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Reference Dose for Chronic Oral Exposure (RfD) [go](#)

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Arsenic, inorganic; CASRN 7440-38-2 (04/10/1998)

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Arsenic, inorganic

File First On-Line 02/10/1988

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	02/01/1993
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	04/10/1998

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Arsenic, inorganic

CASRN — 7440-38-2

Last Revised — 02/01/1993

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration

of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

NOTE: There was not a clear consensus among Agency scientists on the oral RfD. Applying the Agency's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 ug/kg/day. It should be noted, however, that the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude. New data that possibly impact on the recommended RfD for arsenic will be evaluated by the Work Group as it becomes available. Risk managers should recognize the considerable flexibility afforded them in formulating regulatory decisions when uncertainty and lack of clear consensus are taken into account.

__I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses *	UF	MF	RfD
Hyperpigmentation, keratosis and possible vascular complications	NOAEL: 0.009 mg/L converted to 0.0008 mg/kg-day LOAEL: 0.17 mg/L converted to 0.014 mg/kg-day	3	1	3E-4 mg/kg-day
Human Chronic oral exposure				
Tseng, 1977; Tseng et al., 1968				

*Conversion Factors -- NOAEL was based on an arithmetic mean of 0.009 mg/L in a range of arsenic concentration of 0.001 to 0.017 mg/L. This NOAEL also included estimation of arsenic from food. Since experimental data were missing, arsenic concentrations in sweet potatoes and rice were estimated as 0.002 mg/day. Other assumptions included consumption of 4.5 L water/day and 55 kg bw (Abernathy et al., 1989). $NOAEL = [(0.009 \text{ mg/L} \times 4.5 \text{ L/day}) + 0.002 \text{ mg/day}] / 55 \text{ kg} = 0.0008 \text{ mg/kg-day}$. The LOAEL dose was estimated using the same assumptions as the NOAEL starting with an arithmetic mean water concentration from Tseng (1977) of 0.17 mg/L. $LOAEL = [(0.17 \text{ mg/L} \times 4.5 \text{ L/day}) + 0.002 \text{ mg/day}] / 55 \text{ kg} = 0.014 \text{ mg/kg-day}$.

__I.A.2. Principal and Supporting Studies (Oral RfD)

Tseng, W.P. 1977. Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. *Environ. Health Perspect.* 19: 109-119.

Tseng, W.P., H.M. Chu, S.W. How, J.M. Fong, C.S. Lin and S. Yeh. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *J. Natl. Cancer Inst.* 40: 453-463.

The data reported in Tseng (1977) show an increased incidence of blackfoot disease that increases with age and dose. Blackfoot disease is a significant adverse effect. The prevalences (males and females combined) at the low dose are 4.6 per 1000 for the 20-39 year group, 10.5 per 1000 for the 40-59 year group, and 20.3 per 1000 for the >60 year group. Moreover, the prevalence of blackfoot disease in each age group increases with increasing dose. However, a recent report indicates that it may not be strictly due to arsenic exposure (Lu, 1990). The data in Tseng et al. (1968) also show increased incidences of hyperpigmentation and keratosis with age.

The overall prevalences of hyperpigmentation and keratosis in the exposed groups are 184 and 71 per 1000, respectively. The text states that the incidence increases with dose, but data for the individual doses are not shown. These data show that the skin lesions are the more sensitive endpoint. The low dose in the Tseng (1977) study is considered a LOAEL.

The control group described in Tseng et al. (1968; Table 3) shows no evidence of skin lesions and presumably blackfoot disease, although this latter point is not explicitly stated. This group is considered a NOAEL.

The arithmetic mean of the arsenic concentration in the wells used by the individuals in the NOAEL group is 9 ug/L (range: 1-17 ug/L) (Abernathy et al., 1989). The arithmetic mean of the arsenic concentration in the wells used by the individuals in the LOAEL group is 170 ug/L (Tseng, 1977; Figure 4). Using estimates provided by Abernathy et al. (1989), the NOAEL and LOAEL doses for both food and water are as follows: LOAEL - $[170 \text{ ug/L} \times 4.5 \text{ L/day} + 2 \text{ ug/day (contribution of food)}] \times (1/55 \text{ kg}) = 14 \text{ ug/kg/day}$; NOAEL - $[9 \text{ ug/L} \times 4.5 \text{ L/day} + 2 \text{ ug/day (contribution of food)}] \times (1/55 \text{ kg}) = 0.8 \text{ ug/kg/day}$.

Although the control group contained 2552 individuals, only 957 (approximately 38%) were older than 20, and only 431 (approximately 17%) were older than 40. The incidence of skin lesions increases sharply in individuals above 20; the incidence of blackfoot disease increases sharply in individuals above 40 (Tseng, 1968; Figures 5, 6 and 7). This study is less powerful than it appears at first glance. However, it is certainly the most powerful study available on arsenic exposure to people.

This study shows an increase in skin lesions, 22% (64/296) at the high dose vs. 2.2% (7/318) at the low dose. The average arsenic concentration in the wells at the high dose is 410 ug/L and at the low dose is 5 ug/L (Cebrian et al., 1983; Figure 2 and Table 1) or 7 ug/L (cited in the abstract). The average water consumption is 3.5 L/day for males and 2.5 L/day for females. There were about an equal number of males and females in the study. For the dose estimates given below we therefore assume an average of 3 L/day. No data are given on the arsenic exposure from food or the body weight of the participants (we therefore assume 55 kg). The paper states that exposure times are directly related to chronological age in 75% of the cases. Approximately 35% of the participants in the study are more than 20 years old (Figure 1).

Exposure estimates (water only) are: high dose - $410 \text{ ug/L} \times 3 \text{ L/day} \times (1/55 \text{ kg}) = 22 \text{ ug/kg/day}$; low dose - $5\text{-}7 \text{ ug/L} \times 3 \text{ L/day} \times (1/55 \text{ kg}) = 0.3\text{-}0.4 \text{ ug/kg/day}$.

The high-dose group shows a clear increase in skin lesions and is therefore designated a LOAEL. There is some question whether the low dose is a NOAEL or a LOAEL since there is no way of knowing what the incidence of skin lesions would be in a group where the exposure to arsenic is zero. The 2.2% incidence of skin lesions in the low-dose group is higher than that reported in the Tseng et al. (1968) control group, but the dose is lower (0.4 vs. 0.8 ug/kg/day).

The Southwick et al. (1983) study shows a marginally increased incidence of a variety of skin lesions (palmar and plantar keratosis, diffuse palmar or plantar hyperkeratosis, diffuse pigmentation, and arterial insufficiency) in the individuals exposed to arsenic. The incidences are 2.9% (3/105) in the control group and 6.3% (9/144) in the exposed group. There is a slight, but not statistically significant increase in the percent of exposed individuals that have abnormal nerve conduction (8/67 vs. 13/83, or 12% vs. 16% (Southwick et al., 1983; Table 8). The investigators excluded all individuals older than 47 from the nerve conduction portion of the study. These are the individuals most likely to have the longest exposure to arsenic.

Although neither the increased incidence of skin lesions nor the increase in abnormal nerve conduction is statistically significant, these effects may be biologically significant because the

same abnormalities occur at higher doses in other studies. The number of subjects in this study was insufficient to establish statistical significance.

Table 3 (Southwick et al., 1983) shows the annual arsenic exposure from drinking water. No data are given on arsenic exposure from food or the body weight (assume 70 kg). Exposure times are not clearly defined, but are > 5 years, and dose groups are ranges of exposure.

Exposure estimates (water only) are: dosed group - $152.4 \text{ mg/year} \times 1 \text{ year}/365 \text{ days} \times (1/70) \text{ kg} = 6 \text{ ug/kg/day}$; control group - $24.2 \text{ mg/year} \times \text{year}/365 \text{ days} \times (1/70) \text{ kg} = 0.9 \text{ ug/kg/day}$.

Again because there are no data for a group not exposed to arsenic, there is some question if the control group is a NOAEL or a LOAEL. The incidence of skin lesions in this group is about the same as in the low-dose group from the Cebrian et al. (1983) study; the incidence of abnormal nerve conduction in the control group is higher than that from the low-dose group in the Hindmarsh et al. (1977) study described below. The control dose is comparable to the dose to the control group in the Tseng et al. (1968) and Hindmarsh et al. (1977) studies. The dosed group may or may not be a LOAEL, since it does not report statistically significant effects when compared to the control.

This study shows an increased incidence of abnormal clinical findings and abnormal electromyographic findings with increasing dose of arsenic (Hindmarsh et al., 1977; Tables III and VI). However, the sample size is extremely small. Percentages of abnormal clinical signs possibly attributed to As were 10, 16, and 40% at the low, mid and high doses, respectively. Abnormal EMG were 0, 17 and 53% in the same three groups.

The exact doses are not given in the Hindmarsh et al. (1977) paper; however, some well data are reported in Table V. The arithmetic mean of the arsenic concentration in the high-dose and mid-dose wells is 680 and 70 ug/L, respectively. Figure 1 (Hindmarsh et al., 1977) shows that the average arsenic concentration of the low-dose wells is about 25 ug/L. No data are given on arsenic exposure from food. We assume daily water consumption of 2 liters and body weight of 70 kg. Exposure times are not clearly stated.

Exposure estimates (water only) are: low - $25 \text{ ug/L} \times 2 \text{ L/day} \times (1/70) \text{ kg} = 0.7 \text{ ug/kg/day}$; mid - $70 \text{ ug/L} \times 2 \text{ L/day} \times (1/70) \text{ kg} = 2 \text{ ug/kg/day}$; high - $680 \text{ ug/L} \times 2 \text{ L/day} \times (1/70) \text{ kg} = 19 \text{ ug/kg/day}$.

The low dose is a no-effect level for abnormal EMG findings. However, because there is no information on the background incidence of abnormal clinical findings in a population with zero exposure to arsenic, there is no way of knowing if the low dose is a no-effect level or another marginal effect level for abnormal clinical findings. The low dose is comparable to the dose received by the control group in the Tseng (1977) and Southwick et al. (1983) studies.

The responses at the mid dose do not show a statistically significant increase but are part of a statistically significant trend and are biologically significant. This dose is an equivocal NOAEL/LOAEL. The high dose is a clear LOAEL for both responses.

As discussed previously there is no way of knowing whether the low doses in the Cebrian et al. (1983), Southwick et al. (1983) and Hindmarsh et al. (1977) studies are NOAELs for skin lesions and/or abnormal nerve conduction. However, because the next higher dose in the Southwick and Hindmarsh studies only shows marginal effects at doses 3-7 times higher, the Agency feels comfortable in assigning the low doses in these studies as NOAELs.

The Tseng (1977) and Tseng et al. (1968) studies are therefore considered superior for the purposes of developing an RfD and show a NOAEL for a sensitive endpoint. Even discounting the

people < 20 years of age, the control group consisted of 957 people that had a lengthy exposure to arsenic with no evidence of skin lesions.

The following is a summary of the defined doses in mg/kg-day from the principal and supporting studies:

- 1) Tseng (1977): NOAEL = 8E-4; LOAEL = 1.4E-2
- 2) Cebrian et al. (1983): NOAEL = 4E-4; LOAEL = 2.2E-2
- 3) Southwick et al. (1983): NOAEL = 9E-4; LOAEL = none (equivocal effects at 6E-3)
- 4) Hindmarsh et al., 1977: NOAEL = 7E-4; LOAEL = 1.9E-2 (equivocal effects at 2E-3)

___I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The UF of 3 is to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals.

MF — None

___I.A.4. Additional Studies/Comments (Oral RfD)

Ferm and Carpenter (1968) produced malformations in 15-day hamster fetuses via intravenous injections of sodium arsenate into pregnant dams on day 8 of gestation at dose levels of 15, 17.5, or 20 mg/kg bw. Exencephaly, encephaloceles, skeletal defects and genitourinary systems defects were produced. These and other terata were produced in mice and rats all at levels around 20 mg/kg bw. Minimal effects or no effects on fetal development have been observed in studies on chronic oral exposure of pregnant rats or mice to relatively low levels of arsenic via drinking water (Schroeder and Mitchner, 1971). Nadeenko et al. (1978) reported that intubation of rats with arsenic solution at a dose level of 25 ug/kg/day for a period of 7 months, including pregnancy, produced no significant embryotoxic effects and only infrequent slight expansion of ventricles of the cerebrum, renal pelvis and urinary bladder. Hood et al. (1977) reported that very high single oral doses of arsenate solutions (120 mg/kg) to pregnant mice were necessary to cause prenatal fetal toxicity, while multiple doses of 60 mg/kg on 3 days had little effect.

Extensive human pharmacokinetic, metabolic, enzymic and long-term information is known about arsenic and its metabolism. Valentine et al. (1987) established that human blood arsenic levels did not increase until daily water ingestion of arsenic exceeded approximately 250 ug/day (approximately 120 ug of arsenic/L. Methylated species of arsenic are successively 1 order of magnitude less toxic and less teratogenic (Marcus and Rispin, 1988). Some evidence suggests that inorganic arsenic is an essential nutrient in goats, chicks, minipigs and rats (NRC, 1989). No comparable data are available for humans.

___I.A.5. Confidence in the Oral RfD

Study — Medium

Database — Medium

RfD — Medium

Confidence in the chosen study is considered medium. An extremely large number of people were included in the assessment (> 40,000) but the doses were not well-characterized and other contaminants were present. The supporting human toxicity database is extensive but somewhat

flawed. Problems exist with all of the epidemiological studies. For example, the Tseng studies do not look at potential exposure from food or other source. A similar criticism can be made of the Cebrian et al. (1983) study. The U.S. studies are too small in number to resolve several issues. However, the database does support the choice of NOAEL. It garners medium confidence. Medium confidence in the RfD follows.

__I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

This analysis has been reviewed by EPA's Risk Assessment Council on 11/15/1990. This assessment was discussed by the Risk Assessment Council of EPA on 11/15/1990 and verified through a series of meetings during the 1st, 2nd and 3rd quarters of FY91.

Other EPA Documentation — U.S. EPA, 1984, 1988

Agency Work Group Review — 03/24/1988, 05/25/1988, 03/21/1989, 09/19/1989, 08/22/1990, 09/20/1990

Verification Date — 11/15/1990

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Arsenic (inorganic) conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

__I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Arsenic, inorganic
CASRN — 7440-38-2

Not available at this time.

__II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Arsenic, inorganic
CASRN — 7440-38-2
Last Revised — 04/10/1998

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking

water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79): 17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

_II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Classification — A; human carcinogen

Basis — based on sufficient evidence from human data. An increased lung cancer mortality was observed in multiple human populations exposed primarily through inhalation. Also, increased mortality from multiple internal organ cancers (liver, kidney, lung, and bladder) and an increased incidence of skin cancer were observed in populations consuming drinking water high in inorganic arsenic.

__II.A.2. Human Carcinogenicity Data

Sufficient. Studies of smelter worker populations (Tacoma, WA; Magma, UT; Anaconda, MT; Ronnskar, Sweden; Saganoseki-Machii, Japan) have all found an association between occupational arsenic exposure and lung cancer mortality (Enterline and Marsh, 1982; Lee-Feldstein, 1983; Axelson et al., 1978; Tokudome and Kuratsune, 1976; Rencher et al., 1977). Both proportionate mortality and cohort studies of pesticide manufacturing workers have shown an excess of lung cancer deaths among exposed persons (Ott et al., 1974; Mabuchi et al., 1979). One study of a population residing near a pesticide manufacturing plant revealed that these residents were also at an excess risk of lung cancer (Matanoski et al., 1981). Case reports of arsenical pesticide applicators have also corroborated an association between arsenic exposure and lung cancer (Roth, 1958).

A cross-sectional study of 40,000 Taiwanese exposed to arsenic in drinking water found significant excess skin cancer prevalence by comparison to 7500 residents of Taiwan and Matsu who consumed relatively arsenic-free water (Tseng et al., 1968; Tseng, 1977). Although this study demonstrated an association between arsenic exposure and development of skin cancer, it has several weaknesses and uncertainties, including poor nutritional status of the exposed populations, their genetic susceptibility, and their exposure to inorganic arsenic from non-water sources, that limit the study's usefulness in risk estimation. Dietary inorganic arsenic was not considered nor was the potential confounding by contaminants other than arsenic in drinking water. There may have been bias of examiners in the original study since no skin cancer or preneoplastic lesions were seen in 7500 controls; prevalence rates rather than mortality rates are the endpoint; and furthermore there is concern of the applicability of extrapolating data from Taiwanese to the U.S. population because of different background rates of cancer, possibly genetically determined, and differences in diet other than arsenic (e.g., low protein and fat and high carbohydrate) (U.S. EPA, 1988).

A prevalence study of skin lesions was conducted in two towns in Mexico, one with 296 persons exposed to drinking water with 0.4 mg/L arsenic and a similar group with exposure at 0.005 mg/L. The more exposed group had an increased incidence of palmar keratosis, skin hyperpigmentation and hypopigmentation, and four skin cancers (histologically unconfirmed) (Cebrian et al. (1983). The association between skin cancer and arsenic is weak because of the small number of cases,

small cohort size, and short duration follow-up; also there was no unexposed group in either town. No excess skin cancer incidence has been observed in U.S. residents consuming relatively high levels of arsenic in drinking water but the numbers of exposed persons were low (Morton et al., 1976; Southwick et al., 1981). Therapeutic use of Fowler's solution (potassium arsenite) has also been associated with development of skin cancer and hyperkeratosis (Sommers and McManus, 1953; Fierz, 1965); several case reports implicate exposure to Fowler's solution in skin cancer development (U.S. EPA, 1988).

Several follow-up studies of the Taiwanese population exposed to inorganic arsenic in drinking water showed an increase in fatal internal organ cancers as well as an increase in skin cancer. Chen et al. (1985) found that the standard mortality ratios (SMR) and cumulative mortality rates for cancers of the bladder, kidney, skin, lung and liver were significantly greater in the Blackfoot disease endemic area of Taiwan when compared with the age adjusted rates for the general population of Taiwan. Blackfoot disease (BFD, an endemic peripheral artery disease) and these cancers were all associated with high levels of arsenic in drinking water. In the endemic area, SMRs were greater in villages that used only artesian well water (high in arsenic) compared with villages that partially or completely used surface well water (low in arsenic). However, dose-response data were not developed (Chen et al. 1985).

A retrospective case-control study showed a significant association between duration of consuming high-arsenic well water and cancers of the liver, lung and bladder (Chen et al., 1986). In this study, cancer deaths in the Blackfoot disease endemic area between January 1980 and December 1982 were chosen for the case group. About 90% of the 86 lung cancers and 95 bladder cancers in the registry were histologically or cytologically confirmed and over 70% of the liver cancers were confirmed by biopsy or α -fetoprotein presence with a positive liver x-ray image. Only confirmed cancer cases were included in the study. A control group of 400 persons living in the same area was frequency-matched with cases by age and sex. Standardized questionnaires of the cases (by proxy) and controls determined the history of artesian well water use, socioeconomic variables, disease history, dietary habits, and lifestyle. For the cancer cases, the age-sex adjusted odds ratios were increased for bladder (3.90), lung (3.39), and liver (2.67) cancer for persons who had used artesian well water for 40 or more years when compared with controls who had never used artesian well water. Similarly, in a 15-year study of a cohort of 789 patients of Blackfoot disease, an increased mortality from cancers of the liver, lung, bladder and kidney was seen among BFD patients when compared with the general population in the endemic area or when compared with the general population of Taiwan. Multiple logistic regression analysis to adjust for other risk factors including cigarette smoking did not markedly affect the exposure-response relationships or odds ratios (Chen et al., 1988).

A significant dose-response relationship was found between arsenic levels in artesian well water in 42 villages in the southwestern Taiwan and age-adjusted mortality rates from cancers at all sites, cancers of the bladder, kidney, skin, lung, liver and prostate (Wu et al., 1989). An ecological study of cancer mortality rates and arsenic levels in drinking water in 314 townships in Taiwan also corroborated the association between arsenic levels and mortality from the internal cancers (Chen and Wang, 1990).

Chen et al. (1992) conducted a recent analysis of cancer mortality data from the arsenic-exposed population to compare risk of various internal cancers and compare risk between males and females. The study area and population have been described by Wu et al. (1989). It is limited to 42 southwestern coastal villages where residents have used water high in arsenic from deep artesian wells for more than 70 years. Arsenic levels in drinking water ranged from 0.010 to 1.752 ppm. The study population had 898,806 person-years of observation and 202 liver cancer, 304 lung cancer, 202 bladder cancer and 64 kidney cancer deaths. The study population was stratified into four groups according to median arsenic level in well water (< 0.10 ppm, 0.10-0.29 ppm, 0.30-0.59 ppm and 60+ ppm), and also stratified into four age groups (< 30 years, 30-

49 years, 50-69 years and 70+ years). Mortality rates were found to increase significantly with age for all cancers and significant dose- response relationships were observed between arsenic level and mortality from cancer of the liver, lung, bladder and kidney in most age groups of both males and females. The data generated by Chen et al. (1992) provide evidence for an association of the levels of arsenic in drinking water and duration of exposure with the rate of mortality from cancers of the liver, lung, bladder, and kidney. Dose-response relationships are clearly shown by the tabulated data (Tables II-V of Chen et al., 1992). Previous studies summarized in U.S. EPA (1988) showed a similar association in the same Taiwanese population with the prevalence of skin cancers (which are often non-fatal). Bates et al. (1992) and Smith et al. (1992) have recently reviewed and evaluated the evidence for arsenic ingestion and internal cancers.

__II.A.3. Animal Carcinogenicity Data

Inadequate. There has not been consistent demonstration of carcinogenicity in test animals for various chemical forms of arsenic administered by different routes to several species (IARC, 1980). Furst (1983) has cited or reviewed animal carcinogenicity testing studies of nine inorganic arsenic compounds in over nine strains of mice, five strains of rats, in dogs, rabbits, swine and chickens. Testing was by the oral, dermal, inhalation, and parenteral routes. All oxidation states of arsenic were tested. No study demonstrated that inorganic arsenic was carcinogenic in animals. Dimethylarsonic acid (DMA), the end metabolite predominant in humans and animals, has been tested for carcinogenicity in two strains of mice and was not found positive (Innes et al., 1969); however, this was a screening study and no data were provided. The meaning of non-positive data for carcinogenicity of inorganic arsenic is uncertain, the mechanism of action in causing human cancer is not known, and rodents may not be a good model for arsenic carcinogenicity testing. There are some data to indicate that arsenic may produce animal lung tumors if retention time in the lung can be increased (Pershagen et al., 1982, 1984).

__II.A.4. Supporting Data for Carcinogenicity

A retrospective cohort mortality study was conducted on 478 British patients treated between 1945-1969 with Fowler's solution (potassium arsenite). The mean duration of treatment was 8.9 months and the average total oral consumption of arsenic was about 1890 mg (daily dose x duration). In 1980, 139 deaths had occurred. No excess deaths from internal cancers were seen after this 20-year follow-up. Three bladder cancer deaths were observed (1.19 expected, SMR 2.5) (Cuzick et al., 1982). A recent follow-up (Cuzick et al., 1992) indicated no increased mortality from all cancers but a significant excess from bladder cancer (5 cases observed/1.6 expected; SMR of 3.07). A subset of the original cohort (143 persons) had been examined by a dermatologist in 1970 for signs of arsenicism (palmar keratosis). In 1990, there were 80 deaths in the subcohort and 11 deaths from internal cancers. All 11 subjects had skin signs (keratosis-10, hyperpigmentation-5 and skin cancer-3). A case-control study of the prevalence of palmar keratoses in 69 bladder cancer patients, 66 lung cancer patients and 218 hospital controls (Cuzick et al., 1984), indicated an association between skin keratosis (as an indicator of arsenic exposure) and lung and bladder cancer. Above the age of 50, 87% of bladder cancer patients and 71% of lung cancer patients but only 36% of controls had one or more keratoses. Several case reports implicate internal cancers with arsenic ingestion or specifically with use of Fowler's solution but the associations are tentative (U.S. EPA, 1988).

