppi stated that the meeting minutes should document these discussions so that consistency can be achieved. The group agreed on a high TRV of 56.26 mg/kg-day based on the study by Cain and Pafford (1981) and a low TRV of 1.38 based on the same study with an UF of 10 because the study was subchronic.

Nickel/Mammals

Based on a study by Smith and others (1993), a low TRV of 0.133 mg/kg-day and a high TRV of 31.6 mg/kg-day were proposed. The low TRV was based on a dose of 1.33 mg/kg-day to female rats that resulted in no effect on the first litters of pups, but caused an increase in pup mortality among the second litters. A UF of 10 was proposed to convert the effect level to a no effect level equivalent. There was discussion of the need for the uncertainty factor because at day 21 of the study, there was no significant difference in the litter size between the controls and the dosed mice, possibly indicating that the effect was not ecologically significant. The group decided to read the paper during the lunch break before making a final decision. After lunch the group decided that the paper was unclear on the reason for the mortality in the controls, so the significance of the effect could not be dismissed. The group agreed that a UF would be applied to the low TRV. The proposed high TRV was a dose of 31.6 mg/kg-day that resulted in an increased number and proportion of pups born dead or dying shortly after birth, and increased food consumption and decreased water intake in the dosed mothers. The group agreed with the proposed high TRV

Silver/Birds

Very little data were available on the effects of silver on birds. Two or three high quality papers were found, but not enough data were available derive TRVs.

Silver/Mammals

Dr. Holder stated that the literature searches for silver did not produce any useful papers. The ATSDR data were also sparse. She proposed not deriving mammalian TRVs due to insufficient data. Dr.

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Chernoff noted that at Moffett, a silver TRV for rodents had been derived. The low TRV of 1.81 mg/kg-day was based on a dose of 18.1 mg/kg-day reported in a study by Rungby and Danscher (1984) cited in ATSDR that resulted in neurological hypoactivity. The high TRV was based on an effect level of 181.2 mg/kg-day for mortality from a study by Walker (1971) (ATSDR record number 2). Ms. Heins stated that she was uncomfortable using such a small data set to derive a TRV. She added that for the Moffett ecological assessment, the group defaulted to using doses cited in ATSDR due to a lack of sufficient time to fully derive TRVs for silver. The group decided not to derive a TRV for silver.

Thallium/Birds

Dr. Holder stated that searches did not yield any data for thallium and birds, and proposed not deriving a TRV. The group agreed.

Thallium/Mammals

Dr. Holder stated that the literature searches located only one high quality paper for rodents and thallium and that the ATSDR contained very little data. She recommended not deriving a TRV.

The available data included a NOAEL for hair loss, cutaneous, and peripheral nervous system effects at a dose of 1.43 mg/kg-day in feed for 15 week on Wistar rats (Downs and others 1960). This effect also occurred in a study by Manzo and others (1983). The group discussed the ecological relevance of hair loss. Dr. Linder stated that it tends to occur in microtine rodents when they diminish their grooming activity. Dr. Linder agreed that there were not enough data to derive a TRV. Ms. Valoppi and Dr. Chernoff noted that hair loss was a recurring effect in the studies available, and noted that TRVs for thallium and rodents were derived during the Moffett TRV process. Dr. Holder agreed that the available studies demonstrate relevant effects, but stated that she did not feel there was enough information available to justify derivation of a regional TRV. The TRV methodology calls for TRVs to be derived based preferably on a broad data set, including several species of test animals and a great enough number of studies that the effect levels can be bounded. She indicated that this was not the case with thallium. The available information would still be used in a qualitative manner in reports for Naval facilities where thallium is a chemical of concern. The group decided to review the Manzo and others (1983) and Downs and others (1960) papers during the lunch break and make a final decision after lunch.

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After the lunch break, Ms. Valoppi proposed a low TRV based on the study by Downs and others (1960), in which a dose of 0.4 mg/kg-day resulted in no effect on hair loss or growth depression. The Manzo and others (1983) paper corroborated the hair loss no effect level. She stated that she had difficulty selecting a high TRV because hair loss effect levels occurred at levels very close to doses that caused mortality in other studies. The Downs and others (1960) study was discussed. resulting in new proposals for TRVs because 21 percent mortality was observed at a dose of 1.6 mg/kg-day (Downs and others 1960) Before a TRV could be set, these levels would need to be converted to daily doses using the TRV methodology.

The group also discussed the reported doses and effects from the Stoltz and others (1986) paper in the ATSDR, but a copy was not available for review. Dr. Linder reiterated that he did not believe there were enough data available to derive a TRV.

Dr. Black stated that all the papers should be read before deriving a TRV, adding that the Stoltz paper is a 1986 EPA report. The group agreed that the decision would have to be postponed. Ms. Heins stated that there was not enough time to hold another meeting if the TRVs were to be used in the Treasure Island RI report. She requested that the group designate a representative to come to an agreement on the TRV with her. The state agencies selected Ms. Valoppi as their representative. The federal agencies selected Mr. Haas as their representative. Dr. Black agreed to speak to the EPA librarian to try to get a copy of the Stoltz (1986) report. He would be out of town; so he would have the librarian give the paper to Ms. Hillman. Ms. Hillman would forward the paper to Mr. Haas for his review. Mr. Haas would send a copy to Ms. Heins. Ms. Heins agreed that she would calculate the doses associated with the various effects in the papers cited in the ATSDR and fax a summary to Mr. Haas and Ms. Valoppi by Wednesday, September 3, so that a decision could be made that day. The group recognized that the EPA paper might not be available by that date. If it became available later, the decision could be revisited.[9]

[9] On September 3, 1996, Ms. Heins recalculated doses for the studies cited in ATSDR and distributed a spreadsheet of data to Ms. Valoppi and Mr. Haas. Based on the data in the spreadsheets, Ms. Valoppi proposed a low TRV of 0.48 mg/kg-day, a dose that caused no effect on hair loss, and a high TRV of 1.43 mg/kg-day, at which an increase in hair loss was observed. Mr. Haas consented to these doses. The following justification was provided by Ms. Valoppi and Mr. Haas in their September 15, 1997 comments on the TRV technical memorandum: "Ms. Valoppi and Mr. Haas believe the Downs and others (1960) and Manzo and others (1986) studies were sufficient to derive a TRV because similar effects were seen in two different species and using three different forms of thallium with different solubilities. Downs and others (1960) found a clear dose response relationship, a decreased time to effect with increased dose, and an increased severity of effect with an increase in dose. Effects observed from thallium toxicity include mortality, reduced growth rate, peripheral nerve damage, increased thallium in the kidney, increased kidney weights, and significant hair loss. The endpoint of hair loss was viewed as ecologically relevant because it may result in behavioral changes, decreased sensory capabilities, or reduced conservation of body heat."