Sodium arsenate has been shown to transform Syrian hamster embryo cells (Dipaolo and Casto, 1979) and to produce sister chromatid-exchange in DON cells, CHO cells, and human peripheral lymphocytes exposed in vitro (Wan et al., 1982; Ohno et al., 1982; Larramendy et al., 1981; Andersen, 1983; Crossen, 1983). Jacobson-Kram and Montalbano (1985) have reviewed the mutagenicity of inorganic arsenic and concluded that inorganic arsenic is inactive or very weak for induction of gene mutations in vitro but it is clastogenic with trivalent arsenic being an order of magnitude more potent than pentavalent arsenic.

Both the pentavalent and trivalent forms of inorganic arsenic are found in drinking water. In both animals and humans, arsenate (As+5) is reduced to arsenite (As+3) and the trivalent form is methylated to give the metabolites monomethylarsinic acid (MMA) and dimethylarsinic acid (DMA) (Vahter and Marafante, 1988). The genotoxicity of arsenate (As+5) and arsenite (As+3) and the two methylated metabolites, MMA and DMA were compared in the thymidine kinase forward mutation assay in mouse lymphoma cells (Harrington-Brock et al. 1993; Moore et al., 1995, in press). Sodium arsenite (+3) and sodium arsenate (+5) were mutagenic at concentration of 1-2 ug/mL and 10-14 ug/mL, respectively, whereas MMA and DMA were significantly less potent, requiring 2.5-5 mg/mL and 10 mg/mL, respectively, to induce a genotoxic response. Based on small colony size the mutations induced were judged chromosomal rather than point mutations. The authors have previously shown that for chemicals having clastogenic activity (i.e., cause chromosomal mutations), the mutated cells grow more slowly than cells with single gene mutations and this results in small colony size. In the mouse lymphoma assay, chromosomal aberrations were seen at approximately the same arsenic levels as TK forward mutations. Arsenate, arsenite and MMA were considered clastogenic but the aberration response with DMA was insufficient to consider it a clastogen. Since arsenic exerts its genotoxicity by causing chromosomal mutations, it has been suggested by the above authors that it may act in a latter stage of carcinogenesis as a progressor, rather than as a classical initiator or promotor (Moore et al., 1994). A finding which supports this process is that arsenate (8-16 uM) and arsenite (3 uM) have been shown to induce 2-10 fold amplification of the dihydrofolate reductase gene in culture in methotrexate resistant 3T6 mouse cells (Lee et al., 1988). Although the mechanism of induction in rodent cells is not known, gene amplification of oncogenes is observed in many human tumors. Inorganic arsenic has not been shown to mutate bacterial strains, it produces preferential killing of repair deficient strains (Rossman, 1981). Sodium arsenite (As+3) induces DNA-strand breaks which are associated with DNA-protein crosslinks in cultured human fibroblasts at 3 mM but not 10 mM (Dong and Luo, 1993) and it appears that arsenite inhibits the DNA repair process by inhibiting both excision and ligation (Jha et al., 1992; Lee-Chen et al., 1993).

The inhibitory effect of arsenite on strand-break rejoining during DNA repair was found to be reduced by adding glutathione to cell cultures (Huang et al., 1993). The cytotoxic effects of sodium arsenite in Chinese hamster ovary cells also has also found to correlate with the intracellular glutathione levels (Lee et al., 1989).

In vivo studies in rodents have shown that oral exposure of rats to arsenate (As+5) for 2-3 weeks resulted in major chromosomal abnormalities in bone marrow (Datta et al., 1986) and exposure of mice to As (+3) in drinking water for 4 weeks (250 mg As/L as arsenic trioxide) caused chromosomal aberrations in bone marrow cells but not spermatogonia (Poma et al., 1987); micronuclei in bone marrow cells were also induced by intraperitoneal dosing of mice with arsenate (DeKnudt et al., 1986; Tinwell et al., 1991). Chromosomal aberrations and sister chromatid exchange have been seen in patients exposed to arsenic from treatment with Fowler's solution (Burgdorf et al., 1977) and subjects exposed occupationally (Beckman et al., 1977) but no increase in either endpoint was seen in lymphocytes of subjects exposed to arsenic in drinking water (Vig et al., 1984).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 1.5E+0 per (mg/kg)/day

Drinking Water Unit Risk — 5E-5 per (ug/L)

Extrapolation Method — Time- and dose-related formulation of the multistage model (U.S. EPA, 1988)

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E+0 ug/L
E-5 (1 in 100,000)	2E-1 ug/L
E-6 (1 in 1,000,000)	2E-2 ug/L

__II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

The Risk Assessment Forum has completed a reassessment of the carcinogenicity risk associated with ingestion of inorganic arsenic (U.S. EPA, 1988). The data provided in Tseng et al., 1968 and Tseng, 1977 on about 40,000 persons exposed to arsenic in drinking water and 7500 relatively unexposed controls were used to develop dose-response data. The number of persons at risk over three dose intervals and four exposure durations, for males and females separately, were estimated from the reported prevalence rates as percentages. It was assumed that the Taiwanese persons had a constant exposure from birth, and that males consumed 3.5 L drinking water/day and females consumed 2.0 L/day. Doses were converted to equivalent doses for U.S. males and females based on differences in body weights and differences in water consumption and it was assumed that skin cancer risk in the U.S. population would be similar to the Taiwanese population. The multistage model with time was used to predict dose-specific and age-specific skin cancer prevalence rates associated with ingestion of inorganic arsenic; both linear and quadratic model fitting of the data were conducted. The maximum likelihood estimate (MLE) of skin cancer risk for a 70 kg person drinking 2 L of water per day ranged from 1E-3 to 2E-3 for an arsenic intake of 1 ug/kg/day. Expressed as a single value, the cancer unit risk for drinking water is 5E-5 per (ug/L). Details of the assessment are in U.S. EPA (1988).

Dose response data have not been developed for internal cancers for the Taiwanese population. The data of Chen et al. (1992) are considered inadequate at present.

__II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Eastern Research Group, under contract to EPA, convened an Expert Panel on Arsenic Carcinogenicity on May 21 and 22, 1997 (Eastern Research Group, 1997). The Expert Panel believed that, "it is clear from epidemiological studies that arsenic is a human carcinogen via the oral and inhalation routes (p. 20)." They also concluded, "that one important mode of action is unlikely to be operative for arsenic". The panel agreed that arsenic and its metabolites do not appear to directly interact with DNA (pp. 30-31)." In addition, the panel agreed that, "for each of the modes of action regarded as plausible, the dose-response would either show a threshold or would be nonlinear (p. 31)". The panel agreed, however, "that the dose-response for arsenic at low doses would likely be truly nonlinear, i.e., with a decreasing slope as the dose decreased. However, at very low doses such a curve might be linear but with a very shallow slope, probably indistinguishable from a threshold (p. 31)."

__II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

This assessment is based on prevalence of skin cancer rather than mortality because the types of skin cancer studied are not normally fatal. However, competing mortality from Blackfoot disease in

the endemic area of Taiwan would cause the risk of skin cancer to be underestimated. Other sources of inorganic arsenic, in particular those in food sources have not been considered because of lack of reliable information. There is also uncertainty on the amount of water consumed/day by Taiwanese males (3.5 L or 4.5 L) and the temporal variability of arsenic concentrations in specific wells was not known. The concentrations of arsenic in the wells was measured in the early 1960s and varied between 0.01 and 1.82 ppm. For many villages 2 to 5 analyses were conducted on well water and for other villages only one analysis was performed; ranges of values were not provided. Since tap water was supplied to many areas after 1966, the arsenic-containing wells were only used in dry periods. Because of the study design, particular wells used by those developing skin cancer could not be identified and arsenic intake could not be assigned except by village. Several uncertainties in exposure measurement reliability existed and subsequent analysis of drinking water found fluorescent substances in water that are possible confounders or caused synergistic effects. Uncertainties have been discussed in detail in U.S. EPA (1988). Uncertainties in exposure measurement can affect the outcome of dose- response estimation.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 4.3E-3 per (ug/cu.m)

Extrapolation Method — absolute-risk linear model

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E-2 ug/cu.m
E-5 (1 in 100,000)	2E-3 ug/cu.m
E-6 (1 in 1,000,000)	2E-4 ug/cu.m

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type — lung cancer

Test animals — human, male

Route — inhalation, occupational exposure

Reference — Brown and Chu, 1983a,b,c; Lee-Feldstein, 1983; Higgins, 1982; Enterline and Marsh, 1982

Ambient Unit Risk Estimates (per µg/cu.m)				
Exposure Source	Study	Unit Risk	Geometric Mean Unit Risk	Final Estimated Geometric Mean Unit Risk
Anaconda smelter	Brown and Chu	1.25E-3	2.56E-3	4.29E-3
	Lee-Feldstein	2.80E-3		
	Higgins et al.	4.90E-3		
ASARCO smelter	Enterline & Marsh	6.81E-3 7.60E-3	7.19E-3	4.29E-3

__II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

A geometric mean was obtained for data sets obtained with distinct exposed populations (U.S. EPA, 1984). The final estimate is the geometric mean of those two values. It was assumed that the increase in age-specific mortality rate of lung cancer was a function only of cumulative exposures.

The unit risk should not be used if the air concentration exceeds 2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

__II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Overall a large study population was observed. Exposure assessments included air measurements for the Anaconda smelter and both air measurements and urinary arsenic for the ASARCO smelter. Observed lung cancer incidence was significantly increased over expected values. The range of the estimates derived from data from two different exposure areas was within a factor of 6.

_II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

__II.D.1. EPA Documentation

U.S. EPA. 1984, 1988, 1993

A draft of the 1984 Health Assessment Document for Inorganic Arsenic was independently reviewed in public session by the Environmental Health Committee of the U.S. EPA Science Advisory Board on September 22-23, 1983. A draft of the 1988 Special Report on Ingested Inorganic Arsenic; Skin Cancer; Nutritional Essentiality was externally peer reviewed at a two-day workshop of scientific experts on December 2-3, 1986. A draft of the Drinking Water Criteria Document for Arsenic was reviewed by the Drinking Water Committee of the U.S. EPA Science Advisory Board on March 10, 1993. The comments from these reviews were evaluated and considered in the revision and finalization of these reports.

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 01/13/1988, 12/07/1989, 02/03/1994

Verification Date — 02/03/1994

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Arsenic (inorganic) conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

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Note: A TOXICOLOGICAL REVIEW is available for this chemical in Adobe PDF Format (116 Pages, 786 Kbytes). Similar documents can be found in the List of Available IRIS Toxicological Reviews.

Links to specific pages in the toxicological review are available throughout this summary. To utilize this feature, your Web browser and Adobe program must be configured properly so the PDF displays within the browser window. If your browser and Adobe program need configuration, please go to EPA's PDF page for instructions.

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Naphthalene; CASRN 91-20-3 (09/17/1998)

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Naphthalene

File First On-Line 12/01/1990

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	On-line	09/17/1998
Inhalation RfC Assessment (I.B.)	On-line	09/17/1998
Carcinogenicity Assessment (II.)	On-line	09/17/1998

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Naphthalene

CASRN — 91-20-3

Last Revised — 09/17/1998

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

__I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased mean terminal body weight in males	NOAEL: 100 mg/kg-day; 71 mg/kg-day (adjusted)	3000	1	2E-2 mg/kg-day
Subchronic oral rat study				
BCL, 1980a	LOAEL: 200 mg/kg-day; 142 mg/kg-day (adjusted)			

*Conversion Factors and Assumptions — MW = 128.19. Duration adjustment (5/7) of the doses (100, 200 mg/kg-day) arrived at a critical NOAEL/LOAEL pair of 71 and 143 mg/kg-day for decreased mean terminal body weight in male rats.

__I.A.2. Principal and Supporting Studies (Oral RfD)

Battelle's Columbus Laboratories (BCL). (1980a) Unpublished subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Prepared by Battelle Laboratories under NTP Subcontract No. 76-34-106002.

Naphthalene (> 99% pure) in corn oil was administered by gavage to groups of 10 male and 10 female Fischer 344 rats at dose levels of 0, 25, 50, 100, 200, or 400 mg/kg (duration-adjusted 0, 17.9, 35.7, 71.4, 142.9, and 285.7 mg/kg-day), 5 days/week for 13 weeks (BCL, 1980a). Measured parameters included food consumption and body weight weekly, twice-daily observation for clinical signs of toxicity, hematological parameters for blood collected at termination (hemoglobin, hematocrit, total and differential white blood cell count, red blood cell count, mean cell volume, mean cell hemoglobin concentration), necropsy of all rats in the study, and complete histopathological examination of 27 organs and tissues (including the eyes, lungs, stomach, liver, kidney, reproductive organs, thymus, and kidney) from all control and 400-mg/kg rats. Male kidneys and female thymuses from the 200-mg/kg group were also examined histopathologically (according to the histopathology tables; however, the report text states that the 100-mg/kg group was examined). Organ weight data were not reported.

At the highest dose level, two males died during the last week of treatment, and rats of both sexes displayed diarrhea, lethargy, hunched posture, and rough coats at intermittent intervals throughout the study (BCL, 1980a). Food consumption was not affected by exposure, but mean

decreases in terminal body weight greater than 10% compared with control values were found in several groups of exposed rats (over the 13-week period); namely, 23% depression in females at 400 mg/kg and a 29% and 12% depression in males at 400 and 200 mg/kg-day, respectively. Differences between mean values of hematological parameters in exposed groups and control groups were < 10% of control values, except for a 94% increase in numbers of mature neutrophils and a 25.1% decrease in numbers of lymphocytes in male 400-mg/kg rats and a 37.2% increase in mature neutrophils in 400-mg/kg females. Histological examinations revealed low incidences of lesions in exposed male kidneys and exposed female thymuses; no lesions were observed in respective control kidneys or thymuses. Lesions such as focal cortical lymphocytic infiltration or focal tubular regeneration were observed in kidneys of 2/10 male rats exposed to 200 mg/kg naphthalene, and diffuse renal tubular degeneration occurred in 1/10 male rats exposed to 400 mg/kg naphthalene. Other lesions include lymphoid depletion of the thymus, which occurred in 2/10 females exposed to 400 mg/kg naphthalene, but not in any other females. No other tissue lesions were detected. Decreased body weight was the most sensitive effect noted in this study and was identified as the most appropriate critical effect for the purposes of RfD derivation. Mean terminal body weight decreases greater than 10% compared with control values were found in male rats following a 90-day gavage exposure to 200 mg/kg-day (LOAEL). The NOAEL for a > 10% decrease in body weight in this study was 100 mg/kg-day (71 mg/kg-day duration-adjusted).

Shopp, GM; White, KL, Jr.; Holsapple, MP; et al. (1984) Naphthalene toxicity in CD-1 mice: general toxicology and immunotoxicology. *Fundam Appl Toxicol* 4(3 pt 1):406-419.

Groups of male and female albino CD-1 mice (approximately 6 weeks old at the start) were administered gavage doses of 0, 5.3, 53, or 133 mg/kg naphthalene (99.3% pure) in corn oil for 90 consecutive days (Shopp et al., 1984). A naive control group and the 5.3- and 53-mg/kg dose groups each contained 76 male mice and 40 female mice. The vehicle control group contained 112 male mice and 76 female mice. The high-dose group contained 96 male mice and 60 female mice. Significant chemical-related decreases in terminal body weights or survival were not observed in either sex. No significant alterations in absolute or relative organ weights occurred in exposed male mice. Significant decreases in absolute weights of brain, liver, and spleen and relative weight of spleen occurred in high-dose females; however, organ-to-body weight ratios were significantly different only for the spleen. Histopathological examination of organs was not conducted, but the authors noted that cataracts were not formed in exposed mice (methods used to assess the presence of cataracts were not specified). Examination of hematological parameters (including numbers of leukocytes, erythrocytes, and platelets and determination of hematocrit and hemoglobin) at termination revealed only slight, but statistically significant, increases in hemoglobin in high-dose females only; however, the hematological data were not shown in the report. Chemical analysis of serum showed statistically significant decreased blood urea nitrogen in all exposed female groups, and increased serum globulin and protein in the two highest female dose groups. In the same study, no exposure-related responses were found in a battery of immunological assays (humoral immune response, lymphocyte responsiveness, delayed-type hypersensitivity response, popliteal lymph node response, and bone marrow function); immunotoxic responses were observed in positive controls given intraperitoneal injections of 50 mg/kg cyclophosphamide on days 87, 88, 89, and 90. The study identified a LOAEL of 133 mg/kg-day and a NOAEL of 53 mg/kg-day with significant decreases in absolute weight of brain, liver, and spleen and relative weight of spleen in high-dose females. Therefore, the LOAEL of 133 mg/kg-day is based on the observed organ effects, especially the decrease in the relative weight of the spleen along with the suggestive evidence for effects on hepatic enzyme function. The toxicological significance of the statistically significant alterations in hematological and serum chemical parameters is not clear.

The use of the BCL (1980a) study in deriving the RfD was based on the following reasons:

The verification of the chemical dose, animal maintenance, and study design (10 rats/sex/dose

group for 5 dose groups and 1 control group) are consistent with GLP guidelines submitted for 90-day studies, unlike the Shopp et al. (1984) study, in which the numbers of animals actually evaluated compared to those exposed for most endpoints (organ weights, clinical chemistry, and immunological testing) were small.

The decrease in mean terminal body weight in the BCL (1980a) study was not a result of decreased food consumption and was accompanied by clinical signs (diarrhea, lethargy, and rough coats) consistent with sick animals.

Decreases in mean terminal body weight of at least 10% were observed in females and males in the case of the BCL (1980a) study, unlike the Shopp et al. (1984) study, in which no significant changes in body weight were reported at any dose level.

The statistically significant alterations ($p < 0.05$) observed in the absolute (brain, liver, and spleen) and relative weight (spleen) of some organs in the absence of any decrease in body weight (Shopp et al., 1984) is not consistent with the absence of lesions and the lack of significant alterations in the clinical chemistry data, hematology, mixed-function oxidase activity, or the immunotoxicity assays for either sex.

Although the gross and histopathological examination was limited to the control and high-dose group in the BCL (1980a) study, renal lesions of low incidence were observed in the kidneys (focal cortical lymphocytic infiltration, focal and diffuse tubular regeneration) and thymus (lymphoid depletion) in males and females, respectively, at 100 mg/kg (71 mg/kg-day), unlike the Shopp et al. (1984) study, in which gross necropsy (no histopathological examination of tissues) on a randomly selected number of animals revealed no lesions.

___I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 3000.

The duration-adjusted NOAEL for terminal body weight decrease (> 10% of control) in male rats from the BCL (1980a) 90-day gavage study, 71 mg/kg-day, was divided by an uncertainty factor of 3000 (10 to extrapolate from rats to humans, 10 to protect sensitive humans, 10 to extrapolate from subchronic to chronic exposure, and 3 for database deficiencies including the lack of chronic oral exposure studies and 2-generation reproductive toxicity studies) to arrive at a chronic RfD for naphthalene of 2E-2 mg/kg-day.

MF = 1.

___I.A.4. Additional Studies/Comments (Oral RfD)

In deriving the RfD additional studies were evaluated for a variety of critical effects. Nervous system depression in pregnant rats (NTP, 1991) occurring at a lower dose (50 mg/kg-day), was judged to be nonadverse, because the effect was considered to be transient in nature. Data from studies of mice exposed acutely to injections of naphthalene, or 1- or 2-methylnaphthalene (Buckpitt and Franklin, 1989), or chronically to 1- or 2-methylnaphthalene in the diet (Murata et al., 1993, 1997) provide suggestive evidence that chronic oral exposure to naphthalene at low doses may produce lung injury. However, deriving an RfD for naphthalene based on the methylnaphthalene data was judged to be too uncertain, because of metabolic differences between naphthalene and methylnaphthalenes and the absence of lung injury in subchronic oral studies in rats (BCL, 1980a) and mice with naphthalene (BCL, 1980b; Shopp et al., 1984).

A benchmark dose (BMD) approach to modeling the male rat body weight data fits mathematical models for a continuous variable to the data using maximum likelihood methods (see Appendix B to

the Toxicological Review of Naphthalene, "Benchmark Dose Calculations"). In this approach, maximum likelihood estimates (MLEs) of dose (with no duration adjustment) associated with a 10% decrease in mean body weight compared with nonexposure conditions were 171 and 172 mg/kg-day using a polynomial and power model, respectively; respective 95% confidence lower limits on these doses, taken as BMDs, were 130 and 135 mg/kg-day. Assuming that either of these BMDs are surrogates for NOAELs, as suggested by the analysis of developmental toxicity data by Allen et al. (1994a,b) and Kavlock et al. (1995), making duration adjustments (BMD x 5/7) and applying the same 3000 uncertainty factor used for the NOAEL/LOAEL approach arrives at a prospective RfD for naphthalene, $3E-2$ mg/kg-day, that is comparable to the RfD derived with the NOAEL/LOAEL approach.

Benchmark dose approaches to deriving a chronic RfD for naphthalene were also examined using data for maternal body weight decreases in the NTP (1991) rat developmental toxicity study and data for lung proteinosis in mice exposed for 81 weeks to 1-methylnaphthalene in the diet (Murata et al., 1993). Decreased maternal body weight was not selected as the basis of chronic RfD derivation because the pregnant rats were exposed for only a small percentage of their lives. As discussed earlier, deriving the naphthalene RfD based on 1-methylnaphthalene data was judged to be too uncertain because of metabolic differences between naphthalene and methylnaphthalenes and the absence of lung injury in rats and mice orally exposed to naphthalene for subchronic periods.

The benchmark methodology for naphthalene is contained within an appendix of the Toxicological Review for the readers' information, however it was decided to use the LOAEL/NOAEL approach rather than the benchmark approach in the derivation of the RfD/RfC.

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).

___I.A.5. Confidence in the Oral RfD

Study — High
Database — Low
RfD — Low

The principal study was given a high confidence rating because adequate numbers of animals were included and experimental protocols were adequately designed, conducted, and reported. Confidence in the database was rated low because of the lack of adequate chronic oral data for naphthalene; the lack of any dose-response data for naphthalene-induced hemolytic anemia, probably one of the most well-known health Hazards to humans exposed to naphthalene; and the lack of two-generation reproductive toxicity studies. Humans exposed via inhalation, combined inhalation and dermal exposure, and combined inhalation and oral exposure have developed hemolytic anemia. Hemolytic anemia is characterized by findings of lowered hemoglobin, hematocrit, and erythrocyte values, elevated reticulocyte counts, Heinz bodies, elevated serum bilirubin, and fragmentation of erythrocytes. In severe cases, the hemolytic anemia was accompanied by jaundice, high serum levels of bilirubin, cyanosis, and kernicterus with pronounced neurological signs. Neither oral nor inhalation exposure levels were available in human studies reporting anemia (Melzer-Lange and Walsh-Kelly, 1989; Owa, 1989; Owa et al., 1993). Infants deficient in G6PDH are thought to be especially sensitive to naphthalene-induced hemolytic anemia. Resulting confidence in the RfD is low. A quantitative comparison of the acute dog study (7 days at 262 mg/kg-day; free-standing LOAEL of 262 mg/kg-day based hemolytic anemia) with the RfD (chronic oral rat study based on decrease in mean terminal body weight) to determine whether the RfD is protective of hemolytic anemia in humans is not possible since adequate dose-response data in a subchronic or chronic dog study are lacking. Therefore, because of the absence of an appropriate animal model one cannot extrapolate either

qualitatively or quantitatively to humans with respects to hemolytic anemia.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).

__I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 1998

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included in an appendix to the Toxicological Review of Naphthalene in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Other EPA Documentation — U.S. EPA, 1980, 1986, 1987a, 1988

Agency Consensus Date - 07/01/98

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

__I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Naphthalene

CASRN — 91-20-3

Last Revised — 09/17/1998

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/m³. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F, August 1989), and subsequently according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F, October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

__I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	MF	RfC
Nasal effects: hyperplasia	NOAEL: None	3000	1	3E-3 mg/m ³

and metaplasia in respiratory and olfactory epithelium, respectively

LOAEL(HEC): 9.3 mg/m³

Chronic mouse inhalation study

NTP, 1992a

*Conversion Factors and Assumptions — Following the Category 3 guidance (U.S. EPA, 1994), experimental exposure concentrations of 0, 10, and 30 ppm were converted to 0, 52, and 157 mg/m³, respectively; adjusted to a continuous exposure basis in mg/m³ (6/24 hr x 5/7 days) equals mg/m³ x 0.1786: 0, 9.3, and 28 mg/m³. Because the blood:gas (air) coefficients for naphthalene were not available, the default ratio of 1 was used and the values for the LOAEL(HEC) were 0, 9.3, and 28 mg/m³. Scenario -- The LOAEL human equivalent concentration (HEC) was calculated for an extrarrespiratory effect for a category 3 gas. Since the b:a lambda for humans (h) is unknown, a default value of 1.0 is used for this ratio. LOAEL(HEC) x [b:a lambda(animal)/b:a lambda(human)] = 9.3 mg/m³.

__I.B.2. Principal and Supporting Studies (Inhalation RfC)

National Toxicology Program (NTP). (1992a) Toxicology and carcinogenesis studies of naphthalene in B6C3F1 mice (inhalation studies). Technical Report Series No. 410. NIH Publication No. 92-3141.

B6C3F1 mice (75/sex/group) were exposed to naphthalene (scintillation grade, > 99% pure) at target concentrations of 0, 10, and 30 ppm (0, 52, 157 mg/m³) for 6 hr/day, 5 days/week, for 103 weeks (NTP, 1992a). The duration-adjusted levels were 0, 9.3, and 28 mg/m³, respectively. Additional groups of 75 male and 75 female replacement animals were exposed to 30 ppm to ensure that a sufficient number of mice lived to study termination. Naphthalene vapor was generated by direct sublimation and monitored by a software feedback arrangement. Average weekly concentrations were within 20% of target concentrations, except one week when the mean concentration in the low-concentration chamber was 5.5 ppm. Supplemental hematology studies were scheduled with 25 animals/sex/group, but only the first sacrifice (at 14 days) was conducted because of high mortality in the male control group from fighting. Serial slit-lamp biomicroscopy and indirect ophthalmoscopic examinations were conducted on 5 animals/sex/group at 6-mo intervals. Gross necropsies were conducted on all animals. Complete histopathologic examinations of major tissues were conducted on all animals, except that the only tissues examined from low-concentration animals dying or killed after 21 mo of exposure were the lungs and nasal cavities.

Survival of the male controls was significantly lower than in the exposed males. Reduced survival was related to wound trauma and lesions from increased fighting in this group. Similar effects were not seen in the exposed males, because they tended to huddle in cage corners during exposure periods and so fought less. There was no significant difference in survival between the treatment and control females. There were no treatment-related ocular lesions in the selected mice that underwent ophthalmologic examinations at 6-mo intervals. There were no biologically significant changes in hematology parameters at day 14 of the study. Final mean body weights of the treated animals were within 10% of the corresponding controls.

Inflammation, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium were noted in the noses of virtually all exposed mice of both sexes, but in only one control female mouse. These effects were slightly more severe in the high-concentration group. See Table 1 for incidence data. The lesions were focal or multifocal, occurred mainly in the posterior nasal cavity,

and were minimal to mild in severity. Inflammatory lesions included substantia propria edema, congestion, mixed inflammatory cell infiltrates, necrotic debris, and intraluminal serous to fibrinopurulent exudate. Respiratory epithelial hyperplasia resulted in a thickened, folded, irregular mucosal surface. Olfactory epithelial metaplasia often involved ciliated columnar or pseudocolumnar respiratory-like epithelial cells replacing the usual olfactory cell layer. The lesions were collectively considered features of a generalized inflammatory and regenerative process.

Table 1. Incidence of nonneoplastic respiratory lesions in B6C3F1 mice exposed by inhalation to naphthalene, 6 hr/day, 5 days/week for 2 years

Exposure level/sex (ppm)	Respiratory lesion		
	Inflammation, lung	Hyperplasia, nasal respiratory epithelium	Metaplasia, nasal olfactory epithelium
0/male	0/70	0/70	0/70
0/female	3/69	0/69	0/69
10/male	21/69	66/69	66/69
10/female	13/65	65/65	65/65
30/male	56/135	134/135	134/135
30/female	52/135	135/135	135/135

Source: NTP, 1992a.

Minimal to mild lung lesions, including infiltration of histiocytes or lymphocytes, inflammation, hyperplasia of the alveolar epithelium, and bronchial submucosal gland distension, were observed in both controls and treated mice. The incidence and severity were generally higher in the treated groups of both sexes, but there was no clear concentration-response relationship.

Females in the high-exposure group had elevated incidences of alveolar/bronchiolar adenomas and carcinomas (combined incidence 22%, compared with 7% in the control group and 3% in the low-exposure group). The incidence was also above that of historical controls and was considered compound-related. The incidences of alveolar/bronchiolar adenomas and carcinomas in treated males were marginally increased (10%, 25%, and 23%, in the control, low-concentration, and high-concentration groups, respectively). However, because the increase was not statistically significant and was within the range of historical controls, it was not considered exposure related. Instead, it was attributed to the longer life span of the treated animals. Nasal adenomas occurred in the anterior nasal cavities of two females in the low-concentration group. They were not considered compound related because the increase was not concentration related or statistically significant. Therefore, the nasal lesions discussed above should not be considered preneoplastic.

Calculation of the Human Equivalent Concentration (HEC)

Dose conversion: Because of its low water solubility and low reactivity, naphthalene-related effects on the nasal epithelium are expected to result following absorption of naphthalene and metabolism to reactive oxygenated metabolites, rather than being a result of direct contact. This hypothesis is supported by data on naphthalene metabolism indicating that toxic effects on the respiratory tract are due to a naphthalene metabolite that may be formed either in the liver or in the respiratory tract. For example, necrosis of bronchial epithelial (Clara) cells in mice (O'Brien et al., 1985, 1989; Tong et al., 1981) and necrosis of olfactory epithelium in mice, rats, and hamsters (Plopper et al., 1992) occur following intraperitoneal injection of naphthalene. The nasal effects from inhalation exposure to naphthalene were considered to be extra-respiratory effects of a category 3 gas, as defined in the U.S. EPA guidance for deriving RfCs (U.S. EPA, 1994).

Following this guidance, experimental exposure concentrations were adjusted to a mg/m^3 basis (0, 52, and $157 \text{ mg}/\text{m}^3$), adjusted to a continuous exposure basis ($\text{mg}/\text{m}^3 \times 6\text{h}/24\text{h} \times 5\text{d}/7\text{d} = \text{mg}/\text{m}^3 \times 0.1786$: 0, 9.3, and $28 \text{ mg}/\text{m}^3$), and converted to human equivalent concentrations (HECs) by multiplying the adjusted concentrations by the ratio of mouse:human blood/gas partition coefficients. Because the blood/gas coefficients for naphthalene were not available, the default ratio of 1 was used.

Dose-response modeling: Whereas the data from the NTP (1992a) study show nasal effects to be the most sensitive effects from chronic inhalation exposure to naphthalene, they provide no indication of the shape of the dose-response curve because the incidence of nasal lesions at the lowest exposure level was 100% in females and nearly 100% in males (see Table 1). In this case, application of a BMD approach, in which quantal mathematical models are fit to the incidence data for nasal effects, does not sensibly assist in extrapolating to a NOAEL, and a NOAEL/LOAEL approach was taken for deriving an RfC for naphthalene.

___I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 3000.

The adjusted LOAEL(HEC) of $9.3 \text{ mg}/\text{m}^3$ for nasal effects (hyperplasia in respiratory epithelium and metaplasia in olfactory epithelium) was divided by an uncertainty factor of 3000 (10 to extrapolate from mice to humans, 10 to protect sensitive humans, 10 to extrapolate from a LOAEL to a NOAEL, and 3 for database deficiencies including the lack of a 2-generation reproductive toxicity study and chronic inhalation data for other animal species) to arrive at a chronic RfC for naphthalene of $3\text{E}-3 \text{ mg}/\text{m}^3$.

MF = 1.

___I.B.4. Additional Studies/Comments (Inhalation RfC)

SUPPORTING STUDIES

Human experience with acute accidental exposures to naphthalene identifies the development of hemolytic anemia and cataracts as health Hazards of concern. However, information is not available regarding dose-response relationships for these effects in humans with acute, subchronic, or chronic exposure by any route. Animal inhalation studies are restricted to three studies of mice: a 2-year study (NTP, 1992), a 6-mo study (Adkins et al., 1986), and a 4-hr study (Buckpitt, 1982). Results from the chronic study, supported by the subchronic and acute studies, identify nasal and pulmonary injuries as critical effects from chronic inhalation exposure to naphthalene; effects in other organs or tissues were not found. Incidence data for male and female mice with hyperplasia of the nasal respiratory epithelium, metaplasia of the nasal olfactory epithelium, and chronic pulmonary inflammation clearly show that the nose is more sensitive than the lung to chronic inhalation exposure to naphthalene. At both exposure levels (10 and 30 ppm, 6 hr/day, 5 days/week), > 95% of mice of either sex showed nasal lesions, whereas pulmonary lesions were found in < 1/3 and < 1/2 of mice exposed at 10 and 30 ppm, respectively (Table 1). Nasal lesions in the respiratory and olfactory epithelium in mice found in the NTP (1992a) study were therefore selected as the critical effects for the purpose of RfC derivation.

Adkins et al. (1986) exposed female A/J mice (30/group) to 0, 10, or 30 ppm (0, 52, or $157 \text{ mg}/\text{m}^3$) naphthalene for 6 hr/day, 5 days/week for 6 mo, and counted the number of adenomas in each lung. The duration-adjusted concentrations were 0, 9.2, and $28 \text{ mg}/\text{m}^3$, respectively. Exposure to naphthalene caused increases in the total number of adenomas and the percentage

of animals with adenomas, but the differences were not significant. The number of tumors per tumor-bearing mouse lung was significantly increased at both exposure levels.

Buckpitt (1982) subjected groups of five male mice (Swiss Webster) plus control group to 1-hr exposures to naphthalene concentrations of 0, 52.4, 95.8, 204, or 380 mg/m³. Adverse effects were seen only at the highest concentration, and included swelling of cells and sloughing into the airway lumen of cells from either the major and/or terminal airways. The effects were milder in the presence of cytochrome P450 inhibitor and stronger in the presence of a glutathione depletor, suggesting that cytotoxicity is due to a naphthalene metabolite produced by P450 and that glutathione plays a protective role. Naphthalene reduced glutathione levels in the lung, liver, and kidney, but the concentration-response curve was flat.

Following a single 4-hr exposure of five male and five female Wistar Albino rats to 77.7 ppm (407 mg/m³), closed eyes, lacrimation, and mouth breathing were observed (Bushy Run Research Center, 1986). No signs of toxicity were observed postexposure or during the 14-day observation period, and gross necropsy revealed no exposure-related lesions.

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).

___I.B.5. Confidence in the Inhalation RfC

Study — Medium

Database — Low to Medium

RfC -- Low to Medium

The principal study was given medium confidence because adequate numbers of animals were used, and the severity of nasal effects increased at the higher exposure concentration. However, the study produced high mortality, (< 40% survival in the male control group due to wound trauma and secondary lesions resulting from increased fighting). Also, hematological evaluation was not conducted beyond 14 days. The database was given a low-to-medium confidence rating because there are no chronic or subchronic inhalation studies in other animal species, and there are no reproductive or developmental studies for inhalation exposure. In the absence of human or primate toxicity data, the assumption is made that nasal responses in mice to inhaled naphthalene are relevant to humans; however, it cannot be said with certainty that this RfC for naphthalene based on nasal effects will be protective for hemolytic anemia and cataracts, the more well-known human effects from naphthalene exposure. Medium confidence in the RfC follows.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).

___I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 1998

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included in an appendix to the Toxicological Review of Naphthalene in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). ***[To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments \(PDF\)](#).***

Other EPA Documentation — U.S. EPA, 1980, 1986, 1987a, 1988

Agency Consensus Date - 7/1/98

__I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

_II. Carcinogenicity Assessment for Lifetime Exposure

Naphthalene

CASRN — 91-20-3

Last Revised — 09/17/1998

Section II provides information on three aspects of the carcinogenic assessment for the substance in question, the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per µg/m³ air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in the Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996) also utilize those Guidelines where indicated. Users are referred to Section I of this IRIS file for information on long-term effects other than carcinogenicity.

_II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Using criteria of the 1986 Guidelines for Carcinogen Risk Assessment, naphthalene is classified in Group C, a possible human carcinogen. This is based on the inadequate data of carcinogenicity in humans exposed to naphthalene via the oral and inhalation routes, and the limited evidence of carcinogenicity in animals via the inhalation route.

Using the 1996 Proposed Guidelines for Carcinogen Risk Assessment, the human carcinogenic potential of naphthalene via the oral or inhalation routes "cannot be determined" at this time based on human and animal data; however, there is suggestive evidence (observations of benign respiratory tumors and one carcinoma in female mice only exposed to naphthalene by inhalation [NTP, 1992a]). Additional support includes increase in respiratory tumors associated with exposure to 1-methylnaphthalene.

At the present time the mechanism whereby naphthalene produces benign respiratory tract tumors are not fully understood, but are hypothesized to involve oxygenated reactive metabolites produced via the cytochrome P-450 monooxygenase system. However, based on the many negative results obtained in genotoxicity tests, a genotoxic mechanism appears unlikely.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).

__II.A.2. Human Carcinogenicity Data

Available data are inadequate to establish a causal association between exposure to naphthalene and cancer in humans. Adequately scaled epidemiological studies designed to examine a possible association between naphthalene exposure and cancer were not located. Overall, no data are available to evaluate the carcinogenic potential in exposed human populations.

__II.A.3. Animal Carcinogenicity Data

Inhalation: In an NTP (1992a) cancer bioassay, groups of male and female B6C3F1 mice were exposed (whole-body) to naphthalene (> 99% pure) vapors at concentrations of 0 (75 mice/sex), 10 (75 mice/sex), or 30 ppm (150 mice/sex) 6 hr/day, 5 days/week for 2 years. Mice were housed five to a cage. There were 150 mice housed in each of 4 inhalation chambers; 2 chambers were used for the high-exposure level. A comprehensive histological examination was performed on all control and high-dose mice and on low-dose mice that died or were sacrificed before 21 months of exposure. After 21 months of exposure, only the nasal cavity and lung were examined in the low-dose group. In each chamber, 50 animals per sex were designated for the 2-year studies; 5 animals per sex were designated for hematological evaluations at 14 days and 3, 6, 12, and 18 mo. However, because of high mortality in the male control group (see next paragraph), only the 14-day hematological evaluation was conducted. The other surviving interim mice were incorporated into the 2-year study.

Statistically significant decreases in survival were observed in the control male mice compared with the exposed groups. Exposed male mice were observed to huddle in corners of the cages during exposure and were less inclined to fight. Survival percentages at the end of the study were 37% (26/70), 75% (52/69), and 89% (118/133) for the 0, 10, and 30 ppm male groups, respectively. Survival percentages did not include mice sacrificed at 14 days, mice that died before the study began, mice that were accidentally killed, or mice that were lost during the study. Survival at 2 years in the control female mice (86%; 59/69) was comparable to survival in the exposed groups; survival percentages were 88% (57/65) and 76% (102/135) for low- and high-dose females. Body weights were not affected by exposure in either sex.

Statistically significant increases in incidences of nonneoplastic lesions were found in the lung and nose of males and females at both exposure levels. Observed nonneoplastic effects included the following (with respective incidences listed in the order of control, low-, and high-exposure groups): chronic inflammation of the lung (0/70, 21/69, and 56/135 for males; 3/69, 13/65, and 52/135 for females); chronic inflammation (0/70, 67/69, and 133/135 for males and 1/69, 65/65, and 135/135 for females); metaplasia of the olfactory epithelium (0/70, 66/69, and 134/135 for males; 0/69, 65/65, and 135/135 for females); and hyperplasia of the respiratory epithelium in the nose (0/70, 66/69, and 134/135 for males; 0/69, 65/65, and 135/135 for females).

The lung inflammation in the exposed mice was described as consisting of "focal intra-alveolar mixed inflammatory cell exudates and interstitial fibrosis" that in more advanced lesions consisted "primarily of large foamy macrophages, sometimes accompanied by multinucleated giant cells." Foci of alveolar epithelial hyperplasia were noted to occur generally in regions distant to inflammation.

A statistically significant increase in the incidence of alveolar/bronchiolar adenomas was observed in the 30 ppm group of females (28/135), but not in the 10 ppm group (2/65), relative to the control female group (5/69). Among females, an additional mouse in the 30-ppm group displayed

an alveolar/bronchiolar carcinoma. The historical combined incidence of alveolar/bronchiolar adenomas and carcinomas in control B6C3F1 female mice from NTP inhalation studies was cited as 39/466 (8.4%, range 0-12%). The authors commented that alveolar/bronchiolar adenomas and carcinomas constitute a morphologic continuum. The incidences of male mice with alveolar/bronchiolar adenomas were 7/70, 15/69, and 27/135 for the control, 10 ppm, and 30 ppm groups, respectively; for combined adenomas and carcinomas of the alveolar/bronchiolar region, the respective incidences were 7/70, 17/69, and 31/135. A statistical analysis that adjusted for intercurrent mortality (logistics regression analysis) determined that the tumor incidences for control and exposed groups of male mice were not significantly different (NTP, 1992a). Historical incidence for combined alveolar/bronchiolar adenomas and carcinomas in control male B6C3F1 mice from NTP inhalation studies was cited as 94/478 (19.7%, range 10%-30%). The adenomas were described as "locally compressive nodular masses consisting of cords of well-differentiated epithelial cells," whereas the carcinoma was "composed of ribbons and/or coalescing sheets of smaller, more anaplastic, cells which sometimes extended into adjacent parenchyma."

Hemangiosarcomas occurred at various sites within the vascular endothelium in five high-dose female mice (5/135), but not within the other groups of female mice (0/69 and 0/65 for control and 10 ppm females, respectively). The high-dose female incidence (3.7%) was not significantly different from the concurrent control incidence and was within the range of historical control incidences from NTP inhalation studies (range: 0-8%; overall incidence: 17/467 or 3.6%). No significantly elevated incidences of tumors were found at other tissue sites in exposed male or female mice (NTP, 1992a).

Adkins et al. (1986) exposed groups of 30 female A/J strain mice (6 to 8 weeks old) to 0, 10, or 30 ppm naphthalene (98%-99% pure) vapors, 6 hr/day, 5 days/week for 6 mo. After the 6-mo exposure period, excised lungs were examined for tumors. Tumors were examined histologically. The authors did not describe any noncancer histopathological effects that their examinations may have revealed. Survival was not different between the exposed and control groups. Lung tumors were found in all 20 positive control mice given single intraperitoneal injections of 1 g urethane/kg; the mean number of tumors per mouse in the positive control was 28.9. Increased numbers of lung tumors were found in the naphthalene-exposed groups compared with the control group, but the differences were not statistically significant (6, 10, and 11 for the 0, 10, and 30 ppm groups). Tumors were described as alveolar adenomas consisting of "large cuboidal or columnar epithelial cells supported by a sparse fibroblastic stroma and arranged in poorly defined acinar structures with papillary formations." No carcinomas were found. Naphthalene exposure did not significantly increase the percentage of animals with tumors (21%, 29%, and 30% for 0, 10, and 30 ppm mice, respectively). Statistically significant increases in the number of adenomas per tumor-bearing lung were observed in the exposed mice, but there was no increase in response with increasing dose. Mean numbers of tumors per tumor-bearing lung (sd noted in parentheses) were: 1.00 (0.00), 1.25 (0.07), and 1.25 (0.07) for 0, 10, and 30 ppm mice, respectively. Applicability of this study to the assessment of risk for lifetime exposure is limited due to the less-than-lifetime exposure and observation periods, and the limited tissue evaluation examining only the lung. Nevertheless, the finding that only 6 months of exposure caused statistically significant increased numbers of lung tumors per tumor-bearing lung in the exposed groups, coupled with the results of the NTP (1992a) mouse bioassay, provides further suggestive evidence that naphthalene produces a tumorigenic response in the mouse lung.

Oral: Schmahl (1955) reported that naphthalene administered in food did not cause cancer in a group of 28 rats (in-house strains BDI and BDII). Naphthalene (purchased from Merck Co. and described as "Naphthalene puriss. cryst. alcoh. depur. [54935]") was dissolved in oil and given 6 times/week in food. The absorption spectrum of the test material displayed no atypical peaks compared with published data for naphthalene, suggesting high purity. The daily dose was reported to vary between 10 and 20 mg, but further details regarding dose variation were not provided. After reaching a total dose of 10 g/rat (food intake and body weights were not

reported), treatment was stopped on the 700th experimental day, and animals were observed until spontaneous death, between 700 and 800 days of age. Assuming an average daily dose of 15 mg/rat and a body weight of 0.36 kg (U.S. EPA, 1987b, reference body weight for male Fischer 344 rats), an estimated average daily dose of 42 mg/kg is calculated. Autopsies were performed on dead animals, and organs that appeared unusual were examined histologically (the report did not specify which organs were histologically examined). The number of rats in the control group was not reported; survival for control and exposed rats was reported to be similar. Reported results from the autopsy and histological examinations were restricted to the statement that no toxic effects were seen, including eye damage and tumors. Inadequacies in experimental design (e.g., only one dose level was administered, the histopathological examination was not complete, hematological endpoints were not evaluated, and some rats lived as long as 300 days beyond exposure before being examined) and inadequacies in reporting of experimental details and results limit the conclusions that can be drawn from this study regarding either the carcinogenicity or noncarcinogenic toxicity of naphthalene. This study is considered inadequate as a cancer bioassay because of reporting and design inadequacies and the likelihood that the maximum tolerated dose may not have been approached.

Other Routes of Administration: Schmähl (1955) reported that naphthalene repeatedly administered by subcutaneous or intraperitoneal injection did not produce tumors in rats (in-house strains BDI and BDIII). Groups of 10 rats were given either subcutaneous or intraperitoneal weekly injections of naphthalene in oil (20 mg/rat per injection) starting at 100 days of age and continuing for 40 weeks (the total doses were 820 mg/rat). Rats were maintained until spontaneous death occurred. Life spans were reported to be 700 or 900 days for rats with subcutaneous or intraperitoneal doses, respectively. Autopsies were performed on dead animals, and organs which appeared unusual were examined histologically (the report did not specify which organs were examined, if any). The author reported that no toxic effects were found with parenteral administration of naphthalene. No tumors developed in either group. Reported information on control rats was restricted to the statement that lifespan for exposed rats was similar to lifespan for control rats (700 days with subcutaneous doses and 900 days with intraperitoneal doses).

Boyland et al. (1964) implanted naphthalene into the bladder of stock Chester Beatty mice and examined them after 30 weeks in an effort to determine the suitability of naphthalene as a potential vehicle for carcinogenicity testing. The original number of mice implanted with naphthalene was not reported, but 23 mice were reported to have survived 30 weeks. One mouse developed a bladder carcinoma (1/23; 4%); no adenomas or papillomas were found. Tumor incidence was as low as when paraffin wax was used (2-4%), and lower than with the implantation of cholesterol (12%). There are limitations of this study that make it an inadequate lifetime cancer bioassay including the short exposure and observation periods, and the lack of untreated controls.

Coal tar-derived naphthalene that contained approximately 10% unidentified impurities was tested for carcinogenicity by Knake (1956). White rats (40, sex unspecified) were given seven subcutaneous injections of 0 or 500 mg/kg naphthalene in sesame oil at 2-week intervals over an approximate 3.5-month period. Thirty-four of 38 naphthalene rats and 32/38 control rats survived the injection period. Survival was somewhat reduced in the naphthalene-exposed rats compared with the vehicle-control rats during the following 18-month period. Survival incidences at 6, 11, and 17 months after the injection period were 21/34, 6/34, and 0/34 for the naphthalene-exposed rats and 17/32, 12/32, and 4/32 for the control rats. Lymphosarcomas were found in 5/34 (14.7%) exposed rats during the 18-month observation period; one exposed rat showed a mammary fibrosarcoma. Vehicle controls showed a 6% (2/32) incidence of tumors (one with lymphosarcoma and one with mammary fibrosarcoma). Mice (25, inbred black) were painted with 0.5% naphthalene in benzene 5 days/week for life; 21 control mice were painted with benzene alone. Four treated mice developed lymphomatic leukemia, three had lung adenomas, one had

lymphosarcoma, and one had a non-specified tumor (9/25 with tumors). In the benzene controls, one had lymphosarcoma, one had lung adenoma, and one had a non-specified tumor (3/21 with tumors). These studies are limited for the assessment of carcinogenicity due to the presence of unknown impurities that may have carcinogenic properties. Moreover, the vehicle (benzene) in the mouse study has been shown to cause leukemia in humans and rodents, and the site of injection in the rat study was painted, prior to injection, with carbolfuchsin, a known carcinogen.