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Benzo(a)pyrene/Birds

Dr. Holder stated that the literature searches did not yield any data for B(a)p and birds; therefore, a TRV cannot be derived. The group agreed.

Benzo(a)pyrene/Mammals

Dr. Black noted that on the data spreadsheet, a no effect level for the same effect from the same study appeared at two different doses. Dr. Holder stated that she would check the data and make the appropriate correction. Dr. Holder stated that she had reexamined the data set and selected different TRVs than those used in the Moffett ecological assessment. She suggested that the TRVs be based on reproductive effects rather than carcinogenicity, stating that reproductive effects are more ecologically relevant than cancer. In the field, rodents are usually preyed upon before they reach an age at which cancer may develop. If cancer does develop, it most likely occurs later in the life span after the individuals have successfully reproduced. She suggested that cancer may have been used as an endpoint at Moffett because of the high concern over the endangered salt marsh harvest mouse, which was not necessarily appropriate for non-T&E species. The group discussed the possibility of deriving separate TRVs for endangered species and decided against it.

Dr. Holder proposed a low TRV based effects on various reproductive parameters at a dose of 10 mg/kg-day, from a study by Mackenzie and Angevine (1981). An uncertainty factor of 10 would be applied to convert from an effect level to a no effect level equivalent, resulting in a low TRV of 1.0 mg/kg-day. Dr. Chernoff noted that at Moffett, the low TRV selected was 0.015 mg/kg-day, based on the LOAEL for frequency of benign tumors (Brune and others 1981). He added that this was supported by the LOAEL for macroscopically visible benign tumors and the NOAEL for malignant tumors at 0.11 mg/kg-day in Neal and Rigdon 1967. If a UF of 10 for effect to no effect conversion were applied to the Neal and Rigdon (1967) number the doses were comparable (0.015 and 0.011).

Ms. Heins raised the question of whether cancer was an ecologically significant endpoint. Dr. Holder stated that the cancer was not affecting the life span of the mice, so it is not ecologically relevant.

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Dr. Chernoff stated that Neal and Rigdon (1967) found tumors at 110 days. Mr. Haas stated that he disagreed that the tumors are not affecting the mice. Mr. Van Peeters stated that he was comfortable with TRVs of1.31 mg/kg-day and 32.79 mg/kg-day, based on Neal and Rigdon (1967). There was discussion of whether the study duration was subchronic or chronic. Mr. Haas stated that 110 days would be considered chronic for mice.

Ms. Valoppi was not comfortable basing the TRV on the Neal and Rigdon study (1967). She stated that the study was flawed, only looked at gastric organs, and the endpoint of macroscopically visible tumors was not sensitive enough. She noted that Rigdon and Neal (1969) found tumors in several different organ systems that were not examined in Neal and Rigdon (1967). She stated that benign tumors could be considered an injury under a Natural Resource Damage Assessment, reading a portion of the definition of injury. Mr. Haas stated that benign tumors may have an effect on organ function, so he thought it reasonable to use for the low TRV. The group discussed the purpose of deriving TRVs and agreed that the purpose of the low TRV is not to select a level where no effects occur, but where ecologically relevant adverse effects are avoided. Ms. Gladstone (RWQCB) added that monetary damages might still be assessed under NRDA at a site where contamination levels were below the low TRV. Dr. Linder agreed and stated that the use of cancer as an endpoint is not as technically defensible as a reproductive endpoint in terms of the effect on a population. The group discussed cancer as an endpoint and derivation of TRVs for endangered species , which requires protection of individuals, versus other species, where the goal is protection of the population. Dr. Holder pointed out that the Rigdon and Neal (1969) study stated that the mice used in the study were inbred for tumor production, a situation not representative of field conditions.

Ms. Valoppi proposed that the low TRV be at a dose of 1.31 mg/kg-day, based on Neal and Rigdon (1967), a chronic study with a NOAEL for gastric neoplasms and life span. She preferred the 1.31 mg/kg-day with a cancer endpoint over the reproductive effect level at 10 mg/kg-day with a UF of 10 (resulting in 1.0 mg/kg-day) because the reproductive study used gavage to administer the dose. Ms. Valoppi added that the cancer effect was a sensitive endpoint and the reproductive effect corroborates the dose resulting in the cancer effect. The group agreed on the low TRV of 1.31 mg/kg-day and high TRV of 32.79 mg/kg-day. The high TRV was a dose from Rigdon and Neal (1969), at which mice displayed increased pulmonary adenomas.

Naphthalene/Birds

Mr. Haas and Ms. Valoppi asked Ms. Heins whether the egg shell painting studies mentioned during previous meetings were being considered in the reports, in which the TRVs are used. Ms. Heins explained that studies that did not use oral exposure routes may be used for qualitative comparison to site-specific doses when insufficient data were available to derive TRVs. Ms. Heins added that she does not have copies of the egg shell painting reports for PAHs at this time, and requested that Mr. Haas or Ms. Valoppi send her copies of them. She stated that the information could be used qualitatively in the reports. Mr. Haas and Ms. Valoppi agreed to send copies of the studies they had to Ms. Heins.

Dr. Holder stated that no insufficient data on birds and naphthalene was found to derive a TRV. Ms. Valoppi asked Mr. Haas if he had checked on the topic within the FWS. Mr. Haas had not been able to yet. The group discussed the recent toxicological studies on TPH resulting from the Exxon Valdez oil spill. Dr. Linder said he would send a reference from a recent ASTM paper to Ms. Valoppi.

Naphthalene/Mammals

The proposed low TRV was 50 mg/kg-day, based on a study by Navarro and others (1991), that resulted in no effects on body weight gain or water consumption. The same dose resulted in transient lethargy in pregnant rats after dosing. Dr. Black agreed with the proposed TRV. Ms. Valoppi proposed using a UF of 10 to go from a sub-chronic to chronic study. Ms. Heins stated that the dosing took place during gestation, a sensitive life stage, so the group should consider whether a UF was needed. Ms. Valoppi agreed to the proposed low TRV of 50 mg/kg-day, stating that this dose was supported by a study by Shopp and others (1984), in which a dose of 53 mg/kg-day resulted in no change in organ weights. The group agreed to a high TRV of 150 mg/kg-day, based on a study by Navarro and others (1991), in which a decrease in body weight and water consumption was observed.

REVIEW AND SELECTION OF DEFERRED TRVS

The purpose of the second portion of the meeting was to discuss issues that had not been resolved previously, and to select TRVs that had been deferred from previous meetings, including cadmium/bird, copper/larger mammal, lead/rodent and larger mammal, selenium/bird, zinc/bird and larger mammal,

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PCBs/bird and larger mammal TRVs. Ms. Valoppi and Dr. Chernoff requested that the group discuss two issues first: the use of the Great Lakes Water Quality Initiative wildlife values (EPA 1995) and the use of rodent data to calculate TRVs for larger mammals.