La Voie et al. (1988) gave intraperitoneal naphthalene doses (in dimethylsulfoxide) of 0.25, 0.50, and 1.0 μmole to male and female newborn CD-1 mice on days 1, 8, and 15 of life (total dose = 1.75 μmole naphthalene). The report did not specify the purity of the naphthalene tested. Forty-nine pups were treated with naphthalene and 46 control pups were treated with dimethylsulfoxide alone. Mice were maintained (10 mice/cage) until moribund or until 52 weeks when survivors were killed. All gross lesions as well as liver sections from all mice were examined histologically. No statistically significant increased incidence of liver tumors (adenomas or hepatomas) was found in the exposed mice. Reported incidences for the number of mice with liver tumors were (denominators are for the number of mice that lived at least 6 months): 0/16 and 2/31 for exposed females and males, and 0/21 and 4/21 for vehicle-control females and males. This assay is inadequate to assess the carcinogenicity of lifetime exposure to naphthalene because the exposure period (2 weeks) and observation period (52 weeks) were significantly less than the lifetime for mice (approximately 2 years), and complete histological examinations were not conducted.

__II.A.4. Supporting Data for Carcinogenicity

The genotoxic potential of naphthalene has been evaluated in many test systems. Most studies provided negative results. Naphthalene was not mutagenic in *Salmonella typhimurium* assays in the presence or absence of liver metabolic preparations (Bos et al., 1988; Connor et al., 1985; Florin et al., 1980; Godek et al., 1985; McCann et al., 1975; Nakamura et al., 1987; Narbonne et al., 1987; NTP, 1992a; Sakai et al., 1985). Naphthalene did not damage DNA (as assayed by the induction of the SOS-repair system) in *E. coli* PQ37 (Mersch-Sundermann et al., 1993).

NTP (1992a) found that naphthalene induced, in cultured Chinese hamster ovary cells, sister chromatid exchanges within a concentration range of 27 to 90 $\mu\text{g/mL}$ in the presence or absence of metabolic activation, and chromosomal aberrations within a range of 30 to 67.5 $\mu\text{g/mL}$ only in the presence of metabolic activation.

Naphthalene was mutagenic in the marine bacterium *Vibrio fischeri* (Arfsten et al., 1994) and in the *Drosophila melanogaster* wing somatic mutation and recombination test (Delgado-Rodriguez et al., 1995). Culture of mouse embryos in medium containing 0.16 mM naphthalene produced a 10-fold increase in chromosomal damage compared to untreated controls; the genotoxic response to naphthalene was amplified by the inclusion of a hepatic metabolic activation system in the medium (Gollahon et al., 1990).

Incubation of human peripheral lymphocytes in medium containing naphthalene and a human liver metabolic activation system did not produce increased frequency of sister chromatid exchanges compared with controls (Tingle et al., 1993; Wilson et al., 1995). Naphthalene did not induce unscheduled DNA synthesis in cultured rat hepatocytes (Barfknecht et al., 1985) or increased numbers of micronuclei in bone marrow cells of mice following intraperitoneal injection of single 250-mg/kg doses (Sorg et al., 1985). Single oral doses of naphthalene as high as 500 mg/kg did not increase the frequency of micronucleated erythrocytes in exposed mice compared with untreated control mice (Harper et al., 1984). Naphthalene did not induce in vitro transformations of Fischer rat embryo cells (Freeman et al., 1973) or Swiss mouse embryo cells (Rhim et al., 1974). Sina et al. (1983) reported that naphthalene did not induce single-strand DNA breaks in cultured rat hepatocytes as detected by alkaline dilution.

Naphthalene metabolites 1-naphthol and 2-naphthol were not mutagenic in *S. typhimurium*, with or without metabolic activation (Florin et al., 1980; McCann et al., 1975; Narbonne et al., 1987). Another proposed naphthalene metabolite, naphthoquinone, was not mutagenic in several strains of *S. typhimurium* with or without metabolic activation (Sakai et al., 1985), but Flowers-Geary et al. (1994) reported that naphthalene-1,2-dione was mutagenic in strains of *S. typhimurium* without metabolic activation. The naphthalene metabolite, 1-naphthol, failed to produce positive results in several other genotoxicity assays including tests for sex-linked recessive lethal mutations in *Drosophila melanogaster* (Gocke et al., 1981), mutations in mouse L5178Y cells (Amacher and Turner, 1982), unscheduled DNA synthesis in cultured rat hepatocytes (Probst and Hill, 1980), and induction of micronuclei in bone marrow cells of mice (Gocke et al., 1981) and rats (Hossack and Richardson, 1977) after acute in vivo exposure.

Tsuda et al. (1980) found no evidence for neoplastic transformation of liver cells in a group of 10 young adult F344 rats (sex not specified) treated with single gavage doses of 100 mg/kg naphthalene in corn oil compared with a group of 10 vehicle control rats. Rats were given gavage doses of naphthalene or vehicle following partial hepatectomy, but before dietary treatment with an anti-cell proliferation agent (2-acetylaminofluorene) and a necrotizing agent (carbon tetrachloride). Gamma-glutamyl transpeptidase foci (observed following the dietary treatments of exposed and control rats) were used as an indicator of neoplastic transformation. In contrast to naphthalene, a single gavage dose of 200 mg/kg benzo[a]pyrene induced significant increases in the number, area, and size of gamma-glutamyl transpeptidase foci.

_II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

An oral slope factor for naphthalene was not derived because of a lack of chronic oral naphthalene studies.

_II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

An inhalation unit risk estimate for naphthalene was not derived because of the weakness of the evidence (observations of predominant benign respiratory tumors in mice at high dose only) that naphthalene may be carcinogenic in humans.

_II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

__II.D.1. EPA Documentation

Source Document — U.S. EPA, 1998

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included in an appendix to the Toxicological Review of Naphthalene in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF).***

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date - 07/01/1998

Ecological Soil Screening Levels for Copper

Interim Final

OSWER Directive 9285.7-68



**U.S. Environmental Protection Agency
Office of Solid Waste and Emergency Response
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Appendix 6-1	Mammalian Toxicity Data Extracted and Reviewed for Wildlife Toxicity Reference Value (TRV) - Copper

1.0 INTRODUCTION

Ecological Soil Screening Levels (Eco-SSLs) are concentrations of contaminants in soil that are protective of ecological receptors that commonly come into contact with and/or consume biota that live in or on soil. Eco-SSLs are derived separately for four groups of ecological receptors: plants, soil invertebrates, birds, and mammals. As such, these values are presumed to provide adequate protection of terrestrial ecosystems. Eco-SSLs are derived to be protective of the conservative end of the exposure and effects species distribution, and are intended to be applied at the screening stage of an ecological risk assessment. These screening levels should be used to identify the contaminants of potential concern (COPCs) that require further evaluation in the site-specific baseline ecological risk assessment that is completed according to specific guidance (U.S. EPA, 1997, 1998, and 1999). The Eco-SSLs are not designed to be used as cleanup levels and the United States (U.S.) Environmental Protection Agency (EPA) emphasizes that it would be inappropriate to adopt or modify the intended use of these Eco-SSLs as national cleanup standards.

The detailed procedures used to derive Eco-SSL values are described in separate documentation (U.S. EPA, 2003, 2005). The derivation procedures represent the collaborative effort of a multi-stakeholder group consisting of federal, state, consulting, industry, and academic participants led by what is now the U.S. EPA Office of Solid Waste and Emergency Response (OSWER).

This document provides the Eco-SSL values for copper and the documentation for their derivation. This document provides guidance and is designed to communicate national policy on identifying copper concentrations in soil that may present an unacceptable ecological risk to terrestrial receptors. The document does not, however, substitute for EPA's statutes or regulations, nor is it a regulation itself. Thus, it does not impose legally-binding requirements on EPA, states, or the regulated community, and may not apply to a particular situation based upon the circumstances of the site. EPA may change this guidance in the future, as appropriate. EPA and state personnel may use and accept other technically sound approaches, either on their own initiative, or at the suggestion of potentially responsible parties, or other interested parties. Therefore, interested parties are free to raise questions and objections about the substance of this document and the appropriateness of the application of this document to a particular situation. EPA welcomes public comments on this document at any time and may consider such comments in future revisions of this document.

2.0 SUMMARY OF ECO-SSLs FOR COPPER

Copper is a naturally occurring element which can be found in all environmental media: air, soil, sediment, and water. In the metal state, copper is malleable, ductile, and a good conductor of heat and electricity (Alloway, 1990). Copper occurs in numerous minerals including cuprite, tenorite, malachite, azurite, and native copper (George, 1993). Copper forms sulphides, sulphates,

sulphosalts, carbonates and other compounds and occurs in reducing environments as the native metal. Copper ranks 26th, behind zinc in abundance in the lithosphere (Alloway, 1990).

The principal uses of copper are in the production of wire, and of its alloys, brass and bronze (Alloway, 1990). Copper compounds may also be released to the environment through their use in dyes, catalysts, feed additives, pesticides, pigments, iron and steel production, coal and oil combustion, copper sulfate production, municipal incineration, and mining activities (Alloway, 1990; U.S. EPA 1987). Copper may also be released from natural sources, such as volcanoes, windblown dusts, the weathering of soil, decaying vegetation, and forest fires (<http://toxnet.nlm.nih.gov>).

Background concentrations reported for many metals in U.S. soils are described in Attachment 1-4 of the Eco-SSL guidance (U.S. EPA, 2003). Typical background concentrations of copper in U.S. soils are plotted in Figure 2.1 for both eastern and western U.S. soils.

In soils, copper may be present as soluble compounds including nitrates, sulfates, and chlorides, and insoluble compounds such as oxides, hydroxides, carbonates, and sulfides (Bodek et al. 1988; Budavari 1996). Soluble copper compounds strongly sorb to particles of organic matter, clay, soil, or sand, and demonstrate low mobility in soils (Bodek et al. 1988). Insoluble copper compounds are solid salts and are effectively immobile in soils. Most copper compounds have a high melting point and low vapor pressure, and are not expected to volatilize from moist or dry soil surfaces (Bodek et al. 1988; HSDB). Alloway (1990) describes six “pools” of copper in soils including soluble ions, inorganic and organic complexes in soil solution, exchangeable copper, stable organic complexes in humus, copper adsorbed by hydrous oxides of manganese, iron, and aluminum, copper adsorbed on the clay-humus colloidal complex and the crystal lattice-bound copper in soil minerals.

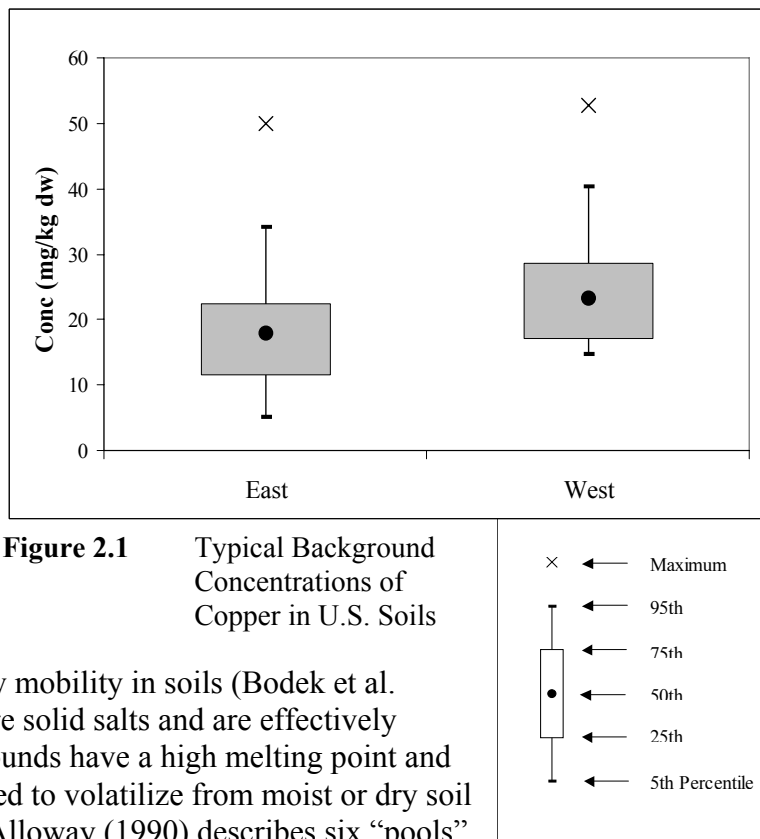


Figure 2.1 Typical Background Concentrations of Copper in U.S. Soils

Copper is an essential element in both plants and animals. In animals, copper is essential for hemoglobin formation, carbohydrate metabolism, catecholamine biosynthesis, and cross-linking of collagen, elastin, and hair keratin (U.S. EPA 1987). Nutritional requirements of copper for common mammalian and avian test organisms are compiled in Attachment 4-3 of the Eco-SSL guidance (U.S. EPA, 2003, 2005). The primary route of exposure for animals to copper is through ingestion. Generally, the normal intake of copper by inhalation is a negligible fraction of the total (Friberg et al., 1986) and absorption through the skin is minimal (Venugopal and

Luckey, 1978). In animal tissues, copper exists as complexes with proteins, peptides, and amino acids in tissues such as the liver, brain, and kidney which retain more copper than do other soft tissues (Seiler et al., 1988). Muscle tissues contain about 35% of the total body copper. In tissues, copper cannot exist in the ionic form in appreciable amounts except in the acidic environment of the stomach (Seiler et al., 1988). Copper is excreted by the biliary system mainly through feces and bile, and to a smaller extent through urine and sweat (Venugopal and Luckey 1978). Absorption, distribution, metabolism, and utilization of copper can be affected by interaction with other metals such as iron, molybdenum, and zinc (U.S. EPA 1987; HSDB).

In plants, copper is especially important in oxidation, photosynthesis, and protein and carbohydrate metabolism. Also, copper concentrations may affect nitrogen fixation, valence changes, and cell wall metabolism (Kabata-Pendias and Pendias, 1992). Since copper is unlikely to be transported across leaf cuticles, the primary route of uptake by plants is through soil as opposed to atmospheric deposition (Hutchinson, 1979). Copper tends to affect various plant species differently, and low growing grasses tend to accumulate copper at higher levels than tree foliage (U.S. EPA, 1987). In plants, copper deficiency is demonstrated by wilting leaves, melanism, white twisted tips, and reduction in panicle formation (HSDB).

In mammals, the mechanism of copper toxicity is complex. Copper can increase cell permeability in erythrocytes leading to lysis and inhibition of intracellular enzymes. Thus, copper poisoning can lead to oxidative stress in erythrocytes and to accelerated loss of intracellular glutathione. In addition, copper ions can cause mitochondrial swelling and inhibit oxygen consumption, which leads to cell degeneration. In copper deficient animals, failure to form collagen in the walls of arterioles leads to subcutaneous bleeding and anemia. Other symptoms of acute copper toxicity in mammals include sporadic fever, tachycardia, hypotension, oliguria, uremia, coma, cardiovascular collapse, and death. Chronic copper poisoning in mammals may induce nausea, vomiting, epigastric pain, dizziness, jaundice, and general debility (Venugopal and Luckey, 1978).

The Eco-SSL values derived to date for copper are summarized in Table 2.1.

Table 2.1 Copper Eco-SSLs (mg/kg dry weight in soil)			
Plants	Soil Invertebrates	Wildlife	
		Avian	Mammalian
70	80	28	49

Eco-SSL values were derived for all receptor groups. The Eco-SSL values for copper range from 28 mg/kg dry weight (dw) for avian wildlife to 80 mg/kg dw for soil invertebrates. With the exception of the avian value, these concentrations are higher than the 95th percentile of reported background soil concentrations of copper in eastern and western U.S. soils (Figure 2.1). The Eco-SSL for avian wildlife is equal to the median value for western U.S. soils and is higher than the median value for eastern U.S. soils.

3.0 ECO-SSL FOR TERRESTRIAL PLANTS

Of the papers identified from the literature search process, 479 papers were selected for acquisition for further review. Of those papers acquired, 49 met all 11 Study Acceptance Criteria (U.S. EPA, 2003; Attachment 3-1). Each of these papers were reviewed and the studies were scored according to the Eco-SSL guidance (U.S. EPA, 2003; Attachment 3-2). Fifty-six study results received an Evaluation Score greater than ten (U.S. EPA, 2003; Attachment 3-1). These studies are listed in Table 3.1.

The studies in Table 3.1 are sorted by bioavailability score. There are 6 studies eligible for Eco-SSL derivation with a bioavailability score of two. These results are used to derive the plant Eco-SSL for copper (U.S. EPA, 2003; Attachment 3-2). The Eco-SSL is the geometric mean of the maximum acceptable toxicant concentration (MATC) and 10% effective concentration (EC₁₀) values for 4 species under different test conditions (pH and % organic matter (OM)) and is equal to 70 mg/kg dw.

4.0 ECO-SSL FOR SOIL INVERTEBRATES

Of the papers identified from the literature search process, 173 papers were selected for acquisition for further review. Of those papers acquired, 44 met all 11 Study Acceptance Criteria (U.S. EPA 2003; Attachment 3-1). Each of these papers were reviewed and the studies were scored according to the Eco-SSL guidance (U.S. EPA, 2003; Attachment 3-2). Fifty-five studies received an Evaluation Score greater than ten. These studies are listed in Table 4.1. The studies in Table 4.1 are sorted by bioavailability score. There are ten studies eligible for Eco-SSL derivation with a bioavailability score of 2 that were used to derive the soil invertebrate Eco-SSL for copper (U.S. EPA, 2003; Attachment 3-2). The Eco-SSL is the geometric mean of the MATC and EC₁₀ values for at least 6 test species under different test conditions (pH and OM%) and is equal to 80 mg/kg dw.

Table 3.1 Plant Toxicity Data - Copper

Reference	IP Number	Study ID	Test Organism		Soil pH	OM%	Bio-availability Score	ERE	Tox Parameter	Tox Value (Soil Conc at mg/kg dw)	Total Evaluation Score	Eligible for Eco-SSL Derivation?	Used for Eco-SSL?
Kjaer and Elmegaard, 1996	4231	c	Black bindweed	<i>Polygonum convolvulus</i>	6.4	1.7	2	REP	MATC	251	14	Y	Y
Mozaffari et al, 1996	4176	b	Citrus cultivar	Cleopatra mandarin	6.0	0.98	2	GRO	MATC	141	13	Y	Y
Torres and De Varennes, 1998	13958	--	Perennial ryegrass	<i>Lolium perenne L.</i>	4.4 - 5.4	1.0	2	GRO	MATC	16	12	Y	Y
Gonzalez, 1991	4609	d	Alfalfa	<i>Medicago sativa</i>	6.3	1.3	2	GRO	EC ₁₀	115	13	Y	Y
Gonzalez, 1991	4609	e	Alfalfa	<i>Medicago sativa</i>	5.5	2.8	2	GRO	EC ₁₀	58	13	Y	Y
Gonzalez, 1991	4609	g	Alfalfa	<i>Medicago sativa</i>	5.4	1.1	2	GRO	EC ₁₀	32	13	Y	Y
Geometric Mean										70			
Data Not Used to Derive Plant Eco-SSL													
Rehab and Wallace, 1978	46710	--	Cotton	<i>Gossypium spp.</i>	6.6	2.4	1	GRO	MATC	141.4	14	Y	N
Chhibba et al, 1994	12325	a	Wheat	<i>Triticum aestivum</i>	7.8	0.2	1	GRO	MATC	28	13	Y	N
Gonzalez, 1991	4609	b	Alfalfa	<i>Medicago sativa</i>	7.8	1.8	1	GRO	EC ₁₀	1253	12	Y	N
Gonzalez, 1991	4609	c	Alfalfa	<i>Medicago sativa</i>	7.5	1.1	1	GRO	EC ₁₀	821	12	Y	N
Gonzalez, 1991	4609	f	Alfalfa	<i>Medicago sativa</i>	7.3	0.5	1	GRO	EC ₁₀	41	12	Y	N
Aquaterra, 2000	22616	a	Alfalfa	<i>Medicago sativa</i>	7.8	2.9	0	GRO	EC ₂₀	326.4	12	Y	N
Aquaterra, 2000	22616	b	Alfalfa	<i>Medicago sativa</i>	8.1	3.5	0	GRO	EC ₂₀	674	12	Y	N
Aquaterra, 2000	22616	c	Barley	<i>Hordeum vulgare</i> var. Chapais	6.1	9.0	0	GRO	EC ₂₀	143	12	Y	N
Aquaterra, 2000	22616	d	Barley	<i>Hordeum vulgare</i> var. Chapais	7.8	2.9	0	GRO	EC ₂₀	0.74	12	Y	N
Aquaterra, 2000	22616	e	Barley	<i>Hordeum vulgare</i> var. Chapais	8.1	3.5	0	GRO	EC ₂₀	234.8	12	Y	N
Aquaterra, 2000	22616	f	Carrot	<i>Daucus carota</i> var. Royal Chatenay	7.8	2.9	0	GRO	EC ₂₀	659.0	12	Y	N
Aquaterra, 2000	22616	g	Corn	<i>Zea mays</i> var. Kandy Korn	7.8	2.9	0	GRO	EC ₂₀	407.6	12	Y	N
Aquaterra, 2000	22616	h	Corn	<i>Zea mays</i> var. Kandy Korn	8.1	3.5	0	GRO	EC ₂₀	776.2	12	Y	N
Aquaterra, 2000	22616	i	Cucumber	<i>Cucumis sativa</i> var. Marketer	7.8	2.9	0	GRO	EC ₂₀	506.0	12	Y	N
Aquaterra, 2000	22616	j	Cucumber	<i>Cucumis sativa</i> var. Marketer	8.1	3.5	0	GRO	EC ₂₀	804.9	12	Y	N
Aquaterra, 2000	22616	k	Gramma grass	<i>Bouteloua gracilis</i>	7.8	2.9	0	GRO	EC ₂₀	471.3	12	Y	N
Aquaterra, 2000	22616	l	Northern wheatgrass	<i>Agropyron dasystachyum</i>	6.1	9.0	0	GRO	EC ₂₀	151.7	12	Y	N
Aquaterra, 2000	22616	m	Northern wheatgrass	<i>Agropyron dasystachyum</i>	7.8	2.9	0	GRO	EC ₂₀	391.3	12	Y	N
Aquaterra, 2000	22616	n	Northern wheatgrass	<i>Agropyron dasystachyum</i>	8.1	3.5	0	GRO	EC ₂₀	801.6	12	Y	N
Aquaterra, 2000	22616	o	Radish	<i>Raphanus sativus</i> var. Champion	7.8	2.9	0	GRO	EC ₂₀	347.3	12	Y	N
Aquaterra, 2000	22616	p	Radish	<i>Raphanus sativus</i> var. Champion	8.1	3.5	0	GRO	EC ₂₀	322.7	12	Y	N
Mitchell et al, 1988	15861	a	Common oat	<i>Avena sativa</i>	5.5	2.0	2	GRO	EC ₅₀	535	14	N	N
Mitchell et al, 1988	15861	b	Cucumber	<i>Cucumis sativus</i>	5.5	2.0	2	GRO	EC ₅₀	540	14	N	N
Mitchell et al, 1988	15861	c	Soybean	<i>Glycine max</i>	5.5	2.0	2	GRO	EC ₅₀	550	14	N	N
Mitchell et al, 1988	15861	d	Heath-leaf banksia	<i>Banksia ericifolia</i>	5.5	2.0	2	GRO	EC ₅₀	610	14	N	N
Mitchell et al, 1988	15861	e	She-oak	<i>Casuarina distyla</i> Vent.	5.5	2.0	2	GRO	EC ₅₀	205	14	N	N
Mitchell et al, 1988	15861	f	Yellow bloodwood	<i>Eucalyptus eximia</i> Shau.	5.5	2.0	2	GRO	EC ₅₀	560	14	N	N
Kjaer and Elmegaard, 1996	4231	a	Black bindweed	<i>Polygonum convolvulus</i>	6.4	1.7	2	GRO	EC ₅₀	272	14	N	N
Kjaer and Elmegaard, 1996	4231	d	Black bindweed	<i>Polygonum convolvulus</i>	6.4	1.7	2	MOR	EC ₅₀	219	14	N	N
Tikhomirav et al, 1988	4757	d	Common oat	<i>Avena sativa</i>	4.6	2.5	2	GRO	LOAEC	150	14	N	N

Table 3.1 Plant Toxicity Data - Copper

Reference	IP Number	Study ID	Test Organism		Soil pH	OM%	Bio-availability Score	ERE	Tox Parameter	Tox Value (Soil Conc at mg/kg dw)	Total Evaluation Score	Eligible for Eco-SSL Derivation?	Used for Eco-SSL?
Mitchell et al, 1988	15861	g	Common oat	<i>Avena sativa</i>	5.5	2.0	2	GRO	LC ₅₀	1765	13	N	N
Mitchell et al, 1988	15861	h	Cucumber	<i>Cucumis sativus</i>	5.5	2.0	2	GRO	LC ₅₀	1725	13	N	N
Mitchell et al, 1988	15861	I	Soybean	<i>Glycine max</i>	5.5	2.0	2	GRO	LC ₅₀	1140	13	N	N
Mitchell et al, 1988	15861	j	Heath-leaf banksia	<i>Banksia ericifolia</i>	5.5	2.0	2	GRO	LC ₅₀	1520	13	N	N
Mitchell et al, 1988	15861	k	She-oak	<i>Casuarina distyla Vent.</i>	5.5	2.0	2	GRO	LC ₅₀	580	13	N	N
Mitchell et al, 1988	15861	l	Yellow bloodwood	<i>Eucalyptus eximia Schau.</i>	5.5	2.0	2	GRO	LC ₅₀	1845	13	N	N
Mozaffari et al, 1996	4176	a	Citrus cultivar	<i>Cleopatra mandarin</i>	5.0	0.98	2	GRO	NOAEC	200	13	N	N
Spencer, 1966	15004	--	citrus cultivar	<i>Cleopatra mandarin</i>	5.4	1.0	2	GRO	LOAEC	5	11	N	N
De Haan, 1985	5048	a	Common oat	<i>Avena sativa</i>	5.6	1.6	2	REP	MATC	283	11	N	N
Pedersen et al, 2000a	56463	a	Black bindweed	<i>Fallopia, convolvulus</i>	6.0-6.7	4.5	1	GRO	EC ₅₀	284	16	N	N
Pedersen et al, 2000a	56463	b	Black bindweed	<i>Fallopia, convolvulus</i>	6.0-6.7	4.5	1	GRO	EC ₅₀	258	16	N	N
Pedersen et al, 2000a	56463	c	Black bindweed	<i>Fallopia, convolvulus</i>	6.0-6.7	4.5	1	GRO	EC ₅₀	259	16	N	N
Pedersen et al, 2000a	56463	d	Black bindweed	<i>Fallopia, convolvulus</i>	6.0-6.7	4.5	1	GRO	EC ₅₀	329	16	N	N
Pedersen et al, 2000a	56463	e	Black bindweed	<i>Fallopia, convolvulus</i>	6.0-6.7	4.5	1	GRO	EC ₅₀	260	16	N	N
Pedersen et al, 2000a	56463	f	Black bindweed	<i>Fallopia, convolvulus</i>	6.0-6.7	4.5	1	GRO	EC ₅₀	291	16	N	N
Genovese, 1978	58147	a	Jack pine	<i>Pinus banksiana</i> Lamb.	0.04	7.7	1	GRO	NOAEC	400	11	N	N
Genovese, 1978	58147	b	Black spruce	<i>Pinus mariana</i> (Mill) B.S.P.	0.04	7.7	1	GRO	NOAEC	400	11	N	N
Tikhomirav et al, 1988	4757	c	Common oat	<i>Avena sativa</i>	5.9	2.9	1	GRO	LOAEC	400	13	N	N
Mozaffari et al, 1996	4176	c	Citrus cultivar	<i>Cleopatra mandarin</i>	7.0	0.98	1	GRO	LOAEC	200	12	N	N
Gonzalez, 1991	4609	a	Alfalfa	<i>Medicago sativa</i>	7.1	0.3	1	GRO	NOAEC	1600	12	N	N

EC₁₀ = Effect concentration for 10% of test population

EC₂₀ = Effect concentration for 10% of test population

EC₅₀ = Effect concentration for 50% of test population

ERE = Ecologically relevant endpoint

GRO = Growth

LOAEC = Lowest observed adverse effect concentration

MATC = Maximum acceptable toxicant concentration. Geometric mean of NOAEC and LOAEC.

N = No

NOAEC = No observed adverse effect concentration

ns = Not specified

OM = Organic matter content

REP = Reproduction

Y = Yes

Bioavailability Score described in *Guidance for Developing Eco-SSLs* (U.S. EPA, 2003)

Total Evaluation Score described in *Guidance for Developing Eco-SSLs* (U.S. EPA, 2003)

Table 4.1 Invertebrate Toxicity Data - Copper

Reference	IP Number	Study ID	Test Organism		Soil pH	OM%	Bio-availability Score	ERE	Tox Parameter	Tox Value (Soil Conc at mg/kg dw)	Total Evaluation Score	Eligible for Eco-SSL Derivation?	Used for Eco-SSL?
Scott-Fordsmand et al., 1997	2288	--	Springtail	<i>Folsomia fimetario</i>	5.5	4.0	2	REP	EC ₁₀	38	16	Y	Y
Svendsen and Weeks, 1997a	11490	--	Earthworm	<i>Eisenia andrei</i>	5.6	<1.0	2	REP	MATC	133	15	Y	Y
Ma, 1984	11146	a	Earthworm	<i>Lumbricus rubellus</i>	4.8	5.7	2	REP	MATC	84	14	Y	Y
Korthals et al., 1996a	7848	a	Nematode	Not available	4.0	3.7	2	POP	MATC	116	14	Y	Y
Korthals et al., 1998	13828	--	Nematode	Not available	4.25	3.3	2	POP	MATC	141	13	Y	Y
Korthals et al., 1996b	4402	a	Nematode	Not available	4.1	3.2	2	REP	MATC	141	13	Y	Y
Svendsen and Weeks, 1997b	4449	--	Earthworm	<i>Lumbricus rubellus</i>	5.6	<1.0	2	GRO	MATC	188	13	Y	Y
Ma, 1988	7854	a	Earthworm	<i>Aporrectodea caliginosa</i>	5	5.0	2	REP	EC ₁₀	27	13	Y	Y
Ma, 1988	7854	b	Earthworm	<i>Allolobophora chlorotica</i>	5	5.0	2	REP	EC ₁₀	28	13	Y	Y
Ma, 1988	7854	c	Earthworm	<i>Lumbricus rubellus</i>	5	5.0	2	REP	EC ₁₀	80	13	Y	Y
Geometric Mean										80			
Data not Used to Derive Soil Invertebrate Eco-SSL													
Kula and Larink, 1997	11046	d	Earthworm	<i>Eisenia fetida</i>	5.8	4.0	1	REP	MATC	18	11	Y	N
Kula and Larink, 1997	11046	b	Earthworm	<i>Eisenia andrei</i>	5.8	4.0	1	REP	MATC	6	11	Y	N
Sandifer and Hopkin, 1996	4056	a	Springtail	<i>Folsomia candida</i>	5.8	10.0	1	REP	MATC	447	16	Y	N
Sandifer and Hopkin, 1996	4056	b	Springtail	<i>Folsomia candida</i>	5.1	10.0	1	REP	MATC	447	16	Y	N
Sandifer and Hopkin, 1996	4056	c	Springtail	<i>Folsomia candida</i>	4.5	10.0	1	REP	MATC	1732	16	Y	N
Bogomolov et al., 1996	4940	a	Earthworm	<i>A. tuberclata</i>	6.3	5.0	1	REP	MATC	141	16	Y	N
Bogomolov et al., 1996	4940	b	Nematode	Not available	6.3	5.0	1	POP	MATC	566	16	Y	N
Van Gestel et al., 1991	6826	b	Earthworm	<i>Eisenia andrei</i>	6.2	10.0	1	GRO	MATC	75	16	Y	N
Ma, 1984	11146	b	Earthworm	<i>Lumbricus rubellus</i>	7.1	5.7	1	REP	MATC	203	14	Y	N
Pedersen et al., 2000b	55995	a	Springtail	<i>Folsomia candida</i>	6.7	4.5	1	REP	EC ₁₀	50	14	Y	N
Pedersen et al., 2000b	55995	b	Springtail	<i>F. fimetaria</i>	6.7	4.5	1	REP	EC ₁₀	141	14	Y	N
Phillips et al., 1996	11508	a	Earthworm	<i>Eisenia fetida</i>	4.7	1.4	1	GRO	MATC	200	13	Y	N
Sandifer and Hopkin, 1997	758	--	Springtail	<i>Folsomia candida</i>	6.0	10.0	1	REP	MATC	447	13	Y	N
Kula and Larink, 1997	11046	a	Earthworm	<i>Eisenia fetida</i>	6.0	10.0	1	REP	MATC	18	11	Y	N
Van Gestel et al., 1989	4111	--	Earthworm	<i>Eisenia andrei</i>	6	10	1	REP	MATC	85	13	Y	N
Kula and Larink, 1997	11046	c	Earthworm	<i>Eisenia andrei</i>	6.0	10.0	1	REP	MATC	179	11	Y	N
Scott-Fordsman et al., 2000	22634	a	Springtail	<i>Folsomia fimetaria L.</i>	6.7-7.1	3.9-5.5	1	REP	MATC	500	15	Y	N
Aquaterra, 2000	22616	e	Springtail	<i>Onychiurus folsomi</i>	6.1	9.0	0	REP	EC ₂₀	425	17	Y	N
Haque and Ebing, 1983	10944	--	Earthworm	<i>Lumbricus terrestris</i>	6.1	1.7	2	MOR	LC ₅₀	98	13	N	N
Donkin and Dusenbery, 1993	7838	a	Nematode	<i>Caenorhabditis elegans</i>	5.2	1.7	2	MOR	LC ₅₀	534	14	N	N
Donkin and Dusenbery, 1993	7838	b	Nematode	<i>Caenorhabditis elegans</i>	5.1	3.0	2	MOR	LC ₅₀	413	13	N	N
Peredney and Williams, 2000b	56449	g	Nematode	<i>Caenorhabditis elegans</i>	4	1.14	2	MOR	LC ₅₀	20	13	N	N
Peredney and Williams, 2000b	56449	h	Nematode	<i>Caenorhabditis elegans</i>	4	1.14	2	MOR	LC ₅₀	25	13	N	N
Peredney and Williams, 2000b	56449	i	Nematode	<i>Caenorhabditis elegans</i>	4	4.2	2	MOR	LC ₅₀	186	13	N	N
Peredney and Williams, 2000b	56449	j	Nematode	<i>Caenorhabditis elegans</i>	4	4.2	2	MOR	LC ₅₀	252	13	N	N
Phillips et al., 1996	11508	b	Earthworm	<i>Eisenia fetida</i>	3.8	5.9	2	MOR	LOAEC	100	12	N	N
Korthals et al., 1996a	7848	b	Nematode	Not available	6.1	3.7	1	POP	NOAEC	168	13	N	N
Kammenga et al., 1996	5515	--	Nematode	<i>Plectus acuminatus</i>	5.5	10.0	1	REP	LOAEC	10	13	N	N
Posthuma et al., 1997	2380	a	Earthworm	<i>Enchytraeus crypticus</i>	5.5	10.0	1	REP	LC ₅₀	477	16	N	N
Posthuma et al., 1997	2380	b	Earthworm	<i>Enchytraeus crypticus</i>	6.0	10.0	1	REP	LC ₅₀	873	16	N	N
Spurgeon et al., 1994	4364	--	Earthworm	<i>Eisenia fetida</i>	6.3	10	1	REP	LC ₅₀	53	15	N	N

Table 4.1 Invertebrate Toxicity Data - Copper

Reference	IP Number	Study ID	Test Organism		Soil pH	OM%	Bio-availability Score	ERE	Tox Parameter	Tox Value (Soil Conc at mg/kg dw)	Total Evaluation Score	Eligible for Eco-SSL Derivation?	Used for Eco-SSL?
Spurgeon and Hopkin, 1995	6822	a	Earthworm	<i>Eisenia fetida</i>	6.1	10.0	1	REP	NOAEC	29	15	N	N
Donkin and Dusenbery, 1993	7838	c	Nematode	<i>Caenorhabditis elegans</i>	6.1	3.4	1	MOR	LC ₅₀	1061	12	N	N
Donkin and Dusenbery, 1993	7838	d	Nematode	<i>Caenorhabditis elegans</i>	6.2	2.2	1	MOR	LC ₅₀	629	12	N	N
Data not Used to Derive Soil Invertebrate Eco-SSL													
Neuhauser et al., 1986	17707	--	Earthworm	<i>Eisenia fetida</i>	6.0	10.0	1	MOR	LC ₅₀	643	14	N	N
Peredney and Williams, 2000a	53082	--	Nematode	<i>Caenorhabditis elegans</i>	4	10	1	MOR	LC ₅₀	1272	12	N	N
Peredney and Williams, 2000b	56449	k	Nematode	<i>Caenorhabditis elegans</i>	4	10	1	MOR	LC ₅₀	431	12	N	N
Peredney and Williams, 2000b	56449	l	Nematode	<i>Caenorhabditis elegans</i>	4	10	1	MOR	LC ₅₀	463	12	N	N
Neuhauser et al., 1985	6812	--	Earthworm	<i>Eisenia fetida</i>	6.0	10.0	1	MOR	LC ₅₀	643	11	N	N
Aquaterra, 2000	22616	aa	Earthworm	<i>Eisenia fetida</i>	6.1	9.0	0	MOR	LC ₅₀	632	15	N	N
Aquaterra, 2000	22616	ab	Earthworm	<i>Lumbricus terrestris</i>	6.1	9.0	0	MOR	LC ₅₀	456	15	N	N
Aquaterra, 2000	22616	ca	Earthworm	<i>Eisenia fetida</i>	7.8	2.9	0	MOR	LC ₅₀	721	14	N	N
Aquaterra, 2000	22616	cb	Earthworm	<i>Lumbricus terrestris</i>	7.8	2.9	0	MOR	LC ₅₀	313	14	N	N
Aquaterra, 2000	22616	da	Earthworm	<i>Eisenia fetida</i>	8.1	3.5	0	MOR	LC ₅₀	596	14	N	N
Aquaterra, 2000	22616	db	Earthworm	<i>Lumbricus terrestris</i>	8.1	3.5	0	MOR	LC ₅₀	486	14	N	N
Data not Used to Derive Soil Invertebrate Eco-SSL													

EC₁₀ = Effect concentration for 10% of test population

EC₂₀ = Effect concentration for 20% of test population

ERE = Ecologically relevant endpoint

GRO = Growth

LC₅₀ = Concentration lethal to 50% of test population

LOAEC = Lowest observed adverse effect concentration

MATC = Maximum acceptable toxicant concentration

MOR = Mortality

N = No

NOAEC = No observed adverse effect concentration

OM = Organic matter content

POP = Population

REP = Reproduction

Y = Yes

Bioavailability Score described in *Guidance for Developing Eco-SSLs* (U.S.EPA, 2003)

Total Evaluation Score described in *Guidance for Developing Eco-SSLs* (U.S. EPA, 2003)

5.0 ECO-SSL FOR AVIAN WILDLIFE

The derivation of the Eco-SSL for avian wildlife was completed as two parts. First, the toxicity reference value (TRV) was derived according to the Eco-SSL guidance (U.S. EPA, 2003; Attachment 4-5). Second, the Eco-SSL (soil concentration) was back-calculated for each of three surrogate species representing different trophic levels based on the wildlife exposure model and the TRV (U.S. EPA, 2003).

5.1 Avian TRV

The literature search completed according to the Eco-SSL guidance (U.S. EPA, 2003; Attachment 4-1) identified 3,365 papers with possible toxicity data for either avian or mammalian species. Of these studies, 3,175 were rejected for use as described in Section 7.5. Of the remaining studies, 107 contained data for avian test species. These papers were reviewed and the data were extracted and scored according to the Eco-SSL guidance (U.S. EPA, 2003; Attachment 4-3 and 4-4). The results of the data extraction and review are provided as Table 5.1. The complete results are included as Appendix 5-1.

Within the reviewed papers, there are 393 results for biochemical (BIO), behavior (BEH), physiology (PHY), pathology (PTH), reproduction (REP), growth (GRO), and survival (MOR) effects that meet the Data Evaluation Score of >65 for use to derive the TRV (U.S. EPA, 2003; Attachment 4-4). These data are plotted in Figure 5.1 and correspond directly with the data presented in Table 5.1. The no-observed adverse effect level (NOAEL) results for growth and reproduction are used to calculate a geometric mean. This result is examined in relationship to the lowest bounded lowest-observed adverse effect level (LOAEL) for reproduction, growth, and survival to derive the TRV according to procedures in the Eco-SSL guidance (U.S. EPA, 2003; Attachment 4-5).

A geometric mean of the NOAEL values for reproduction and growth was calculated at 18.5 mg copper/kg bw/day. This value, however, is higher than the lowest bounded LOAEL for reproduction, growth, or survival. Therefore, the TRV is equal to the highest bounded NOAEL lower than the lowest bounded LOAEL for reproduction, growth or survival and is equal to 4.05 mg copper/kg bw/day.

Table 5.1
Avian Toxicity Data Extracted for Wildlife Toxicity Reference Value (TRV)
Copper
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Result #	Reference	Ref No.	Test Organism	# of Conc/ Doses	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Type	Effect Measure	Response Site	NOAEL Dose* (mg/kg bw/day)	LOAEL Dose* (mg/kg bw/day)	Total
Biochemical (BIO)																		
1	Rangachar and Jayprakash, 1979	6530	Chicken (<i>Gallus domesticus</i>)	2	U	FD	105	d	10	w	JV	M	CHM	HMGL	BL	5.31		69
2	Chiou et al, 1999	2048	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	3	w	JV	NR	ENZ	CRKI	BL	5.32	13.3	77
3	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	2	M	DR	14	d	4	d	JV	NR	CHM	GLUC	BL	10.1		71
4	Pearce et al, 1983	2294	Chicken (<i>Gallus domesticus</i>)	4	U	FD	5	d	27	w	JV	F	CHM	LIPD	BL	12.3	24.7	75
5	Jackson et al, 1979	2160	Chicken (<i>Gallus domesticus</i>)	5	U	FD	224	d	17	w	SM	F	CHM	LIPD	LI	12.5	23.2	77
6	Pearce et al, 1983	2294	Chicken (<i>Gallus domesticus</i>)	5	U	FD	6	d	26	w	SM	F	CHM	LIPD	LI	13.9	27.8	76
7	Poupoulis and Jensen, 1976	36263	Chicken (<i>Gallus domesticus</i>)	5	U	FD	4	w	1	d	JV	M	CHM	FFTA	LD	14.3	28.7	69
8	Ward et al, 1995	6788	Turkey (<i>Melagris gallopavo</i>)	2	M	FD	10	d	5	d	JV	M	CHM	HMGL	BL	18.3		67
9	Stevenson and Jackson, 1980	2293	Chicken (<i>Gallus domesticus</i>)	4	U	FD	8	w	24	w	SM	F	CHM	LIPD	LI	22.6	45.2	76
10	Chiou et al, 1998	2049	Chicken (<i>Gallus domesticus</i>)	4	U	FD	1	w	38	w	SM	F	ENZ	LADH	SR	25.5	30.6	75
11	Chiou et al, 1997	2050	Chicken (<i>Gallus domesticus</i>)	5	M	FD	4	w	28	w	SM	F	ENZ	ASAT	SR	27.5	40.6	82
12	Jackson and Stevenson, 1981	2158	Chicken (<i>Gallus domesticus</i>)	6	U	FD	280	d	18	w	SM	F	CHM	LIPD	LI	30.0	37.5	76
13	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	CHM	LIPD	LI	35.3	44.1	77
14	Ledoux et al, 1987	2194	Chicken (<i>Gallus domesticus</i>)	3	UX	FD	21	d	1	d	JV	F	ENZ	GOTR	SR	36.3		73
15	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	CHM	LIPD	LI	40.0	50.0	77
16	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	5	M	DR	14	d	4	d	JV	NR	CHM	URIC	BL	51.6	258	75
17	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	2	M	FD	35	d	3	d	JV	NR	CHM	HEMT	BL	75.5		69
18	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	4	M	FD	35	d	3	d	JV	NR	CHM	GLUC	SR	297		76
19	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	M	CHM	CHOL	BT		2.21	69
20	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	3	U	FD	42	d	1	d	JV	M	CHM	CHOL	BT		2.80	69
21	Jackson et al, 1979	2160	Chicken (<i>Gallus domesticus</i>)	5	U	FD	336	d	17	w	SM	F	CHM	LIPD	LI		5.11	71
22	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	3	U	FD	42	d	1	d	JV	M	CHM	CHOL	BT		5.57	69
23	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	4	U	FD	21	d	1	d	JV	M	CHM	CHOL	PL		5.83	69
24	Gill et al, 1995	2107	Chicken (<i>Gallus domesticus</i>)	4	U	FD	2	w	4	w	JV	M	ENZ	SGOT	SR		7.99	71
25	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	2	U	FD	42	d	1	d	JV	M	CHM	CHOL	BT		8.19	69
26	Skrivan et al, 2000	25969	Chicken (<i>Gallus domesticus</i>)	2	M	FD	38	d	1	d	JV	M	CHM	CHOL	AD		9.72	75
27	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	2	U	FD	42	d	21	d	JV	M	CHM	CHOL	BT		11.5	69
28	Nam et al, 1984	2226	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	3	d	JV	NR	CHM	GBCM	NR		13.4	70
29	Poupoulis and Jensen 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	CHM	PHPH	GZ		14.3	69
30	Bakalli et al, 1995	3717	Chicken (<i>Gallus domesticus</i>)	2	U	FD	20	d	1	d	JV	M	CHM	CHOL	PL		17.8	69
31	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	SM	F	ENZ	AATT	SR		23.9	76
32	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	SM	F	ENZ	AATT	SR		30.4	76
33	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	SM	F	ENZ	AATT	SR		35.2	76
34	Ekperigin and Vohra, 1981	2084	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	12	d	JV	NR	CHM	GLCN	LI		35.5	69
35	Van Vleet et al, 1981	80	Duck (<i>Anas platyrhynchos</i>)	2	U	FD	15	d	1	d	JV	M	ENZ	GLPX	BL		201	69
Behavior (BEH)																		
36	Hoda and Maha, 1995	2007	Chicken (<i>Gallus domesticus</i>)	3	U	FD	6	w	1	d	JV	NR	FDB	FCNS	WO	1.92		67
37	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	FDB	FCNS	WO	10.4	20.8	80
38	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	2	M	DR	14	d	4	d	JV	NR	FDB	WCON	WO	12.6		67
39	Chiou et al, 1999	2048	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	3	w	JV	NR	FDB	FCNS	WO	13.3	26.6	80
40	Jenkins et al, 1970	2162	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	1	d	JV	B	FDB	FCNS	WO	13.4		69
41	Harms and Buresh, 1986	2117	Chicken (<i>Gallus domesticus</i>)	3	U	FD	6	w	64	w	SM	F	FDB	FCNS	WO	13.9	19.5	72
42	Ledoux et al, 1989	5812	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	1	d	JV	M	FDB	FCNS	WO	15.2	22.8	74
43	Funk and Baker, 1991	2099	Chicken (<i>Gallus domesticus</i>)	3	U	FD	14	d	8	d	JV	M	FDB	FCNS	WO	15.7	25.8	80
44	Miles et al, 1998	2221	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	B	FDB	FCNS	WO	16.5	24.7	80
45	Pearce et al, 1983	2294	Chicken (<i>Gallus domesticus</i>)	5	U	FD	48	d	26	w	SM	F	FDB	FCNS	WO	16.6	33.1	79
46	Stevenson and Jackson, 1980	2292	Chicken (<i>Gallus domesticus</i>)	5	U	FD	6	d	24	w	SM	F	FDB	FCNS	WO	16.7	33.4	79
47	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	FDB	FCNS	WO	17.0	25.5	80
48	Miles et al, 1998	2221	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	B	FDB	FCNS	WO	17.2	25.8	80
49	Jensen and Maurice, 1978	2165	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	FDB	FEFF	WO	17.8	35.5	79
50	Jackson and Stevenson, 1981	2158	Chicken (<i>Gallus domesticus</i>)	6	U	FD	280	d	18	w	SM	F	FDB	FCNS	WO	17.9	26.9	80
51	Stevenson et al, 1983	6170	Chicken (<i>Gallus domesticus</i>)	4	U	FD	5	d	27	w	SM	F	FDB	FCNS	WO	18.0	28.0	76
52	Ward et al, 1995	6788	Turkey (<i>Melagris gallopavo</i>)	2	M	FD	10	d	5	d	JV	M	FDB	WCON	WO	18.3		70
53	Funk and Baker, 1991	2099	Chicken (<i>Gallus domesticus</i>)	5	U	FD	14	d	8	d	JV	M	FDB	FCNS	WO	19.6	30.5	80
54	Jackson and Stevenson, 1981	2158	Chicken (<i>Gallus domesticus</i>)	6	U	FD	280	d	18	w	SM	F	FDB	FCNS	WO	20.1	26.8	80
55	Pimentel et al, 1992	5617	Chicken (<i>Gallus domesticus</i>)	2	U	FD	3	w	1	d	JV	B	FDB	FCNS	WO	20.9		66
56	Miles et al, 1998	2221	Chicken (<i>Gallus domesticus</i>)	4	M	FD	21	d	1	d	JV	B	FDB	FCNS	WO	21.9	34.0	85
57	Kassim and Suwanpradit, 1996	2172	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	1	d	JV	M	FDB	FCNS	WO	22.7	34.1	79
58	Jackson et al, 1979	2160	Chicken (<i>Gallus domesticus</i>)	5	U	FD	224	d	17	w	SM	F	FDB	FCNS	WO	23.2	29.9	80
59	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	SM	F	FDB	FCNS	WO	23.9		70
60	Ledoux et al, 1987	2194	Chicken (<i>Gallus domesticus</i>)	3	UX	FD	21	d	1	d	JV	F	FDB	FCNS	WO	25.7	51.5	84