Use of Great Lakes Water Quality Initiative Wildlife Values

Ms. Valoppi started the discussion by pointing out a study of mercury in black ducks cited in Eisler (1987). The study indicated significantly impaired reproductive function at 3 ppm mercury in the feed. Ms. Valoppi calculated a dose of 0.174 mg/kg-day using a black duck body weight from the Great Lakes documents. She applied a UF of 10 to go from a LOAEL to a NOAEL to get a low TRV proposal of 0.0174 mg/kg-day. She indicated that she would prefer to use this number rather than the number selected in the Great Lakes document. She also wondered why the current regional TRV (0.039 mg/kg-day) was different from the Moffett TRV (0.013 mg/kg-day) when they were both based on the Great Lakes value, which was 0.013. Ms. Heins explained that the difference was that the Great Lakes methodology included using an interspecies extrapolation factor of 3. In the methodology employed by the Navy and PRC, interspecies extrapolation factors are not used. The methodology for dealing with interspecies uncertainty is to allometrically convert the doses using the endpoint species body weights and apply confidence ratings that consider the number of species in the data set. This is the only difference between the PRC and Great Lakes methodologies; otherwise, the processes are exactly the same. Ms. Valoppi stated that she thought the agreement was that the Moffett numbers would be used, including the interspecies extrapolation factor. Ms. Heins reiterated that interspecies extrapolation factors are not a part of the agreed upon TRV methodology and would not be used. She stated that it would be inconsistent to apply interspecies extrapolation factors to only some of the TRVs.

Dr. Chernoff stated that the issue was that a different process was being used to derive the regional TRVs than the Moffett ones. For example, the mercury/bird TRV had a UF of 2 for LOAEL to NOAEL as well as the interspecies factor of 3. Ms. Gade (PRC) asked why the LOAEL to NOAEL factor was 2 instead of 10. Ms. Heins responded that the PRC methodology is that a UF of 10 will be used as a default unless there is alternative UFs for a particular TRV are available and agreed upon by the group. The Great Lakes document had recommended 2, and the group had agreed in advance to use the UFs recommended by EPA for the TRVs based on the Great Lakes values. Ms. Valoppi reiterated that she would prefer to

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use the Great Lakes number with the interspecies UF (0.013) or the dose calculated from the study cited in Eisler (1987) (0.017). Dr. Linder said that the study should be read by the group before basing a TRV on it. He recommended against using an interspecies factor in order to maintain consistent methodology. Dr. Black pointed out that this discussion only affects the mercury/bird and DDT/rodent numbers, since those were only ones taken from the Great Lakes document that used an interspecies UF. According to Ms. Heins, the mercury/bird TRV would differ by a factor of 3 and the DDT/rodent number would change by a factor of 10. Mr. Van Peeters stated that the problem is not with the individual numbers, but with maintaining consistent methodology.

In order to remain consistent with PRC methodology, the following options were available: 1) Use the Great Lakes number with a LOAEL to NOAEL UF of 2, as proposed; or 2) Read all the papers and select a TRV separate from that recommended in the Great Lakes document. DTSC representatives still wanted the interspecies UF to be applied to the Great Lakes numbers. A discussion ensued about the fact that these numbers are going to be issued in a Navy report, with the understanding that every member of the work group may not agree with all the proposed TRVs. Mr. Van Peeters stated that in general, he had been in favor of reaching consensus on all TRVs, but that this may not be possible in every case. He added that, for regulatory use, the agencies could add a cover sheet to the report stating that they did not agree with certain numbers, and disagreements could be handled at individual Naval facilities.

Ms. Valoppi stated that she would prefer the use of an interspecies factor because it is more conservative. Allometric conversion of doses to endpoint species smaller than the test organism results in a higher, less protective dose. She requested that the minutes reflect that she disagreed with the low TRV for mercury/birds. She would prefer that the number be based on the black duck study in Eisler or on the pheasant number presented in the Great Lakes document.

USE OF RAT DATA IN CALCULATING DOSES FOR RODENTS AND LARGER MAMMALS

Dr. Chernoff stated that there had been inconsistency in the use of mice, rat, and combinations of the species in developing rodent TRVs. Ms. Heins explained that studies on mice had been used preferentially, with rat data added only when there was not enough mouse data. This method had been used because the original plan was to derive separate TRVs for rodents and larger mammals. The problem of insufficient data being available to develop separate TRVs for larger mammals had not been

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foreseen. Dr. Chernoff stated that for TRVs for rodents in general (as opposed to mice) and for larger mammals, rat data should be included. He stated that rats are more sensitive to some metals than mice. Ms. Heins explained that she and Dr. Chernoff had reached an agreement that Dr. Chernoff would look through the data sets and flag those where rats may be more sensitive than mice but were not well represented. Dr. Chernoff stated that he was concerned with the data sets for copper, lead, selenium, and zinc. The group agreed that Dr. Chernoff and Ms. Heins would divide up the work and make the appropriate revisions.

TRVS DEFERRED FROM PREVIOUS MEETINGS

Cadmium/Birds

Ms. Valoppi had faxed comments on the spreadsheets to Ms. Heins the night before the meeting. Ms. Heins stated that in the studies where measured concentrations of chemicals were given, the nominal concentration on the spreads were changed to the measured concentrations. Other changes made were:

1) Study number 7 is a LOAEL, not a NOAEL.
2) The reference to testes in study number 4 was deleted.
3) Study number 7a was added (NOAEL for 7).
4) Study number 7 summary had "spermatogenesis ceased" added.

Ms. Valoppi proposed a low TRV based on a study by Cain and others (1983), in which a dose of 0.78 mg/kg-day resulted in no effect on blood chemistry (packed cell volume, hemoglobin, red blood cell counts, mean corpuscular hemoglobin count and volume), serum chemistry, body and liver weight, and femur density in mallard ducklings. She stated that this dose was supported by other no effect levels, such as o degenerative effects on the gizzard, proventriculus, intestine, liver, heart, thymus, lung, spleen or skeletal muscle, in the same study at the same dose. She recommended application of a UF of 10 for LOAEL to NOAEL conversion resulting in a dose of 0.07 mg/kg-day. The group agreed on the proposed TRV.

Ms. Valoppi proposed a high TRV of 4.23 mg/kg-day based on a dose reported by Leach and others (1979) that caused a 25% reduction in egg production. She felt that the high proposed by PRC-

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(19.08 mg/kg-day) was not acceptable because testicular atrophy had occurred in only 90 days of dosing. She remarked that she would prefer to have a paper with reproductive data for both male and female birds. Ms. Gade (PRC) proposed a high TRV of 10.43 mg/kg-day that resulted in a decrease in body and testis weight, hematocrit and hemoglobin; changes in liver trace element stores; histological effects to the duodenum, bone marrow, and adrenal gland; and increased heart weight based on a study on Japanese quails by Richardson and others (1974). Ms. Valoppi stated that she thought the decreased egg production was a more significant endpoint. Mr. Van Peeters pointed out that the egg production studies had only been done on chickens for the purpose of enhancing egg production and may be biased in that respect. Ms. Heins stated that the range of effects occurred at doses from 1 to 51 mg/kg-day, with the reproductive effects occurring in the range of 1 to 20 mg/kg-day. The proposed dose of 10.43 mg/kg-day from Richardson and others (1974) is about in the middle of that range, so it is appropriate for a high TRV. The group agreed.

Copper/Larger Mammals

In the meeting on August 20, 1997, Dr. Linder had agreed to review papers cited in the ATSDR toxicity profile and report on their usefulness for TRV derivation. In this meeting, Dr. Linder spoke about studies on copper in mink and ferrets. He discussed Aulerich and others (1982) (ATSDR records 34 and 35) and Bleavins and others (1983) and concluded that the rodent number would be protective of minks and larger mammals. He stated that the Bleavins and others (1983) paper was not very useful. Ms. Heins reminded the group that at the last meeting the group had agreed that rodent numbers were generally protective of the larger mammals when allometrically converted. The group agreed to use the rodent TRVs for copper for larger mammals.

Zinc/Larger Mammals

In the meeting on August 20, 1997, Dr. Linder had agreed to review papers cited in the ATSDR toxicity profile and report on whether they would be useful for TRV derivation. In this meeting, Dr. Linder reported that the zinc papers (Bleavins and others 1983 and Straub 1980) were not very strong, and that it seemed that the rodent TRV would be protective of the larger mammals. He would double-check to make sure.

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Lead/Larger Mammals

In the meetings on August 12, 1996, and August 20, 1996, Dr. Chernoff had agreed to review several papers in relation to lead TRVs for larger mammals. In this meeting, Dr. Chernoff discussed the Navy and ATSDR data sets for lead. He reported that none of the studies he had reviewed addressed reproductive or other ecologically relevant effects. He suggested the use of the rodent TRV adjusted to include rat data, giving a low TRV of 0.002 mg/kg-day from an ATSDR study by Krasovskii and others (1979), in which no reproductive, hematological, or neurological effects were observed at this dose. There was some discussion over whether this number was too conservative, but the group agreed.[10]

Selenium/Birds

Ms. Valoppi stated that she had not finished her review of the proposed numbers. She stated that she would finish her review, propose numbers, and fax them to Ms. Heins on Tuesday, September 3, 1996.[11]

Zinc/Birds

Ms. Valoppi stated that, according to Gasaway and Buss (1972), zinc compounds increase in toxicity in the following order: zinc oxide, zinc sulfate, zinc carbonate. She did not agree with the low TRV proposed by PRC. She proposed basing the TRVs on studies by Gasaway and Buss (1972) and Kazacos and Van Vleet (1989). These studies showed significant mortality, pancreatic effects, leg paralysis, diarrhea, increased kidney:body weight ratios, and decreased testes:body weight ratios. The evaluated these effects in chicks 7 weeks old. These effects were seen at an effect level of 172 mg/kg-day. Ms. Valoppi proposed using this number for the high TRV. For the low TRV, she proposed using the same dose with a UF of 5 for subchronic to chronic and a UF of 10 for the effect level to no effect level conversions. Applying both UFs would bring the low TRV to 3.44 mg/kg-day.

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[10] The dose reported in the study by Krasovskii and others (1979) was actually 0.0015 mg/kg-day. The TRV was revised to reflect this correction.

[11] In a telephone message on September 12, 1996, Ms. Valoppi proposed a low TRV based on a concentration of 2.6 ppm in the diet. Ms. Heins was unable to calculate a TRV without the reference from which the dose was taken. See meeting minutes for the October 3, 1996 meeting for resolution of this issue.

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Dr. Linder pointed out that this number is below nutritional requirements. According to Eisler (1993), 25 to 38 ppm Zn is required to prevent zinc deficiency, and 93 to 120 ppm is optimal. For ducks, the minimum zinc requirement for a 1172 g duck ingesting 64 g food /day is 3.3 mg/kg-day. The optimal amount of dietary zinc for a Japanese quail is 9.9 mg/kg-day, according to a table in Poultry metabolic disorders and microtoxins. Dr. Black expressed concern with the TRV being equal to the dietary optimum. Ms. Valoppi stated that her concern was the form of the zinc, as some are more toxic than others. The group discussed which forms of zinc were most likely found in soil. Ms. Valoppi proposed that the TRV be based on information on zinc carbonate, the most toxic form, if no data on the form of zinc in the soil could be found. Ms. Heins stated that she agreed with the UF of 10 for LOAEL to NOAEL, but stated that one was not required for subchronic to chronic because the study was conducted on a sensitive life stage using juvenile birds. The group agreed and the low TRV was set at 17.2 mg/kg-day. The high TRV was set at 172 mg/kg-day.

PCBs/Larger Mammals

Dr. Chernoff was unable to access the data he needed to propose TRVs for PCBs. He stated he would print his summary and fax it to Ms. Heins the following day, August 30. The group agreed to allow Dr. Chernoff to select TRVs for PCBs.

PCBs/Birds

Ms. Valoppi stated that she looked at both the PRC and Great Lakes data sets and picked the best studies in her opinion. She proposed a low TRV based on Platonow and Rhinehart (1973). The study showed a LOAEL for egg production at 0.34 mg/kg-day during a 39-week study. Studies in the PRC data set did not last over 8 weeks, but the Platonow and Rhinehart (1973) study showed that the concentration in the eggs did not reach its maximum of 5 ppm for 4 months. A UF of 10 was applied to go from a LOAEL to a NOAEL, resulting in a low TRV of 0.034 mg/kg-day. Ms. Valoppi stated that she would send copies of the papers to Ms. Heins by the end of the following week (September 6). The proposed high TRV of 1.27 mg/kg-day was based on a study by Britton and Huston (1973), that caused a decrease in hatchability Ms. Valoppi stated that the number used for the Great Lakes wildlife criterion was based on a study by Dahlgren and others (1972), which lasted only 17 weeks, while other studies lasted 39 weeks.

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Ms. Valoppi gave the PCB papers to Ms. Heins to copy and return, except for three papers which were already in the PRC EMI library. The group agreed with Ms. Valoppi's proposed TRVs.