Table 5.1
Avian Toxicity Data Extracted for Wildlife Toxicity Reference Value (TRV)
Copper
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Result #	Reference	Ref No.	Test Organism	# of Conc/ Doses	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Type	Effect Measure	Response Site	NOAEL Dose* (mg/kg bw/day)	LOAEL Dose* (mg/kg bw/day)	Total
61	Chiou et al, 1997	2050	Chicken (<i>Gallus domesticus</i>)	5	M	FD	4	w	28	w	SM	F	FDB	FCNS	WO	27.5	40.6	85
62	Jackson, 1977	2157	Chicken (<i>Gallus domesticus</i>)	6	U	FD	35	d	NR	NR	SM	F	FDB	FCNS	WO	29.1	47.5	80
63	Miles et al, 1998	2221	Chicken (<i>Gallus domesticus</i>)	4	M	FD	21	d	1	d	JV	B	FDB	FCNS	WO	29.5		79
64	Hill, 1990	5734	Chicken (<i>Gallus domesticus</i>)	4	U	FD	19	d	1	d	JV	F	FDB	FCNS	WO	30.4		72
65	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	SM	F	FDB	FCNS	WO	30.4		70
66	Chiou et al, 1998	2049	Chicken (<i>Gallus domesticus</i>)	4	U	FD	4	w	38	w	SM	F	FDB	FCNS	WO	33.4	40.1	80
67	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	SM	F	FDB	FCNS	WO	35.2		70
68	Funk and Baker, 1991	2099	Chicken (<i>Gallus domesticus</i>)	5	U	FD	14	d	8	d	JV	M	FDB	FCNS	WO	35.2	63.9	80
69	Funk and Baker, 1991	2099	Chicken (<i>Gallus domesticus</i>)	3	U	FD	14	d	8	d	JV	M	FDB	FCNS	WO	36.3		74
70	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	5	M	DR	14	d	4	d	JV	NR	FDB	WCON	WO	51.6	258	78
71	Stevenson et al, 1983	6170	Chicken (<i>Gallus domesticus</i>)		U	GV	5	d	27	w	SM	F	FDB	FCNS	WO	65.4		68
72	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	2	M	FD	35	d	3	d	JV	NR	FDB	FCNS	WO	75.5		72
73	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	2	M	FD	35	d	3	d	JV	NR	FDB	FCNS	WO	143		67
74	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	4	M	FD	35	d	3	d	JV	NR	FDB	FCNS	WO	246		72
75	Ko et al, 1985	2181	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	3	d	JV	M	FDB	FCNS	WO		2.69	74
76	Gill et al, 1995	2107	Chicken (<i>Gallus domesticus</i>)	4	U	FD	4	w	4	w	JV	M	FDB	FCNS	WO		7.99	74
77	Griminger, 1977	2112	Chicken (<i>Gallus domesticus</i>)	5	U	FD	2	w	7	mo	SM	F	FDB	FCNS	WO		22.4	73
78	Stevenson and Jackson, 1980	2293	Chicken (<i>Gallus domesticus</i>)	4	U	FD	8	w	24	w	SM	F	FDB	FCNS	WO		22.6	73
79	Yannakopoulos et al., 1990	2333	Japanese quail (<i>Coturnix japonica</i>)	4	U	FD	34	d	7	d	JV	B	FDB	FCNS	WO		27.5	74
80	Harms and Buresh, 1986	2118	Turkey (<i>Melagris gallopavo</i>)	3	U	FD	21	d	1	d	JV	B	FDB	FCNS	WO		30.8	74
81	Christmas and Harms, 1979	2052	Turkey (<i>Melagris gallopavo</i>)	3	U	FD	21	d	1	d	JV	B	FDB	FCNS	WO		31.4	74
82	Jensen and Maurice, 1978	2165	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	FDB	FEFF	WO		34.9	73
83	Jensen, 1975	1403	Chicken (<i>Gallus domesticus</i>)	2	U	FD	14	d	1	d	JV	M	FDB	FCNS	WO		92.9	74
Physiology (PHY)																		
84	Rangachar and Hegde, 1975	2259	Chicken (<i>Gallus domesticus</i>)	3	U	FD	120	d	1	d	JV	F	PHY	PROT	PL	3.93		72
85	Ankari et al, 1998	2006	Chicken (<i>Gallus domesticus</i>)	4	U	FD	84	d	25	w	SM	F	PHY	FDCV	WO	4.05	12.1	74
86	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	M	PHY	FDCV	WO	4.43		72
87	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	3	U	FD	42	d	1	d	JV	M	PHY	FDCV	WO	5.56		72
88	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	M	PHY	FDCV	WO	5.83	11.7	78
89	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	2	U	FD	42	d	1	d	JV	M	PHY	FDCV	WO	8.19		72
90	Skrivan et al, 2000	25969	Chicken (<i>Gallus domesticus</i>)	2	M	FD	39	d	1	d	JV	B	PHY	FDCV	WO	9.72		69
91	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	5	U	FD	35	d	1	d	JV	M	PHY	FDCV	WO	11.9		72
92	Jackson et al, 1979	2160	Chicken (<i>Gallus domesticus</i>)	5	U	FD	224	d	17	w	SM	F	PHY	FDCV	WO	12.5	23.2	80
93	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	PHY	FDCV	WO	14.3	28.7	78
94	Miles et al, 1998	2221	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	B	PHY	FDCV	WO	16.5	24.7	80
95	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	PHY	FDCV	WO	17.0	25.5	80
96	Miles et al, 1998	2221	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	B	PHY	FDCV	WO	17.2	25.8	80
97	Jackson and Stevenson, 1981	2158	Chicken (<i>Gallus domesticus</i>)	6	U	FD	280	d	18	w	SM	F	PHY	FDCV	WO	17.9	26.9	80
98	Ward et al, 1995	6788	Turkey (<i>Meleagris gallopavo</i>)	2	M	FD	10	d	5	d	JV	M	PHY	FDCV	WO	18.3		70
99	Jensen and Maurice, 1979	2166	Chicken (<i>Gallus domesticus</i>)	4	U	FD	4	w	1	d	JV	NR	PHY	FDCV	WO	18.5	37.1	79
100	Robbins and Baker, 1980	2267	Chicken (<i>Gallus domesticus</i>)	3	U	FD	14	d	8	d	JV	NR	PHY	FDCV	WO	21.3	42.7	79
101	Ekperigin and Vohra, 1981	6474	Chicken (<i>Gallus domesticus</i>)	2	U	FD	8	d	7	d	JV	NR	PHY	FDCV	WO	21.5		72
102	Jackson and Stevenson, 1981	2158	Chicken (<i>Gallus domesticus</i>)	6	U	FD	280	d	18	w	SM	F	PHY	FDCV	WO	25.3	31.6	80
103	Robbins and Baker, 1980	2266	Chicken (<i>Gallus domesticus</i>)	3	U	FD	8	d	8	d	JV	M	PHY	FDCV	WO	26.4	52.8	79
104	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	w	26	w	SM	F	PHY	FDCV	WO	27.2	36.2	80
105	Chiou et al, 1999	2048	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	3	w	JV	NR	PHY	FDCV	WO	28.4		74
106	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	5	U	FD	4	w	1	d	JV	NR	PHY	FDCV	WO	28.7	57.4	78
107	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	4	U	FD	4	w	1	d	JV	NR	PHY	FDCV	WO	28.7	57.4	78
108	Wang et al, 1987	2319	Chicken (<i>Gallus domesticus</i>)	2	U	FD	3	w	1	d	JV	M	PHY	FDCV	WO	35.5		72
109	Wang et al, 1987	2319	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	1	d	JV	M	PHY	FDCV	WO	35.5		72
110	Ledoux et al, 1987	2194	Chicken (<i>Gallus domesticus</i>)	3	UX	FD	21	d	1	d	JV	F	PHY	FDCV	WO	45.4		78
111	Funk and Baker, 1991	2099	Chicken (<i>Gallus domesticus</i>)	5	U	FD	14	d	8	d	JV	M	PHY	FDCV	WO	46.7	53.6	80
112	Yannakopoulos et al, 1990	2333	Japanese quail (<i>Coturnix japonica</i>)	4	U	FD	34	d	7	d	JV	B	PHY	FDCV	WO	82.0		74
113	Mehring and Brumbaugh, 1960	22	Chicken (<i>Gallus domesticus</i>)	5	M	FD	10	w	1	d	JV	B	PHY	FDCV	WO	84.3		69
114	Ko et al, 1985	2181	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	3	d	JV	M	PHY	FDCV	WO		2.69	74
115	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	2	U	FD	42	d	1	d	JV	M	PHY	FDCV	WO		2.70	72
116	Kashani et al, 1986	2171	Turkey (<i>Meleagris gallopavo</i>)	2	U	FD	8	w	1	d	JV	M	PHY	FDCV	WO		4.88	73
117	Pesti and Bakalli 1996	2244	Chicken (<i>Gallus domesticus</i>)	2	U	FD	42	d	1	d	JV	M	PHY	FDCV	WO		5.43	72
118	Jensen and Maurice 1978	2164	Chicken (<i>Gallus domesticus</i>)	3	U	FD	3	w	1	d	JV	NR	PHY	GPHY	WO		9.43	67
119	Pesti and Bakalli 1996	2244	Chicken (<i>Gallus domesticus</i>)	2	U	FD	42	d	21	d	JV	M	PHY	FDCV	WO		11.5	72
120	Nam et al 1984	2226	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	3	d	JV	NR	PHY	FDCV	WO		13.4	73
121	Bakalli et al, 1995	3717	Chicken (<i>Gallus domesticus</i>)	2	U	FD	41	d	1	d	JV	M	PHY	FDCV	WO		14.3	72

Table 5.1
Avian Toxicity Data Extracted for Wildlife Toxicity Reference Value (TRV)
Copper
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Result #	Reference	Ref No.	Test Organism	# of Conc/ Doses	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Type	Effect Measure	Response Site	NOAEL Dose* (mg/kg bw/day)	LOAEL Dose* (mg/kg bw/day)	Total
122	Jensen and Maurice, 1978	2164	Chicken (<i>Gallus domesticus</i>)	2	U	FD	4	w	1	d	JV	NR	PHY	IRRI	FE		16.6	67
123	Jensen and Maurice, 1978	2164	Chicken (<i>Gallus domesticus</i>)	2	U	FD	3	w	1	d	JV	NR	PHY	GPHY	DT		18.2	73
124	Jensen and Maurice, 1978	2164	Chicken (<i>Gallus domesticus</i>)	2	U	FD	3	w	1	d	JV	NR	PHY	GPHY	DT		18.3	73
125	Jensen and Maurice, 1978	2164	Chicken (<i>Gallus domesticus</i>)	2	U	FD	3	w	1	d	JV	NR	PHY	GPHY	DT		18.4	73
126	Jensen and Maurice, 1978	2164	Chicken (<i>Gallus domesticus</i>)	2	U	FD	3	w	1	d	JV	NR	PHY	GPHY	DT		18.6	73
127	Griminger, 1977	2112	Chicken (<i>Gallus domesticus</i>)	5	U	FD	2	w	7	mo	SM	F	PHY	IRRI	FE		22.4	73
128	Robbins and Baker, 1980	2266	Chicken (<i>Gallus domesticus</i>)	3	U	FD	8	d	8	d	JV	M	PHY	FDCV	WO		26.4	73
129	Jensen and Maurice, 1979	2166	Chicken (<i>Gallus domesticus</i>)	2	U	FD	4	w	1	d	JV	NR	PHY	FDCV	WO		36.6	73
130	Robbins and Baker, 1980	2267	Chicken (<i>Gallus domesticus</i>)	2	U	FD	12	d	8	d	JV	NR	PHY	FDCV	WO		50.1	73
131	Robbins and Baker, 1980	2266	Chicken (<i>Gallus domesticus</i>)	2	U	FD	8	d	8	d	JV	M	PHY	FDCV	WO		55.2	73
132	Robbins and Baker, 1980	2267	Chicken (<i>Gallus domesticus</i>)	2	U	FD	8	d	8	d	JV	NR	PHY	FDCV	WO		57.2	73
133	Robbins and Baker, 1980	2267	Chicken (<i>Gallus domesticus</i>)	2	U	FD	12	d	8	d	JV	NR	PHY	FDCV	WO		59.0	73
Pathology (PTH)																		
134	Guenther et al, 1978	2114	Turkey (<i>Melagris gallopavo</i>)	2	U	FD	24	w	1	d	JV	M	HIS	GHIS	HE	2.97		73
135	Hoda and Maha, 1995	2007	Chicken (<i>Gallus domesticus</i>)	3	U	FD	6	w	1	d	JV	M	ORW	SMIX	AT	3.61	7.21	80
136	Chiou et al, 1999	2048	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	3	w	JV	NR	HIS	GHIS	DT	5.73	14.3	80
137	Hoda and Maha, 1995	2007	Chicken (<i>Gallus domesticus</i>)	3	U	FD	6	w	1	d	JV	NR	ORW	SMIX	LI	6.28		67
138	Jensen et al, 1991	2163	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	1	d	JV	M	HIS	GLSN	MH	8.40	16.8	79
139	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	HIS	GHIS	GZ	12.3	24.7	78
140	Pearce et al, 1983	2294	Chicken (<i>Gallus domesticus</i>)	4	U	FD	5	d	27	w	JV	F	ORW	SMIX	LI	12.3	24.7	78
141	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	5	U	FD	4	w	1	d	JV	NR	HIS	GHIS	GZ	14.3	28.7	78
142	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	4	U	FD	4	w	1	d	JV	NR	HIS	GHIS	GZ	14.3	28.7	78
143	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	5	U	FD	4	w	1	d	JV	NR	HIS	GHIS	GZ	14.3	28.7	78
144	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	HIS	GHIS	GZ	14.3	28.7	78
145	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	HIS	GHIS	GZ	14.3	28.7	78
146	Wideman et al, 1996	2325	Chicken (<i>Gallus domesticus</i>)	5	M	FD	2	w	1	d	JV	M	HIS	GHIS	PR	15.7	21.2	78
147	Pearce et al, 1983	2294	Chicken (<i>Gallus domesticus</i>)	5	U	FD	12	d	26	w	SM	F	ORW	SMIX	LI	15.8	31.6	79
148	Jensen and Maurice, 1978	2165	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	HIS	USTR	GZ	17.8	35.5	79
149	Stevenson et al, 1983	6170	Chicken (<i>Gallus domesticus</i>)	4	U	FD	5	d	27	w	SM	F	ORW	SMIX	LI	18.0	28.0	76
150	Wood and Worden, 1973	36216	Duck (<i>Anas platyrhynchos</i>)	2	U	FD	16	d	2	d	JV	B	ITX	GITX	WO	18.1		72
151	Jackson et al, 1979	2160	Chicken (<i>Gallus domesticus</i>)	5	U	FD	232	d	17	w	SM	F	ORW	ORWT	LI	23.2	29.9	80
152	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	ORW	ORWT	LI	23.7	29.7	80
153	Stevenson and Jackson 1980	2292	Chicken (<i>Gallus domesticus</i>)	5	U	FD	6	d	24	w	SM	F	ORW	SMIX	LI	27.2	54.4	79
154	Chiou et al 1997	2050	Chicken (<i>Gallus domesticus</i>)	5	M	FD	4	w	28	w	SM	F	HIS	GHIS	LI	27.9	35.3	85
155	Stevenson et al, 1983	6170	Chicken (<i>Gallus domesticus</i>)	4	U	GV	5	d	27	w	SM	F	ORW	SMIX	LI	34.0	65.4	79
156	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	ORW	SMIX	GZ	35.3	44.1	80
157	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	ORW	ORWT	GZ	40.0	50.0	80
158	Ledoux et al, 1987	2194	Chicken (<i>Gallus domesticus</i>)	3	UX	FD	21	d	1	d	JV	F	ORW	SMIX	LI	45.4		78
159	Jackson, 1977	2157	Chicken (<i>Gallus domesticus</i>)	6	U	FD	35	d	NR	NR	SM	F	ORW	ORWT	LI	49.9	54.8	80
160	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	5	M	DR	14	d	4	d	JV	NR	HIS	GLSN	WO	51.6	258	78
161	Van Vleet et al, 1981	80	Duck (<i>Anas platyrhynchos</i>)	2	U	FD	28	d	1	d	JV	M	HIS	NCRO	GZ	201		72
162	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	4	M	FD	35	d	3	d	JV	NR	HIS	GLSN	LI	297		70
163	Shivanandappa et al, 1983	3727	Chicken (<i>Gallus domesticus</i>)	6	U	OR	3	w	25	w	JV	M	PTH	ORWT	LI	637		66
164	Hoda and Maha, 1995	2007	Chicken (<i>Gallus domesticus</i>)	3	U	FD	6	w	1	d	JV	M	ORW	SMIX	AT		1.02	74
165	Wood and Worden, 1973	36216	Chicken (<i>Gallus domesticus</i>)	2	U	FD	21	d	2	d	JV	B	ORW	ORWT	LI		3.55	72
166	King, 1975	2177	Duck (<i>Anas platyrhynchos</i>)	2	U	FD	56	d	8	d	JV	B	ORW	SMIX	IN		4.15	72
167	King, 1972	2178	Chicken (<i>Gallus domesticus</i>)	2	U	FD	9	w	1	d	JV	B	ORW	SMIX	IN		4.65	72
168	Jackson et al, 1979	2160	Chicken (<i>Gallus domesticus</i>)	5	U	FD	336	d	17	w	SM	F	ORW	ORWT	LI		5.11	74
169	Jensen and Maurice, 1978	2164	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	ORW	SMIX	LI		7.87	67
170	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	ORW	ORWT	GZ		8.58	74
171	Wideman et al, 1996	2325	Chicken (<i>Gallus domesticus</i>)	4	U	FD	2	w	1	d	JV	M	HIS	GHIS	PR		13.3	72
172	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	2	U	FD	4	w	1	d	JV	NR	HIS	GHIS	GZ		14.3	72
173	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	HIS	GHIS	GZ		14.3	72
174	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	HIS	GHIS	GZ		14.3	72
175	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	HIS	GHIS	GZ		14.3	72
176	Jensen and Maurice, 1978	2164	Chicken (<i>Gallus domesticus</i>)	2	U	FD	4	w	1	d	JV	NR	HIS	GHIS	GZ		16.6	67
177	Latymer and Coates, 1981	2191	Chicken (<i>Gallus domesticus</i>)	2	U	FD	24	d	1	d	JV	B	ORW	ORWT	LI		21.3	73
178	Robbins and Baker, 1980	2267	Chicken (<i>Gallus domesticus</i>)	3	U	FD	14	d	8	d	JV	NR	HIS	GHIS	GZ		21.3	73
179	Stevenson and Jackson, 1980	2293	Chicken (<i>Gallus domesticus</i>)	4	U	FD	8	w	24	w	SM	F	ORW	SMIX	LI		22.6	73
180	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	SM	F	ORW	ORWT	KI		23.9	79
181	Smith, 1969	2284	Chicken (<i>Gallus domesticus</i>)	4	U	FD	25	d	1	d	JV	M	ORW	ORWT	LI		30.3	73
182	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	SM	F	ORW	ORWT	KI		30.4	79