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SAN FRANCISCO BAY REGIONAL TOXICITY REFERENCE VALUES
WORKING MEETING
OCTOBER 3, 1996

Date: October 3, 1996
Time: 9:30 a.m.
Location: Department of Toxic Substance Control, Berkeley, CA

Participant	Organization
Ned Black	U.S. Environmental Protection Agency (EPA)
Mary Blevins	EPA
Clarence Callahan	EPA
Eugenia McNaughton	EPA
Gerald Chernoff	Department of Toxic Substance Control (DTSC)
Helen Hillman	National Oceanic and Atmospheric Administration (NOAA)
Susan Ellis	California Department of Fish and Game (DFG)
William Van Peeters	EFA West
Cooper Heins	PRC Environmental Management Inc. (PRC)
Greg Linder	PRC
Martha Burford	PRC
Catherine Westbrook	PRC
Jennifer Holder	Entrix

INTRODUCTION

This was the sixth meeting of the work group to develop regional toxicity reference values (TRV). The main objective of these meetings is for the Navy, regulatory, and trustee agencies to reach consensus on regional TRVs in order to assess risk to higher trophic level receptors form site contaminants at Naval installations.

The objective of this meeting were to: 1) resolve outstanding issues including review of TRVs for larger mammals and selenium/bird TRVs, and 2) discuss and select TRVs for manganese, dibutyltin, tributyltin, lindane, aldrin, heptachlor, and methoxychlor. Ms. Heins (PRC) stated that these values needed to be selected by the end of the day in order to be used in an upcoming Hunter's Point Shipyard report. Objective 1 was partially completed, as the members who agreed to report back on selenium/bird TRVs were absent from the meeting. Dr. Callahan (EPA) and Ms. McNaughton (EPA) agreed to report their findings on the sub-committees decision. If the sub-committee had not reached a decision by October 10, 1996 the TRV for selenium/birds would default to the numbers used for the ecological assessment at

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Moffett Federal Airfield (Moffett). Objective 2 was completed. Attachment A contains the agenda of the meeting.

OUTSTANDING TRVS

TRVs for Larger Mammals

Dr. Chernoff (DTSC) asked for clarification on the use of allometrically converted rodent data to derive the larger mammal TRVs. Ms. Heins explained that the group had looked at larger mammal data from literature searches (including mink, rabbit, and dogs) and in the Agency for Toxic Substances and Disease Registry (ATSDR) toxicity profiles. There were not enough data found to provide a large mammal data set from which to derive TRVs, and most of the large mammal data were inappropriate for deriving TRVs. Ms. Heins had recommended using the rodent data, ATSDR toxicity profiles, and any additional large mammal data to determine TRVs for larger mammals. As a result, the group considered whether it would be appropriate to use the rodent data sets to derive TRVs for larger mammals. The larger mammal doses from both ATSDR and literature searches were allometrically converted and compared to allometrically converted rodent doses. Several trials with different studies resulted in allometrically converted rodent data being close to, and in most cases slightly lower than, the large mammal data from the literature and ATSDR. For most of the chemicals of potential concern (COPCs) the group processed the data allometrically and each time the group agreed that using rodent data to allometrically convert to larger mammal TRVs was more protective because the data were of higher quality and was supported by the data set as a whole.

Dr. Chernoff indicated that he had concerns about using allometric conversion instead of interspecies uncertainty factors (UF). Ms. Heins stated that the decision had been made in the past to use allometric conversion over interspecies UFs. She explained that these two methods were not considered to be the same but that the group had chosen to use allometric conversions originally during the Moffett TRV derivation effort. Dr. Chernoff indicated that he understood that but that DTSC guidance calls for interspecies UFs in risk assessments. He explained that he just wanted the methodologies and DTSC's opinion on the matter made clear so that there was no confusion.

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Selenium/Birds

At the meeting on August 20, 1996, Ms. Valoppi (DTSC) indicated that she would review Joe Skorupa's report on selenium effects on birds and propose new numbers at the August 29, 1996 meeting. At the August 29, 1996 meeting, Ms. Valoppi indicated that she was not finished reviewing the proposed numbers and would propose numbers and fax them to Ms. Heins on Tuesday, September 3, 1996. At this meeting, October 3, 1996, a new sub-committee was established due to Ms. Valoppi's absence from the meeting. Dr. Callahan indicated that the sub-committee would report back to Ms. Heins by October 10, 1996 and if the information was not found or the deadline was missed the group would default to the TRVs already approved in the Moffett effort for selenium effects on birds.[12]

NEW TRVS FOR BIRDS AND MAMMALS

Manganese/Birds

Jennifer Holder (Entrix) explained that extensive literature searches on the effects of manganese on birds had not produced sufficient data to derive a TRV. There was a general questions about the method for deciding whether or not the data were sufficient for deriving TRVs. Ms. Heins said that the decision often has to do with the quality of the papers retrieved, not the quantity. Dr. Chernoff pointed out that in the study by Laskey and Edens (1985), an effect was observed at 776 mg/kg-day. In this study, Japanese quail were given manganese oxide in food for 75-80 days. At a dose of 776 mg/kg-day, reduction in motor skills and aggressive behavior were reported. Also at this dose, no significant effects were reported on serum testosterone levels. Dr. Chernoff pointed out that the study was chronic, looked at significant endpoints, and used an appropriate exposure route. He proposed using this dose as the low TRV and applying a UF of 10 for a effect level to a no effect level conversion. The group agreed to the adjusted dose of 77.6 mg/kg-day for the low TRV and the unadjusted dose of 776 mg/kg-day for the low TRV.

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[12] The avian TRVs for selenium that were derived for the ecological assessment at Moffett were used for the regional TRVs but were recalculated using an expanded table of body weights and ingestion rates and incorporating revisions based on quality control reviews of the Moffett data set. The low TRV was 0.23 mg/kg-day from a study by Heinz and others (1989), and the high TRV was 0.93 mg/kg-day from the same study.

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Manganese/Mammals

Dr. Holder proposed a low TRV of 65 mg/kg-day with an UF of 10 applied for an effect to no effect conversion, resulting in a low TRV of 6.5 mg/kg-day. This was based on a report by Joardar and Sharma (1990). In this study, effects were reported on reproductive and cytotoxic endpoints. Dr. Chernoff requested that the dose of 13.8 mg/kg-day from Kontur and Fetcher (1988) reporting no effects on neurological endpoints be considered for the low TRV. He also pointed out that a UF of 10 should be applied for a sub-chronic to chronic conversion for the low TRV. This would result in a low dose of 1.4 mg/kg-day. Ms. Heins explained that the nutritional requirements of manganese for rodents was 4.67 mg/kg-day. She also indicated that if the duration of the study was 10 to 25 percent of the life span of the animal that the test duration would be considered chronic. The group agreed that the study by Kontur and Fetcher (1988) had a chronic duration and therefore the dose of 13.8 mg/kg-day would not have a UF applied. Dr. Holder pointed out that the study by Gray and Laskey (1980), with a dose of 136.56 mg/kg-day, reported an adverse effect on mice with a reproductive endpoint. A UF would be applied to this dose for an effect to no effect conversion, resulting in a dose of 13.7 mg/kg-day. The dose of 13.7 mg/kg-day was above nutritional levels of manganese for rodents, was close to the other no effects in the data set, and had a reproductive endpoint. This dose was chosen for the low TRV.

Dr. Holder proposed a high TRV of 159.09 mg/kg-day from a study by Gray and Lasky (1980). At this dose, adverse effects were reported on reproduction. Also at this dose, no neurological effects were reported. The dose of 159.09 mg/kg-day was in the mid-range of effects. The group agreed on a high TRV of 159.09 mg/kg-day.

Dibutyltin (DBT)/Birds

Dr. Holder indicated that the quality and quantity of reports on dibutyltin toxicity to birds was limited. She explained that there were very few data on higher trophic levels exposure to dibutyltin; most of the work has been done on sediments and the associated biota. Dr. Callahan suggested that the group look at the relationship between DBT and tributyltin (TBT) and perhaps combine the data for deriving a number for butyltins. The group agreed that, as long as the number was based on the more toxic of the two, it would be sufficient. Mr. Van Peeters (EFA West) indicated that he would investigate the combining the two butlytins. Mr. Van Peeters agreed to call Ms. Heins if there were reasons not to combine data TBT

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and DBT together. The group agreed to combine the data sets to develop a single TRV for DBT and TBT.

Dibutyltin (DBT) and Tributyltin (TBT)/Birds

The proposed low TRV for butyltins was 7.34 mg/kg-day from a study by Schlatterer and others (1993). An UF of ten was applied for a sub-chronic to chronic conversion resulting in a low TRV of 0.73 mg/kg-day. The dose was below adverse effects that were reported in the DBT data set. This was a reproductive study reporting no adverse effects at the dose of 7.34 mg/kg-day for the number of eggs laid per week, egg-shell thickness, fertility, mortality, or number of chicks that hatched. The group agreed on a dose of 7.34 mg/kg-day with a UF of 10 applied, resulting in a low TRV of 0.73 mg/kg-day for butyltins.

The proposed high TRV was 45 mg/kg-day from a study by Schlatterer and other (1993). This study had an ecologically relevant endpoint and was in the mid-range of effects for both data sets. The group agreed on a high TRV of 45 mg/kg-day for butyltins.

Dibutyltin (DBT) and Tributyltin (TBT)/Mammals

The group agreed to use both data sets to derive a butyltin number for mammals due to the sparseness of the DBT data set.

In the DBT data set, at a dose of 10 mg/kg-day in a study by Ema and others (1995), adverse effects were reported on a reproductive endpoint. This effect occurred at a low dose in the DBT data set required an effect to no effect UF of 10. The group considered the resulting low TRV of 0.10 mg/kg-day. In the TBT data set, Smialowicz and others (1989) reported a no effect level of 2.5 mg/kg-day. Applying a UF of 10 for a sub-chronic to chronic conversion would result in a dose of 0.25 mg/kg-day. This dose was one of the lowest no effect levels in the TBT data set and had immunological endpoint. The group decided to base the low TRV on the immunological endpoint for TBT at the dose of 0.25 mg/kg-day because many parameters were tested in this study, including systemic endpoints.

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Dr. Holder stated that, at a dose of 25 mg/kg-day in the TBT data set all fetuses died in a study by Itami and others (1990). Therefore, to be below mortality levels, the high TRV would have to be below this dose. She also pointed out that at the dose of 15 mg/kg-day in the same study there were no significant effects on fetal mortality. Dr. Black (EPA) proposed using a dose of 20 mg/kg-day in a study by Smialowicz and others (1989), stating that this dose was close to the mid-range of effects in the TBT data set. Dr. Holder, responded that the response curve for adverse effects was not known for TBT from 20 mg/kg-day to the 25 mg/kg-day; therefore, it may be more appropriate to use a lower number. Dr. Holder suggested that the dose of 10 mg/kg-day of TBT from a study by Smialowicz and others (1989) was a reasonable dose for the high TRV. In the DBT data set, the dose of 15 mg/kg-day from a Ema and others (1995) reporting adverse reproductive effects was also reasonable for the high TRV. Dr. Holder also indicated that in the DBT data set, at the dose of 10 mg/kg-day in a study by Ema and others (1996), adverse reproductive effects were reported. The group agreed to use 10 mg/kg-day represented in both the TBT and DBT data set for the high TRV.

Discussion of TRVs for Organochlorine Pesticides

Dr. Callahan stated that, for lindane, aldrin, heptachlor, and methoxychlor, it may be appropriate to combine the data and derive a single TRV for total organochlorines since very little data were available in some cases. Dr. Callahan suggested lumping lindane, aldrin, heptachlor, and methoxychlor together with DDT and deriving a organochlorine number. Mr. Van Peeters indicated that usually, DDT was considered separately from the other organochlorines. Dr. Holder pointed out that sufficient data were available to derive individual mammalian TRVs some of the organochlorines, but the bird data were not sufficient for any individual organochlorines except for DDT. The group decided to go through each of the organochlorines individually and derive TRVs if sufficient data were available. At the end of the meeting the group agreed to continue the discussion on what to do in cases where data were insufficient to derive TRVs.

Lindane/Birds

Three studies were examined for deriving avian TRVs for lindane. Based on the quality and the range of effects of the studies, the group decided that the data set was insufficient to derive a TRV.

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Lindane/Mammals

The proposed low dose for lindane was 0.05 mg/kg-day from a study by Naishtein and Leibovich (1971). This study looked at a reproductive endpoint and was a chronic study on a sensitive life stage. The group agreed on a low TRV of 0.05 mg/kg-day.

The proposed high TRV for lindane was 10 mg/kg-day from a study by Cooper and others (1989). At this dose, adverse reproductive effects were reported. Dr. Holder reported that Sircar and Lahiri (1989) also reported reproductive effects at doses of 6.25 mg/kg-day and 3.75 mg/kg-day in a study that dosed the sensitive life stage of the test organism. The group agreed to use the 3.75 mg/kg-day for the high TRV.

Aldrin/Birds

Dr. Holder reported that there were insufficient data to derive an avian TRV for aldrin. The group agreed.