Table 5.1
Avian Toxicity Data Extracted for Wildlife Toxicity Reference Value (TRV)
Copper
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Result #	Reference	Ref No.	Test Organism	# of Conc/ Doses	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Type	Effect Measure	Response Site	NOAEL Dose* (mg/kg bw/day)	LOAEL Dose* (mg/kg bw/day)	Total	
183	Christmas and Harms, 1979	2052	Turkey (<i>Melagris gallopavo</i>)	3	U	FD	21	d	1	d	JV	B	HIS	USTR	GZ		31.4	74	
184	Jensen and Maurice, 1978	2165	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	ORW	SMIX	GZ		34.9	73	
185	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	SM	F	ORW	ORWT	KI		35.2	79	
186	Jensen and Maurice, 1979	2166	Chicken (<i>Gallus domesticus</i>)	2	U	FD	4	w	1	d	JV	NR	ORW	SMIX	SP		36.6	73	
187	Van Vleet et al, 1981	80	Duck (<i>Anas platyrhynchos</i>)	2	U	FD	15	d	1	d	JV	M	HIS	NCRO	GZ		201	72	
188	Shivanandappa et al, 1983	3727	Chicken (<i>Gallus domesticus</i>)	5	U	OR	3	w	25	w	JV	M	ORW	ORWT	LI		536	75	
Reproduction (REP)																			
189	Ankari et al, 1998	2006	Chicken (<i>Gallus domesticus</i>)	4	U	FD	84	d	25	w	LB	F	REP	EGPN	WO	4.05	12.1	80	
190	Harms and Buresh, 1986	2117	Chicken (<i>Gallus domesticus</i>)	3	U	FD	6	w	64	w	LB	F	REP	EGPN	WO	13.9	19.5	85	
191	Jackson and Stevenson, 1981	2158	Chicken (<i>Gallus domesticus</i>)	6	U	FD	280	d	18	w	LB	F	EGG	EGWT	EG	15.6	23.3	86	
192	Stevenson et al, 1983	6170	Chicken (<i>Gallus domesticus</i>)	4	U	GV	5	d	27	w	LB	F	REP	PROG	WO	16.7	34.0	89	
193	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	LB	F	REP	EGPN	WO	17.0	25.5	86	
194	Stevenson et al, 1983	6170	Chicken (<i>Gallus domesticus</i>)	4	U	FD	5	d	27	w	LB	F	REP	PROG	WO	18.0	28.0	86	
195	Jackson and Stevenson, 1981	2158	Chicken (<i>Gallus domesticus</i>)	6	U	FD	280	d	18	w	LB	F	EGG	EGWT	EG	19.4	29.0	86	
196	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	LB	F	REP	EGPN	WO	20.5	30.7	86	
197	Jackson et al, 1979	2160	Chicken (<i>Gallus domesticus</i>)	5	U	FD	336	d	17	w	LB	F	REP	EGPN	WO	21.6		71	
198	Griminger, 1977	2112	Chicken (<i>Gallus domesticus</i>)	5	U	FD	2	w	7	mo	LB	F	EGG	ESTH	EG	22.4	44.8	85	
199	Pearce et al, 1983	2294	Chicken (<i>Gallus domesticus</i>)	5	U	FD	12	d	26	w	LB	F	REP	EGPN	WO	22.5	45.0	85	
200	Jackson et al, 1979	2160	Chicken (<i>Gallus domesticus</i>)	5	U	FD	232	d	17	w	LB	F	REP	EGPN	WO	23.2	29.9	86	
201	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	LB	F	REP	EGPN	WO	23.9		76	
202	Stevenson and Jackson, 1980	2292	Chicken (<i>Gallus domesticus</i>)	5	U	FD	6	d	24	w	LB	F	REP	EGPN	WO	27.2	54.4	85	
203	Chiou et al, 1997	2050	Chicken (<i>Gallus domesticus</i>)	5	M	FD	4	w	28	w	LB	F	REP	EGPN	WO	27.5	40.6	91	
204	Jackson, 1977	2157	Chicken (<i>Gallus domesticus</i>)	6	U	FD	35	d	NR	NR	LB	F	REP	PROG	WO	29.1	47.5	86	
205	Jackson and Stevenson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	LB	F	REP	EGPN	WO	30.4		76	
206	Chiou et al, 1998	2049	Chicken (<i>Gallus domesticus</i>)	4	U	FD	4	w	38	w	LB	F	REP	EGPN	WO	33.4	40.1	86	
207	Jackson and Stevenson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	LB	F	REP	EGPN	WO	35.2		76	
208	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	LB	F	REP	ORWT	OV	40.0	50.0	86	
209	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	LB	F	REP	EGPN	WO	43.3		71	
210	Shivanandappa et al, 1983	3727	Chicken (<i>Gallus domesticus</i>)	6	U	OR	3	w	25	w	JV	M	REP	SPCV	TE	239	318	87	
211	Kadirvel and Kothandaraman, 1978	11876	Chicken (<i>Gallus domesticus</i>)	2	U	FD	28	w	12	w	LB	F	EGG	EGWT	WO		19.7	80	
212	Stevenson and Jackson, 1980	2293	Chicken (<i>Gallus domesticus</i>)	4	U	FD	8	w	24	w	LB	F	REP	EGPN	WO		22.6	79	
213	Shivanandappa et al, 1983	3727	Chicken (<i>Gallus domesticus</i>)	5	U	OR	3	w	25	w	JV	M	REP	SPCV	TE		536	81	
Growth (GRO)																			
214	Hoda and Maha, 1995	2007	Chicken (<i>Gallus domesticus</i>)	3	U	FD	6	w	1	d	JV	M	GRO	BDWT	WO	1.92		78	
215	Kashani et al, 1986	2171	Turkey (<i>Melagris gallopavo</i>)	4	U	FD	8	w	1	d	JV	M	GRO	BDWT	WO	2.34	4.68	83	
216	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	2	U	FD	42	d	1	d	JV	M	GRO	BDWT	WO	2.70		76	
217	Hill, 1974	1369	Chicken (<i>Gallus domesticus</i>)	2	U	FD	2	w	1	d	JV	B	GRO	BDWT	WO	2.75		76	
218	Guenther et al, 1978	2114	Turkey (<i>Melagris gallopavo</i>)	2	U	FD	24	w	1	d	JV	M	GRO	BDWT	WO	2.97		68	
219	McGhee et al, 1965	14453	Chicken (<i>Gallus domesticus</i>)	5	U	FD	4	w	NR	NR	JV	NR	GRO	BDWT	WO	3.83	7.67	83	
220	King, 1975	2177	Duck (<i>Anas platyrhynchos</i>)	2	U	FD	56	d	8	d	JV	B	GRO	BDWT	WO	4.15		76	
221	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	M	GRO	BDWT	WO	4.43		76	
222	King, 1972	2178	Chicken (<i>Gallus domesticus</i>)	2	U	FD	9	w	1	d	JV	B	GRO	BDWT	WO	4.65		67	
223	Kayongo-Male and Palmer, 1998	5149	Turkey (<i>Melagris gallopavo</i>)	3	U	FD	4	w	NR	NR	JV	NR	GRO	BDWT	WO	4.75		68	
224	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	2	U	FD	42	d	1	d	JV	M	GRO	BDWT	WO	5.43		76	
225	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	3	U	FD	42	d	1	d	JV	M	GRO	BDWT	WO	5.56		76	
226	Waibel et al, 1964	14405	Turkey (<i>Melagris gallopavo</i>)	3	U	FD	3	w	7	d	JV	NR	GRO	BDWT	WO	5.82	46.6	75	
227	Hoda and Maha, 1995	2007	Chicken (<i>Gallus domesticus</i>)	3	U	FD	6	w	1	d	JV	NR	GRO	BDWT	WO	6.28		78	
228	Hoda and Maha, 1995	2007	Chicken (<i>Gallus domesticus</i>)	3	U	FD	6	w	1	d	JV	NR	GRO	BDWT	WO	7.55		78	
229	Hill, 1974	92	Chicken (<i>Gallus domesticus</i>)	2	U	FD	2	w	1	d	JV	B	GRO	BDWT	WI	7.63		76	
230	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	2	U	FD	42	d	1	d	JV	M	GRO	BDWT	WO	8.19		76	
231	Ko et al, 1985	2181	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	3	d	JV	M	GRO	BDWT	WO	8.40		69	
232	Ekperigin and Vohra, 1981	6474	Chicken (<i>Gallus domesticus</i>)	4	U	FD	7	d	6	d	JV	NR	GRO	BDWT	WO	8.59	42.9	80	
233	Ekperigin and Vohra, 1981	6474	Chicken (<i>Gallus domesticus</i>)	3	U	FD	7	d	7	d	JV	NR	GRO	BDWT	WO	8.59	42.9	80	
234	Gill et al, 1995	2107	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	4	w	JV	M	GRO	BDWT	WO	9.52	19.0	84	
235	Skrivan et al, 2000	25969	Chicken (<i>Gallus domesticus</i>)	2	M	FD	38	d	1	d	JV	B	GRO	BDWT	WO	9.72		82	
236	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	5	M	DR	14	d	4	d	JV	NR	GRO	BDWT	WO	10.2	51.6	82	
237	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	3	U	FD	42	d	1	d	JV	M	GRO	BDWT	WO	11.1		76	
238	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	2	U	FD	42	d	21	d	JV	M	GRO	BDWT	WO	11.5		67	
239	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	5	U	FD	35	d	1	d	JV	M	GRO	BDWT	WO	11.9		76	
240	Nam et al, 1984	2226	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	3	d	JV	NR	GRO	BDWT	WO	12.2	24.3	83	
241	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	2	M	DR	14	d	4	d	JV	NR	GRO	BDWT	WO	12.6		78	
242	Chiou et al, 1999	2048	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	3	w	JV	NR	GRO	BDWT	WO	13.3	26.6	84	

Table 5.1
Avian Toxicity Data Extracted for Wildlife Toxicity Reference Value (TRV)
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Result #	Reference	Ref No.	Test Organism	# of Conc/ Doses	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Type	Effect Measure	Response Site	NOAEL Dose* (mg/kg bw/day)	LOAEL Dose* (mg/kg bw/day)	Total
243	Jenkins et al, 1970	2162	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	1	d	JV	B	GRO	BDWT	WO	13.4		73
244	Marron et al, 2001	25968	Chicken (<i>Gallus domesticus</i>)	2	U	FD	21	d	7	d	JV	M	GRO	BDWT	WO	14.2		68
245	Hill, 1990	5734	Chicken (<i>Gallus domesticus</i>)	5	U	FD	19	d	1	d	JV	F	GRO	BDWT	WO	14.2		76
246	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO	14.3	28.7	82
247	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	5	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO	14.3	28.7	82
248	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO	14.3	28.7	82
249	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	5	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO	14.3	28.7	82
250	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO	14.3	28.7	82
251	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	2	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO	14.3		67
252	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	2	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO	14.3		67
253	Bakalli et al, 1995	3717	Chicken (<i>Gallus domesticus</i>)	2	U	FD	41	d	1	d	JV	M	GRO	BDWT	WO	14.3		76
254	Funk and Baker, 1991	2099	Chicken (<i>Gallus domesticus</i>)	3	U	FD	14	d	8	d	JV	M	GRO	BDWT	WO	15.7	25.8	84
255	Miles et al, 1998	2221	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	B	GRO	BDWT	WO	16.5	24.7	84
256	Stevenson and Jackson, 1980	2292	Chicken (<i>Gallus domesticus</i>)	5	U	FD	6	d	24	w	SM	F	GRO	BDWT	WO	16.7	33.4	83
257	Miles et al, 1998	2221	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	B	GRO	BDWT	WO	17.2	25.8	84
258	Pesti and Bakalli, 1996	2244	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	M	GRO	BDWT	WO	17.5		76
259	Smith, 1969	2284	Chicken (<i>Gallus domesticus</i>)	4	U	FD	25	d	1	d	JV	M	GRO	BDWT	WO	17.8	31.1	83
260	Wang et al, 1987	2319	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	1	d	JV	M	GRO	BDWT	WO	17.8	35.5	82
261	Stevenson et al, 1983	6170	Chicken (<i>Gallus domesticus</i>)	4	U	FD	5	d	27	w	SM	F	GRO	BDWT	WO	18.0	28.0	80
262	Jensen and Maurice, 1978	2164	Chicken (<i>Gallus domesticus</i>)	2	U	FD	3	w	1	d	JV	NR	GRO	BDWT	WO	18.2		68
263	Ward et al, 1995	6788	Turkey (<i>Melagris gallopavo</i>)	2	M	FD	10	d	5	d	JV	M	GRO	BDWT	WO	18.3		74
264	Jensen and Maurice, 1978	2164	Chicken (<i>Gallus domesticus</i>)	2	U	FD	3	w	1	d	JV	NR	GRO	BDWT	WO	18.3		68
265	Jensen and Maurice, 1978	2164	Chicken (<i>Gallus domesticus</i>)	2	U	FD	3	w	1	d	JV	NR	GRO	BDWT	WO	18.4		68
266	Jensen and Maurice, 1978	2166	Chicken (<i>Gallus domesticus</i>)	4	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO	18.5	37.1	83
267	Jensen and Maurice, 1978	2164	Chicken (<i>Gallus domesticus</i>)	2	U	FD	3	w	1	d	JV	NR	GRO	BDWT	WO	18.6		68
268	Funk and Baker, 1991	2099	Chicken (<i>Gallus domesticus</i>)	5	U	FD	14	d	8	d	JV	M	GRO	BDWT	WO	19.6	30.5	84
269	Kadirvel and Kothandaraman, 1978	11876	Chicken (<i>Gallus domesticus</i>)	2	U	FD	28	w	12	w	SM	F	GRO	BDWT	WO	19.7		69
270	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	GRO	BDWT	WO	20.5	30.7	84
271	Pimentel et al, 1992	5617	Chicken (<i>Gallus domesticus</i>)	2	U	FD	3	w	1	d	JV	B	GRO	BDWT	WO	20.9		68
272	Robbins and Baker, 1980	2267	Chicken (<i>Gallus domesticus</i>)	3	U	FD	14	d	8	d	JV	NR	GRO	BDWT	WO	21.3	42.7	83
273	Ekperigin and Vohra, 1981	6474	Chicken (<i>Gallus domesticus</i>)	5	U	FD	7	d	9	d	JV	NR	GRO	BDWT	WO	21.5	42.9	82
274	Ekperigin and Vohra, 1981	6474	Chicken (<i>Gallus domesticus</i>)	2	U	FD	8	d	9	d	JV	NR	GRO	BDWT	WO	21.5		76
275	Jackson et al, 1979	2160	Chicken (<i>Gallus domesticus</i>)	5	U	FD	336	d	17	w	SM	F	GRO	BDWT	WO	21.6		68
276	Wideman et al, 1996	2325	Chicken (<i>Gallus domesticus</i>)	5	M	FD	2	w	1	d	JV	M	GRO	BDWT	WO	21.7		76
277	Miles et al, 1998	2221	Chicken (<i>Gallus domesticus</i>)	4	M	FD	21	d	1	d	JV	B	GRO	BDWT	WO	21.9	34.0	89
278	Griminger, 1977	2112	Chicken (<i>Gallus domesticus</i>)	5	U	FD	2	w	7	mo	SM	F	GRO	BDWT	WO	22.4	44.8	83
279	Kassim and Suwanpradit, 1996	2172	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	1	d	JV	M	GRO	BDWT	WO	22.7	34.1	83
280	Jackson and Stevenson, 1981	2158	Chicken (<i>Gallus domesticus</i>)	6	U	FD	280	d	18	w	SM	F	GRO	BDWT	WO	23.0	30.7	84
281	Jackson et al, 1979	2160	Chicken (<i>Gallus domesticus</i>)	5	U	FD	232	d	17	w	SM	F	GRO	BDWT	WO	23.2	29.9	84
282	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	GRO	BDWT	WO	23.3	31.0	84
283	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	SM	F	GRO	BDWT	WO	23.9		74
284	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO	24.7		67
285	Jackson and Stevenson, 1981	2158	Chicken (<i>Gallus domesticus</i>)	6	U	FD	280	d	18	w	SM	F	GRO	BDWT	WO	26.4	35.2	84
286	Ward et al, 1995	6788	Turkey (<i>Melagris gallopavo</i>)	2	M	DR	10	d	5	d	JV	M	GRO	BDWT	WO	26.6		69
287	Ledoux et al, 1989	5812	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	1	d	JV	M	GRO	BDWT	WO	26.9	40.4	78
288	Chiou et al, 1997	2050	Chicken (<i>Gallus domesticus</i>)	5	M	FD	28	d	28	w	SM	F	GRO	BDWT	WO	27.9	35.3	89
289	Hill, 1989	7091	Chicken (<i>Gallus domesticus</i>)	4	U	FD	19	d	NR	NR	JV	NR	GRO	BDWT	WO	28.4		70
290	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	4	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO	28.7	57.4	82
291	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO	28.7		67
292	Miles et al, 1998	2221	Chicken (<i>Gallus domesticus</i>)	4	M	FD	21	d	1	d	JV	B	GRO	BDWT	WO	29.5		83
293	Vohra and Kratzer, 1968	14404	Turkey (<i>Melagris gallopavo</i>)	3	U	FD	21	d	NR	NR	JV	B	GRO	BDWT	WO	29.7	59.3	82
294	Hill, 1990	5734	Chicken (<i>Gallus domesticus</i>)	4	U	FD	19	d	1	d	JV	F	GRO	BDWT	WO	30.4		76
295	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	SM	F	GRO	BDWT	WO	30.7		74
296	Mehring and Brumbaugh, 1960	22	Chicken (<i>Gallus domesticus</i>)	5	M	FD	10	w	1	d	JV	B	GRO	BDWT	WO	33.0	43.3	88
297	Jensen et al, 1991	2163	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	1	d	JV	M	GRO	BDWT	WO	34.1		68
298	Harms and Buresh, 1986	2118	Turkey (<i>Melagris gallopavo</i>)	3	U	FD	21	d	1	d	JV	B	GRO	BDWT	WO	34.6	51.9	84
299	Funk and Baker, 1991	2099	Chicken (<i>Gallus domesticus</i>)	5	U	FD	14	d	8	d	JV	M	GRO	BDWT	WO	35.2	63.9	83
300	Bafundo et al, 1984	2517	Chicken (<i>Gallus domesticus</i>)	2	U	FD	14	d	8	d	JV	M	GRO	BDWT	WO	35.5		67
301	Hill, 1990	5734	Chicken (<i>Gallus domesticus</i>)	2	U	FD	19	d	1	d	JV	F	GRO	BDWT	WO	35.5		76
302	Funk and Baker, 1991	2099	Chicken (<i>Gallus domesticus</i>)	3	U	FD	14	d	8	d	JV	M	GRO	BDWT	WO	36.3		78
303	Jensen and Maurice, 1979	2166	Chicken (<i>Gallus domesticus</i>)	2	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO	36.6		77
304	Davis et al, 1996	1278	Chicken (<i>Gallus domesticus</i>)	2	U	FD	21	d	14	d	JV	M	GRO	BDWT	WO	37.1		69

Table 5.1
Avian Toxicity Data Extracted for Wildlife Toxicity Reference Value (TRV)
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Result #	Reference	Ref No.	Test Organism	# of Conc/ Doses	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Type	Effect Measure	Response Site	NOAEL Dose* (mg/kg bw/day)	LOAEL Dose* (mg/kg bw/day)	Total
305	Chiou et al, 1998	2049	Chicken (<i>Gallus domesticus</i>)	4	U	FD	4	w	38	w	SM	F	GRO	BDWT	WO	40.1		69
306	Southern and Baker, 1983	6368	Chicken (<i>Gallus domesticus</i>)	2	U	FD	14	d	8	d	JV	M	GRO	BDWT	WO	41.0		68
307	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	GRO	BDWT	WO	43.3		69
308	Kassim and Suwanpradit, 1996	2172	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	3	w	JV	M	GRO	BDWT	WO	49.5	74.2	83
309	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	GRO	BDWT	WO	50.0		69
310	Vohra and Kratzer, 1968	14404	Turkey (<i>Melagris gallopavo</i>)	3	U	FD	21	d	NR	NR	JV	B	GRO	BDWT	WO	50.1		76
311	Jackson, 1977	2157	Chicken (<i>Gallus domesticus</i>)	6	U	FD	35	d	1	yr	SM	F	GRO	BDWT	WO	50.9	55.9	84
312	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	4	M	FD	35	d	3	d	JV	NR	GRO	BDWT	WO	56.8	109	89
313	Vohra and Kratzer, 1968	14404	Turkey (<i>Melagris gallopavo</i>)	5	U	FD	21	d	NR	NR	JV	B	GRO	BDWT	WO	60.0	120	82
314	Stevenson et al, 1983	6170	Chicken (<i>Gallus domesticus</i>)	4	U	GV	5	d	27	w	SM	F	GRO	BDWT	WO	65.4		68
315	Yannakopoulos et al., 1990	2333	Japanese quail (<i>Coturnix japonica</i>)	4	U	FD	34	d	7	d	JV	B	GRO	BDWT	WO	82.0		78
316	Leeson and Summers, 1982	2196	Chicken (<i>Gallus domesticus</i>)	4	U	FD	21	d	1	d	JV	M	GRO	BDWT	WO	103		68
317	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	2	M	FD	35	d	3	d	JV	NR	GRO	BDWT	WO	143		78
318	Ko et al, 1985	2181	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	3	d	JV	M	GRO	BDWT	WO		2.69	78
319	Kashani et al, 1986	2171	Turkey (<i>Melagris gallopavo</i>)	2	U	FD	8	w	1	d	JV	M	GRO	BDWT	WO		4.88	77
320	Harms and Eberst, 1974	9234	Turkey (<i>Melagris gallopavo</i>)	2	U	FD	3	w	1	d	JV	NR	GRO	GGRO	WO		10.3	77
321	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO		14.3	76
322	Jensen and Maurice, 1978	2165	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO		17.5	77
323	Latymer and Coates, 1981	2191	Chicken (<i>Gallus domesticus</i>)	2	U	FD	24	d	1	d	JV	B	GRO	BDWT	WO		21.3	77
324	Stevenson and Jackson, 1980	2293	Chicken (<i>Gallus domesticus</i>)	4	U	FD	8	w	24	w	SM	F	GRO	BDWT	WO		22.6	77
325	Ledoux et al, 1987	2194	Chicken (<i>Gallus domesticus</i>)	3	UX	FD	21	d	1	d	JV	F	GRO	BDWT	WO		22.7	82
326	Robbins and Baker, 1980	2266	Chicken (<i>Gallus domesticus</i>)	3	U	FD	8	d	8	d	JV	M	GRO	BDWT	WO		26.4	77
327	Robbins and Baker, 1980	2266	Chicken (<i>Gallus domesticus</i>)	3	U	FD	8	d	8	d	JV	M	GRO	BDWT	WO		26.4	77
328	Hill, 1974	1369	Chicken (<i>Gallus domesticus</i>)	2	U	FD	5	w	1	d	JV	B	GRO	BDWT	WO		28.7	76
329	Christmas and Harms, 1979	2052	Turkey (<i>Melagris gallopavo</i>)	3	U	FD	21	d	1	d	JV	B	GRO	BDWT	WO		31.4	78
330	Jensen and Maurice, 1978	2165	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	GRO	BDWT	WO		34.9	77
331	Stevenson and Jackson, 1981	2291	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	24	w	SM	F	GRO	BDWT	WO		35.2	83
332	Ekperigin and Vohra, 1981	2084	Chicken (<i>Gallus domesticus</i>)	3	U	FD	1	w	12	d	JV	B	GRO	BDWT	WO		35.5	76
333	Wang et al, 1987	2319	Chicken (<i>Gallus domesticus</i>)	2	U	FD	3	w	1	d	JV	M	GRO	BDWT	WO		35.5	76
334	Hill, 1974	92	Chicken (<i>Gallus domesticus</i>)	6	U	FD	2	w	1	d	JV	B	GRO	BDWT	WO		42.9	76
335	Robbins and Baker, 1980	2267	Chicken (<i>Gallus domesticus</i>)	2	U	FD	12	d	8	d	JV	NR	GRO	BDWT	WO		50.1	77
336	Robbins and Baker, 1980	2266	Chicken (<i>Gallus domesticus</i>)	2	U	FD	8	d	8	d	JV	M	GRO	BDWT	WO		55.2	77
337	Robbins and Baker, 1980	2267	Chicken (<i>Gallus domesticus</i>)	2	U	FD	8	d	8	d	JV	NR	GRO	BDWT	WO		57.2	77
338	Robbins and Baker, 1980	2267	Chicken (<i>Gallus domesticus</i>)	2	U	FD	12	d	8	d	JV	NR	GRO	BDWT	WO		59.0	77
339	Vohra and Kratzer, 1968	14404	Turkey (<i>Melagris gallopavo</i>)	4	U	FD	21	d	NR	NR	JV	B	GRO	BDWT	WO		60.0	76
340	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	2	M	FD	35	d	3	d	JV	NR	GRO	BDWT	WO		75.5	83
341	Hill, 1979	1370	Chicken (<i>Gallus domesticus</i>)	2	U	FD	2	w	1	d	JV	NR	GRO	BDWT	WO		85.9	76
342	Jensen, 1975	1403	Chicken (<i>Gallus domesticus</i>)	2	U	FD	14	d	1	d	JV	NR	GRO	BDWT	WO		92.9	78
343	Hill, 1980	395	Chicken (<i>Gallus domesticus</i>)	2	U	FD	1	w	1	d	JV	F	GRO	BDWT	WO		138	70
Survival (MOR)																		
344	Hill, 1974	1369	Chicken (<i>Gallus domesticus</i>)	2	U	FD	2	w	NR	NR	JV	B	MOR	MORT	WO	2.75		70
345	Wood and Worden, 1973	36216	Chicken (<i>Gallus domesticus</i>)	2	U	FD	49	d	2	d	JV	B	MOR	MORT	WO	3.55		77
346	Wood and Worden, 1973	36216	Duck (<i>Anas platyrhynchos</i>)	2	U	FD	49	d	2	d	JV	B	MOR	MORT	WO	6.69		77
347	Hill, 1974	92	Chicken (<i>Gallus domesticus</i>)	2	U	FD	5	w	1	d	JV	B	MOR	MORT	WO	7.63		68
348	McGhee et al, 1965	14453	Chicken (<i>Gallus domesticus</i>)	5	U	FD	4	w	NR	NR	JV	NR	MOR	MORT	WO	8.14	16.3	84
349	Ko et al, 1985	2181	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	3	d	JV	M	MOR	MORT	WO	8.40		79
350	Skrivan et al, 2000	25969	Chicken (<i>Gallus domesticus</i>)	2	M	FD	38	d	1	d	JV	B	MOR	MORT	WO	9.72		74
351	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	MOR	MORT	WO	11.7		68
352	Jenkins et al, 1970	2162	Chicken (<i>Gallus domesticus</i>)	2	M	FD	6	w	1	d	JV	B	MOR	MORT	WO	13.4		83
353	Marron et al, 2001	25968	Chicken (<i>Gallus domesticus</i>)	2	U	FD	21	d	7	d	JV	M	MOR	MORT	WO	14.2		78
354	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	5	U	FD	4	w	1	d	JV	NR	MOR	MORT	WO	14.3	28.7	83
355	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	MOR	MORT	WO	14.3	28.7	83
356	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	2	U	FD	4	w	1	d	JV	NR	MOR	MORT	WO	14.3		77
357	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	2	U	FD	4	w	1	d	JV	NR	MOR	MORT	WO	14.3		77
358	Wood and Worden, 1973	36216	Duck (<i>Anas platyrhynchos</i>)	2	U	FD	16	d	2	d	JV	B	MOR	MORT	WO	18.1		77
359	Ward et al, 1995	6788	Turkey (<i>Melagris gallopavo</i>)	2	M	FD	10	d	5	d	JV	M	MOR	MORT	WO	18.3		84
360	Ankari et al, 1998	2006	Chicken (<i>Gallus domesticus</i>)	4	U	FD	84	d	25	w	SM	F	MOR	MORT	WO	19.9		73
361	Latymer and Coates, 1981	2191	Chicken (<i>Gallus domesticus</i>)	2	U	FD	24	d	1	d	JV	B	MOR	MORT	WO	21.3		69
362	Jackson et al, 1979	2160	Chicken (<i>Gallus domesticus</i>)	5	U	FD	336	d	17	w	SM	F	MOR	MORT	WO	21.6		79
363	Ward et al, 1995	6788	Turkey (<i>Melagris gallopavo</i>)	2	M	DR	10	d	5	d	JV	M	MOR	MORT	WO	26.6		79
364	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	4	U	FD	4	w	1	d	JV	NR	MOR	MORT	WO	28.7	57.4	83
365	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	5	U	FD	4	w	1	d	JV	NR	MOR	MORT	WO	28.7	57.4	83