Aldrin/Mammals

Dr. Holder found four studies that could be considered relevant for deriving TRVs, of these four studies three were high quality and one was medium quality. She pointed out that the data from these four studies were not appropriate for TRV derivation. Dr. Holder added that data from ATSDR may be more helpful in finding a dose from which to derive a TRV. She discussed ATSDR record numbers 14 (Treon and others 1953), record numbers 17 and 20 (Fitzhugh and others 1964), and record numbers 24 and 25 (Treon and others 1954). Fitzhugh and others (1964) used statistical analysis for mortality and organ weight, but used subjective measurements for pathology. The paper was considered to be of medium quality due to the analysis of trends rather than statistical differences. In the studies by Treon and others (1953 and 1954), the doses were taken from end of the year reports from the Treon laboratory. There was very little information to support the means by which they came up with these doses. Both Dr. Holder and Ms. Heins indicated that they were unable to find the actual study from which the doses in

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the study were taken. The group agreed not to set a dose for the low and high TRV at this time based on insufficient data[13].

Heptachlor/Birds

There was insufficient data to derive heptachlor TRVs for birds.

Heptachlor/Mammals

The proposed low TRV was 1.29 mg/kg-day, which would have a UF of 10 applied for a effect to no effect conversion, resulting in a TRV of 0.129 mg/kg-day. This dose was from a study by Shain and others (1977). This study demonstrated adverse reproductive effects. The group agreed that this should be used for the low TRV.

The proposed high TRV was 6.80 mg/kg-day from a reproductive study by Narotsky and others (1995). The group agreed that this should be used for the high TRV.

Methoxychlor/Birds

There was insufficient data to derive methoxychlor TRVs for birds.

Methoxychlor/Mammals

The proposed low TRV was based on a dose of 25 mg/kg-day, divided by a UF of 10 for effect level to no effect conversion, resulting in a dose of 2.5 mg/kg-day. This was reproductive study by Gray and others (1989). Dr. Holder indicated that this dose was the lowest dose in the spreadsheet that was ecologically relevant. The group agreed that the dose of 2.5 mg/kg-day should be used for the low TRV.

[13] Dr. Chernoff (DTSC) responded in a subsequent phone conversation indicating that 0.1 mg/kg-day should be used for the low TRV and 1 mg/kg-day should be used for the high TRV for aldrin and rodents. This decision was based on a report by Paul and others (1992) found in the PRC data set study number 3 and 4. Dr. Chernoff pointed out that this decision was based on both the PRC and ATSDR data set. For the low TRV the 1 mg/kg-day was divided by a UF of 10 for a EL to NEL conversion resulting in the 0.1 mg/kg-day dose.

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The proposed high TRV was 25 mg/kg-day from the same study. The group discussed this proposal and felt that the dose of 25 mg/kg-day was too low and not in the mid-range of effects. Dr. Holder proposed a dose of 71.13 mg/kg-day, based on a study by Harris and others (1974) for the high dose for the high TRV. Dr. Chernoff proposed using the dose of 50 mg/kg-day from a study by Gray and others (1989), stating that it was a significant reproductive study. The group agreed to use the dose of 50 mg/kg-day for the high TRV.

Continued Discussion on Organochlorines

The group decided to discuss the case of combining the data for individual organochlorines to derive a low and high TRV for total organochlorines. Table 1 was constructed on a chalk board by Dr. Holder to help the group look at the data for each individual organochlorine.

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TABLE 1

TRVS FOR ORGANOCHLORINES

	BIRDS		MAMMALS	
	low dose[a]	high dose	low dose	high dose
DDT	0.009	1.5	0.8	16
Aldrin	NA	NA	NA	NA
Heptachlor	NA	NA	0.129	6.8
Methoxychlor	NA	NA	2.5	50
Lindane	NA	NA	0.05	3.75
Chlordane[b]	NA	NA	0.18	8
Endosulfan[b]	NA	NA	1.5	10
Endrin[b]	0.07	0.16	0.15	0.9
Dieldrin[b]	0.04	2.12	0.002	6.0

[a] all doses are in mg/kg-day

[b] these doses were included for the purpose of discussion: the doses were decided in previous meetings or were used in previous ecological assessments.

Dr. Holder asked whether the group would rather combine data when data were available to derive individual organochlorine TRVs or only combine data in cases where there was insufficient data to derive individual TRVs. Dr. Chernoff responded that data should be combined only for birds since individual TRVs were derived for each organochlorine except aldrin. There was some discussion about deriving an aldrin TRV for mammals. Dr. Chernoff said that he would investigate other sources of information for deriving a mammalian TRV for aldrin. He agreed that if nothing was found after 10 days that aldrin should be treated qualitatively in individual ecological assessments. The group agreed[14].

With regards to avian organochlorine TRVs, Dr. Chernoff suggested using the avian TRVs derived for DDT as a course first screening for individual organochlorines such as aldrin, heptachlor, methoxychlor, and lindane. If the total organochlorine value is less than the DDT value then there is no need for further

14 In a subsequent telephone conversation, Dr. Chernoff stated that he had reviewed several papers and felt that an appropriate dose for the low TRV was 1 mg/kg-day. The TRV was based on a 90 day study by Paul and others (1992). At a dose of 1 mg/kg-day, motor coordination was adversely affected. Motor coordination was considered an important endpoint because it may limit an animal's ability to avoid predators. Moreover, the dose of 1 mg/kg-day was corroborated by similar doses reported in ATSDR (1993). A UF of 10 was applied to convert the effect level to a no effect level equivalent, resulting in a low TRV of 0.1 mg/kg-day. The unadjusted dose was the basis for the high TRV.

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investigation if the opposite is true than the total organochlorines may be looked at qualitatively for birds. The group agreed that this was an appropriate way to handle the insufficient data for individual organochlorines TRVs for birds.

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ATTACHMENT A

AGENDA

AGENDA
Regional TRV Working Meeting
October 3, 1996

Meeting Time: 9:30 a.m.
Meeting Place: Department of Toxic Substances Control
Auditorium Room, 3rd Floor
700 Heinz Ave., Berkeley, CA

I. Introductions

II. Resolve Outstanding Issues

a. Explanation of TRVs for Larger Mammals
b. Selenium/Birds

III. New TRVs for Birds and Mammals

a. Manganese
b. Dibutyltin
c. Tributyltin
d. Lindane
e. Aldrin
f. Heptachlor
g. Methoxychlor

APPENDIX E

BODY WEIGHTS OF TEST ORGANISMS

Use of Appendix E

This table of body weights summarizes information presented in Section 5 of the technical memorandum, where body weights of test organisms are given in each subsection along with the mammalian TRVs. The mammalian body weights should be used in the allometric conversion equation presented in Section 3.3 (Equation 1). Avian body weights are presented for information purposes only; no avian allometric conversions are recommended.

TABLE E-1 TEST ORGANISM BODY WEIGHTS

Chemical		Low TRV (mg/kg-day)	Test Organism	Body Weight (g)	High TRV (mg/kg-day)	Test Organism	Body Weight (g)
Aldrin	Mammal	0.1	Wistar rat	65	1.0	Wistar rat	65
	Bird	No Avian TRV: Insufficient Data					
Arsenic	Mammal	0.32	Long-Evans rat	332	4.70	Sprague-Dawley rat	110
	Bird	5.5	mallard	1172.20	22.01	mallard	1172.20
Benzo(a)pyrene	Mammal	1.31	CFW mouse	30.5	32.79	CFW mouse	30.5
	Bird	No Avian TRV: Insufficient Data					
Butlytin	Mammal	0.25	Fischer rat	188	15	Wistar rat	241
	Bird	0.73	Japanese quail	96.5	45.85	Japanese quail	96.5
Cadmium	Mammal	0.06	QS mouse	32.2	2.64	CD mouse	31.41
	Bird	0.08	mallard	798.5	10.43	mallard	84
Cobalt	Mammal	1.2	laboratory rat	275	20	laboratory rat	200
	Bird	No Avian TRV: Insufficient Data					
Copper	Mammal	2.67	C57BL/6 mouse	30	631.58	B6C3F1 mouse	24.7
	Bird	2.3	broiler chick	639	52.26	Cobb broiler chick	409
DDT, DDE, DDD	Mammal	0.8	laboratory rat	320	16	Wistar rat	320
	Bird	0.009	pelican	3500	DDT - 1.5 DDE - 0.6	mallard mallard	1000
Heptachlor	Mammal	0.13	Sprague-Dawley rat	100	6.8	Fischer-344 rat	204
	Bird	No Avian TRV: Insufficient Data					
Lead	Mammal	0.0015	white rat	208	240.64	MF-1 mouse	18.7
	Bird	0.014	Japanese quail	84 / 103[1]	8.75	chicken	800
Lindane	Mammal	0.05	laboratory rat	176	3.75	Swiss mouse	24
	Bird	No Avian TRV: Insufficient Data					
Manganese	Mammal	13.7	CD-1 mouse	34.6	159.09	CD-1 mouse	29.7
	Bird	77.6	Japanese quail	196.5	776	Japanese quail	196.5

TABLE E-1 TEST ORGANISM BODY WEIGHTS (continued)

Chemical		Low TRV (mg/kg-day)	Test Organism	Body Weight (g)	High TRV (mg/kg-day)	Test Organism.	Body Weight (g)
Mercury	Rodent	0.25	rat	187.5	4	rat	428
	Large Mammal	0.027	mink	800	0.27	mink	800
	Bird	0.039	mallard	1000	0.18	mallard	1000
Methoxychlor	Mammal	2.5	Long-Evans rat	332	50	Long-Evans rat	332
	Bird	No Avian TRV: Insufficient Data					
Napthalene	Mammal	50.0	Sprague-Dawley rat	276.5	150	Sprague-Dawley rat	270.2
	Bird	No Avian TRV: Insufficient Data					
Nickel	Mammal	0.133	Long-Evans rat	248.6	31.6	Long-Evans rat	248.6
	Bird	1.38	mallard	613.75	55.26	mallard	580
PCBs	Mammal	0.36	white-footed mouse	20.62	1.28	white-footed mouse	22.85
	Bird	0.09	chicken	800	1.27	single-comb white leghorn chicken	1715.4
Selenium	Mammal	0.05	Wistar rat	186.5	1.21	CD mouse	24.6
	Bird	0.23	mallard	1107.7	0.93	mallard	1107.7
Thallium	Mammal	0.48	Wistar rat	65	1.43	Wistar rat	65
	Bird	No Avian TRV: Insufficient Data					
Zinc	Mammal	9.6	C3H mouse	25.5	411.43	nulliparous rat	175
	Bird	17.2	mallard	955	172	mallard	955

Note: Body weights were taken directly from the study on which the TRV was based. When body weights were not given, grand means of means reported from a variety of references were used.

[1] TRV based on two studies: Edens and others (1976) bw = 84 g; Edens and Garlich (1983) bw = 103 g.

APPENDIX F

GLOSSARY OF TERMS

GLOSSARY OF TERMS

The terms listed below are defined as they were used for the derivation of toxicity reference values (TRVs). Many of these terms have multiple meanings or are subject to interpretation. In such cases, the definitions may not apply in other circumstances.

Acute exposure	Single dose exposure of a test organism to a chemical
ALAD	D-aminolevulinic acid dehydrase. A biomarker of exposure to specific chemicals
Allometric conversion	Extrapolation from a dose to a test organism to a dose to a different species based on body scaling
Allometry	The study of the change in proportion of various parts of an organism as a consequence of growth
Ataxia	Loss or lack of muscle coordination
Avian	Of or pertaining to birds
Background	Naturally occurring concentrations of a chemical
Biomarker	A chemical or enzyme in the body whose presence or elevated presence indicates a biological response to an introduced chemical
Chronic exposure	Exposure of a test organism to a chemical for at least 10 to 25 percent of its life span
Effect level	A dose or concentration of a chemical that causes a measured effect in a test organism
Endpoint	In toxicological laboratory studies refers to a specific effect or type of effect
Exposure route	The method of administration of a chemical to an organism, e.g. oral ingestion, or injection
Gallinaceous	Belonging to the order Galliformes. Includes domestic fowl, pheasant, and turkeys
Gavage	Forced feeding through a tube
High TRV	A chronic dose level at which a particular adverse biological effect may occur in an organism, based on laboratory investigations
Hazard Quotient	A site-specific estimated dose compared to a TRV (HQ = Dose / TRV). The HQ approach indicates that receptors may be at risk if the HQ exceeds 1.0

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GLOSSARY OF TERMS (Continued)

Ingestion rate	The amount of food, water, soil, or sediment a given organism ingests per unit time
LOAEL	The lowest experimental dose in a study at which a given effect to the test organism is observed. A LOAEL is always bounded by a lower dose (NOAEL) at which the effect is not observed.
Low TRV	A chronic dose level at which a particular biological effect does not occur in an organism based on laboratory investigations
NOAEL	The highest experimental dose in a study at which a given effect to the test organism is not observed. A NOAEL is always bounded by a higher dose (LOAEL) at which the effect is observed.
No effect level	A dose or concentration of a chemical at which a measured effect is not observed in a test organism
Raptor	A bird of prey
Site specific dose	A daily chemical dose to a specific receptor that is estimated based on measured concentrations in media from a site and a range of assumptions
Subchronic exposure	Exposure of a test organism to a chemical for a duration less than 10 percent of the organism's life span
Sensitive life stage	The stage of life extending from conception through development
Uncertainty factor	A value by which a TRV is divided to overlay a level of conservatism to data that are, for one reason or another, incomplete

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