Table 5.1
Avian Toxicity Data Extracted for Wildlife Toxicity Reference Value (TRV)
Copper
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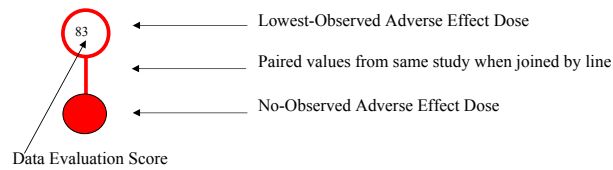
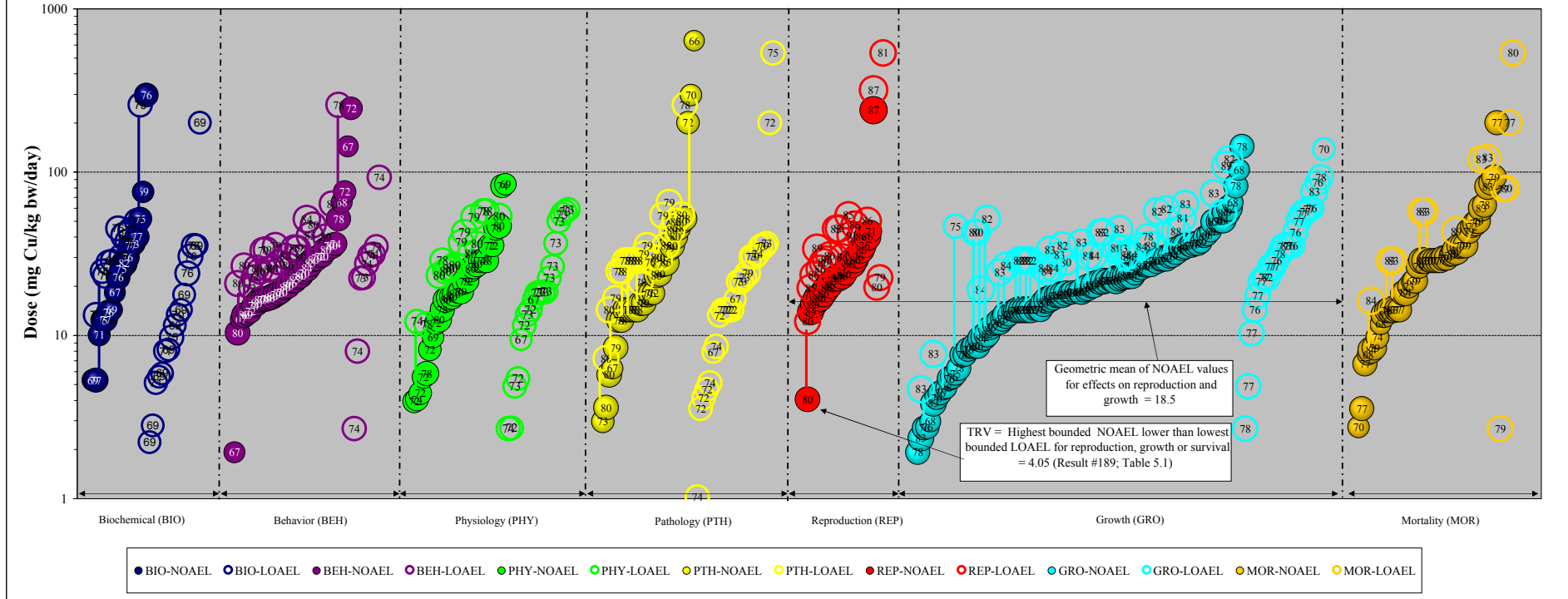
Result #	Reference	Ref No.	Test Organism	# of Conc/ Doses	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Type	Effect Measure	Response Site	NOAEL Dose* (mg/kg bw/day)	LOAEL Dose* (mg/kg bw/day)	Total
366	Hill, 1974	1369	Chicken (<i>Gallus domesticus</i>)	2	U	FD	5	w	1	d	JV	M	MOR	MORT	WO	28.7		70
367	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	MOR	MORT	WO	28.7		77
368	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	MOR	MORT	WO	28.7		77
369	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	MOR	MORT	WO	28.7		77
370	Poupoulis and Jensen, 1976	2250	Chicken (<i>Gallus domesticus</i>)	3	U	FD	4	w	1	d	JV	NR	MOR	MORT	WO	28.7		77
371	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	MOR	MORT	WO	29.7		79
372	Miles et al, 1998	2221	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	B	MOR	MORT	WO	29.7		79
373	Miles et al, 1998	2221	Chicken (<i>Gallus domesticus</i>)	4	U	FD	42	d	1	d	JV	B	MOR	MORT	WO	30.8		70
374	Jackson and Stevenson, 1981	2158	Chicken (<i>Gallus domesticus</i>)	6	U	FD	280	d	18	w	SM	F	MOR	MORT	WO	31.6		79
375	Mehring and Brumbaugh, 1960	22	Chicken (<i>Gallus domesticus</i>)	5	M	FD	10	w	1	d	JV	B	MOR	MORT	WO	33.0	43.3	89
376	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	MOR	MORT	WO	35.2		79
377	Jackson and Stevenson, 1981	2158	Chicken (<i>Gallus domesticus</i>)	6	U	FD	280	d	18	w	SM	F	MOR	MORT	WO	35.4		79
378	Jackson et al, 1979	2160	Chicken (<i>Gallus domesticus</i>)	5	U	FD	232	d	17	w	SM	F	MOR	MORT	WO	35.5		79
379	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	MOR	MORT	WO	43.3		79
380	Waibel et al, 1964	14405	Turkey (<i>Melagris gallopavo</i>)	3	U	FD	3	w	7	d	JV	NR	MOR	SURV	WO	46.6		72
381	Christmas and Harms, 1979	2052	Turkey (<i>Melagris gallopavo</i>)	3	U	FD	21	d	1	d	JV	B	MOR	MORT	WO	48.3		79
382	Jackson and Stevenson, 1981	2159	Chicken (<i>Gallus domesticus</i>)	6	U	FD	336	d	26	w	SM	F	MOR	MORT	WO	50.0		79
383	Vohra and Kratzer, 1968	14404	Turkey (<i>Melagris gallopavo</i>)	5	U	FD	21	d	NR	NR	JV	B	MOR	MORT	WO	60.0	120	83
384	Jackson, 1977	2157	Chicken (<i>Gallus domesticus</i>)	6	U	FD	35	d	NR	NR	SM	F	MOR	MORT	WO	62.7		78
385	Hill, 1974	92	Chicken (<i>Gallus domesticus</i>)	6	U	FD	5	w	1	d	JV	F	MOR	MORT	WO	81.6	122	83
386	Hill, 1979	1370	Chicken (<i>Gallus domesticus</i>)	2	U	FD	2	w	1	d	JV	B	MOR	MORT	WO	85.9		77
387	Jensen, 1975	1403	Chicken (<i>Gallus domesticus</i>)	2	U	FD	14	d	1	d	JV	NR	MOR	MORT	WO	92.9		79
388	Van Vleet et al, 1981	80	Duck (<i>Anas platyrhynchos</i>)	2	U	FD	15	d	1	d	JV	M	MOR	MORT	WO	201		77
389	Ko et al, 1985	2181	Chicken (<i>Gallus domesticus</i>)	4	U	FD	3	w	3	d	JV	M	MOR	MORT	WO		2.69	79
390	Foster, 1999	18769	Duck (<i>Anas platyrhynchos</i>)	2	M	DR	4	d	4	d	JV	NR	MOR	MORT	WO		78.5	77
391	Shivanandappa et al, 1983	3727	Chicken (<i>Gallus domesticus</i>)	6	U	OR	3	w	25	w	JV	M	MOR	MORT	WO		79.6	80
392	Van Vleet et al, 1981	80	Duck (<i>Anas platyrhynchos</i>)	2	U	FD	15	d	1	d	JV	M	MOR	MORT	WO		201	77
393	Shivanandappa et al, 1983	3727	Chicken (<i>Gallus domesticus</i>)	5	U	OR	4	d	25	w	JV	M	MOR	MORT	WO		536	80

AATT = alanine aminotransferase; AD = adipose tissue; ASAT = aspartate aminotransferase; AT = alimentary tract; B = both; BDWT = body weight changes; BEH = behavior; BIO = biochemical; BL = blood; BT = breast; bw = body weight; CHM = chemical changes; CHOL = cholesterol; CRKI = creatine kinase; d = day; DR = drinking water; DT = digestive tract; EG = egg; EGG = egg; EGP = eggs per nest; EGWT = egg weight; ENZ = enzyme level changes; ESTH = eggshell thickness; F = female; FCNS = food consumption; FD = food; FDB = feeding behavior; FDCV = food conversion efficiency; FE = feathers; FEFF = feeding efficiency; FFTA = free fatty acids; GCHM = general biochemical changes; GGRO = general growth; GHIS = general histology; GITX = general intoxication; GLCN = glycine; GLPX = glutathione peroxidase; GLSN = gross lesions; GLUC = glucose; GOTR = glutamic-oxaloacetic transaminase; GPXY = general physiology changes; GRO = growth; GV = gavage; GZ = gizzard; HE = heart; HEMT = general hematology; HIS = histological changes; HMGL = hemoglobin; IN = intestinal tract; IRR1 = skin irritation; ITX = intoxication; JV = juvenile; kg = kilograms; KI = kidney; LADH = lactate dehydrogenase; LB = egg-laying bird; LD = lipid; LI = liver; LIPD = lipid; LOAEL = lowest observed adverse effect level; mg = milligram; M = measured; MH = mouth; MOR = effects on mortality and survival; MORT = mortality; NCRO = necrosis; NOAEL = No Observed Adverse Effect Level; NR = Not reported; OR = other oral; ORW = organ weight changes; ORWT = organ weight changes; OV = ovaries; PHPH = pH; PHY = physiology; PL = plasma; PR = proventriculus; PROG = progeny counts/numbers; PROT = prothrombin time; PTH = pathology; REP = reproduction; SGOT = serum glutamate oxaloacetate transaminase; SK = skin; SM = sexually mature; SMIX = weight relative to body weight; SP = spleen; SPCV = sperm cell viability; SR = serum; SURV = survival; TE = testes; U = unmeasured; URIC = uric acid; USTR = ultrastructural changes; UX = measured but values not reported; w = weeks; WCON = water consumption; WI = wings; WO = whole organism; yr = year.

*NOAEL and LOAEL values that are equal and from the same reference represent different experimental designs.

These are designated with different Phase numbers in Appendix 5.1.

Figure 5.1 Avian TRV Derivation for Copper



Wildlife TRV Derivation Process

- 1) There are at least three results available for two test species within the growth, reproduction, and mortality effect groups. There are enough data to derive a TRV.
- 2) There are at least three NOAEL results available within the growth and reproduction effect groups for calculation of a geometric mean.
- 3) The geometric mean is equal to 18.5 mg copper/kg bw/d and is higher than the lowest bounded LOAEL for results within the reproduction, growth, and survival (MOR) effect groups.
- 3) The avian wildlife TRV for copper is equal to 4.05 mg copper/kg bw/day which is the highest NOAEL value lower than the lowest bound LOAEL value for effects on reproduction, growth or survival.

5.2 Estimation of Dose and Calculation of the Eco-SSL

Three separate Eco-SSL values were calculated for avian wildlife, one for each of three surrogate receptor species representing different trophic levels. The avian Eco-SSLs were calculated according to the Eco-SSL guidance (U.S. EPA, 2003) and are summarized in Table 5.2.

Table 5.2 Calculation of the Avian Eco-SSLs for Copper					
Surrogate Receptor Group	TRV for Copper (mg dw/kg bw/d) ¹	Food Ingestion Rate (FIR) ² (kg dw/kg bw/d)	Soil Ingestion as Proportion of Diet (P) ²	Concentration of Copper in Biota Type (i) ^{2,3} (B _i) (mg/kg dw)	Eco-SSL (mg/kg dw) ⁴
Avian herbivore (dove)	4.05	0.190	0.139	$\ln(B_i) = 0.394 * \ln(\text{Soil}_i) + 0.688$ where i = plants	76
Avian ground insectivore (woodcock)	4.05	0.214	0.164	$B_i = 0.515 * \text{Soil}_i$ where i = earthworms	28
Avian carnivore (hawk)	4.05	0.0353	0.057	$\ln(B_i) = 0.1444 * \ln(\text{Soil}_i) + 2.042$ where i = mammals	1600

¹ The process for derivation of wildlife TRVs is described in Attachment 4-5 of U.S. EPA (2003).
² Parameters (FIR, P_s, B_i values, regressions) are provided in U.S. EPA (2003) Attachment 4-1 (revised February 2005).
³ B_i = Concentration in biota type (i) which represents 100% of the diet for the respective receptor.
⁴ HQ = [FIR * (Soil_i * P_s + B_i)] / TRV solved for HQ=1 where Soil_i = Eco-SSL (Equation 4-2; U.S. EPA, 2003).

6.0 ECO-SSL FOR MAMMALIAN WILDLIFE

The derivation of the Eco-SSL for mammalian wildlife was completed as two parts. First, the TRV was derived according to the Eco-SSL guidance (U.S. EPA, 2003; Attachment 4-5). Second, the Eco-SSL (soil concentration) was back-calculated for each of three surrogate receptor species based on the wildlife exposure model and the TRV (U.S. EPA, 2003).

6.1 Mammalian TRV

The literature search was completed according to the Eco-SSL guidance (U.S. EPA, 2003; Attachment 4-2) and identified 3,365 papers with possible toxicity data for copper for either avian or mammalian species. Of these studies, 3,175 were rejected for use as described in Section 7.5. Of the remaining papers, 97 contained data for mammalian test species. These papers were reviewed and the data were extracted and scored according to the Eco-SSL guidance (U.S. EPA, 2003; Attachment 4-3 and 4-4). The results of the data extraction and review are summarized in Table 6.1. The complete results are provided as Appendix 6-1.

Table 6.1 Mammalian Toxicity Data Extracted for Wildlife Toxicity Reference Value (TRV)

Copper
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Result #	Reference	Ref No.	Test Organism	# of Conc/Doses	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Type	Effect Measure	Response Site	NOAEL Dose* (mg/kg bw/day)	LOAEL Dose* (mg/kg bw/day)	Total
Biochemical (BIO)																		
1	Cerklewski and Forbes, 1977	2625	Rat (<i>Rattus norvegicus</i>)	2	U	FD	1	w	NR	NR	JV	M	CHM	HMGL	UR	1.53		71
2	Uthus, 2001	36349	Rat (<i>Rattus norvegicus</i>)	2	U	FD	62	d	NR	NR	JV	M	CHM	HMGL	BL	2.07		70
3	Amer, et al, 1973	10086	Cattle (<i>Bos taurus</i>)	3	M	FD	4	w	3	d	JV	M	ENZ	GENZ	BL	2.71	5.09	80
4	Miranda et al, 1981	36240	Rat (<i>Rattus norvegicus</i>)	2	M	FD	5	w	NR	NR	JV	M	ENZ	ASAT	PL	3.60		74
5	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	FD	13	w	6	w	JV	B	ENZ	AATT	BL	6.02	12.0	77
6	Irie, 1990	21243	Pig (<i>Sus scrofa</i>)	3	U	FD	8	w	4	mo	JV	NR	CHM	FFTA	WO	6.07		70
7	Thacker, 1991	2304	Pig (<i>Sus scrofa</i>)	2	U	FD	7	d	NR	NR	GE	F	CHM	PRTL	MK	6.51		70
8	Kline et al, 1971	20975	Pig (<i>Sus scrofa</i>)	4	M	FD	88	d	69	d	JV	NR	CHM	HMGL	BL	7.63		66
9	Kornegay et al, 1986	2182	Pig (<i>Sus scrofa</i>)	3	U	FD	25	d	NR	NR	JV	B	CHM	HMGL	BL	8.59	17.2	71
10	Brandt, 1983	2033	Mink (<i>Mustela vison</i>)	3	M	FD	4	mo	90	d	JV	M	CHM	HMGL	PL	10.2	19.6	81
11	Suttle and Mills, 1966	3757	Pig (<i>Sus scrofa</i>)	3	U	FD	34	d	NR	NR	JV	F	ENZ	ASAT	SR	11.9	20.3	77
12	Smith et al, 1975	3756	Horse - Shetland pony (<i>Equus caballus</i>)	4	M	FD	84	d	NR	NR	JV	NR	CHM	PCLV	BL	13.8		67
13	Moffitt and Murphy, 1973	12718	Rat (<i>Rattus norvegicus</i>)	4	U	DR	15	d	NR	NR	JV	B	ENZ	AHDX	LI	17.1	51.2	71
14	Bassuny, 1991	2020	Rabbit (<i>Oryctolagus cuniculus</i>)	5	U	FD	7	w	35	d	JV	M	CHM	PRTL	BL		0.758	71
15	Solaiman et al, 2001	36748	Goat (<i>Capra hircus</i>)	3	U	GV	9	w	7-8	mo	JV	F	ENZ	GGTR	PL		1.47	73
16	Kakela et al, 1999	36231	Mink (<i>Mustela vison</i>)	2	U	FD	28	d	6	mo	JV	F	CHM	VTMA	PL		4.01	70
17	Kakela and Hyvarinen, 1999	36248	Mink (<i>Mustela vison</i>)	2	U	FD	28	d	6	mo	JV	F	CHM	FFTA	LD		4.01	70
18	Adam et al, 1977	3752	Goat (<i>Capra hircus</i>)	4	U	GV	144	d	12	mo	AD	B	CHM	GLYC	LI		5.36	73
19	DeGoe et al, 1971	2064	Pig (<i>Sus scrofa</i>)	2	U	FD	98	d	NR	mo	JV	NR	CHM	HMGL	BL		7.46	71
20	Gipp et al, 1973	14396	Pig (<i>Sus scrofa</i>)	2	U	FD	12	w	NR	NR	JV	F	CHM	HMGL	BL		7.66	70
21	Myres and Bowland, 1973	12809	Pig (<i>Sus scrofa</i>)	2	U	FD	10	w	70	d	JV	B	CHM	FFTA	LD		7.84	71
22	Ritchie et al, 1963	14402	Pig (<i>Sus scrofa</i>)	2	U	FD	15	w	7	w	JV	NR	CHM	HMGL	WO		8.08	70
23	Onifade and Abu, 1998	2237	Rabbit (<i>Oryctolagus cuniculus</i>)	4	U	FD	70	d	7	w	JV	NR	CHM	TWBC	BL		9.47	70
24	Gipp et al, 1974	14397	Pig (<i>Sus scrofa</i>)	2	U	FD	35	d	3	w	JV	B	CHM	HMGL	BL		9.93	71
25	Radecki et al, 1992	2255	Pig (<i>Sus scrofa</i>)	2	U	FD	14	d	21	d	JV	B	ENZ	G6PD	GT		12.0	70
26	DeGoe et al, 1971	2064	Pig (<i>Sus scrofa</i>)	2	U	FD	23	d	NR	mo	JV	NR	CHM	HMGL	BL		15.5	70
27	Rana and Kumar, 1980	2256	Rat (<i>Rattus norvegicus</i>)	2	U	GV	20	d	90	d	JV	M	CHM	RBCE	BL		39.8	77
28	Kumar et al, 1987	2186	Rat (<i>Rattus norvegicus</i>)	2	U	GV	45	d	90	d	JV	M	CHM	PRTL	KI		39.8	77
29	Gautam et al, 2001	36346	Rat (<i>Rattus norvegicus</i>)	2	U	FD	2	w	NR	NR	JV	NR	CHM	CALC	LI		39.8	74
30	DeVries et al, 1986	10891	Rat (<i>Rattus norvegicus</i>)	2	U	DR	11	mo	3	w	JV	F	HRM	GHRM	BR		45.8	66
31	Aburto et al, 2001	25964	Rat (<i>Rattus norvegicus</i>)	2	U	FD	6	mo	10	w	JV	M	CHM	GCHM	LI		48.7	70
32	Pribyl et al, 1980	23825	Rat (<i>Rattus norvegicus</i>)	2	U	FD	4	d	NR	NR	JV	M	ENZ	GENZ	SR		63.5	70
33	Rana and Verma, 1997	36247	Rat (<i>Rattus norvegicus</i>)	2	U	FD	30	d	NR	NR	JV	M	CHM	GLTH	LI		75.0	79
34	Tatum et al, 2000	36389	Rat (<i>Rattus norvegicus</i>)	2	U	FD	6	w	NR	NR	JV	F	ENZ	GENZ	PL		75.7	70
35	Rana et al, 1985	13236	Rat (<i>Rattus norvegicus</i>)	2	U	GV	30	d	90	d	JV	M	CHM	GLYC	LI		100	77
36	Fuentealba et al, 2000	36364	Rat (<i>Rattus norvegicus</i>)	2	U	FD	12	w	21	d	JV	B	ENZ	AATT	LI		122	69
37	Fuentealba et al, 2000	36364	Rat (<i>Rattus norvegicus</i>)	2	U	FD	18	w	NR	NR	GE	F	ENZ	AATT	LI		132	69
38	Fuentealba et al, 1993	2097	Rat (<i>Rattus norvegicus</i>)	2	U	FD	1	w	NR	mo	JV	M	CHM	GBCM	LI		135	69
39	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	4	U	FD	92	d	6	w	JV	M	ENZ	AATT	BL		146	69
40	Haywood and Comerford, 1980	2123	Rat (<i>Rattus norvegicus</i>)	2	U	FD	1	w	NR	mo	JV	M	ENZ	AATT	BL		178	69
41	Zhang et al, 2000	36355	Rat (<i>Rattus norvegicus</i>)	2	U	GV	8	w	8	w	JV	B	ENZ	GENZ	SR		357	79
42	Pettersen, et al, 2002	36374	Mouse (<i>Mus musculus</i>)	3	U	FD	3	w	4	w	JV	B	CHM	NACO	HE		494	70
43	Gooneratne and Howell, 1980	36200	Sheep (<i>Ovis aries</i>)	2	U	DR	66	d	9-12	mo	JV	M	ENZ	GLPX	LI		1820	69
44	Sansinanea et al, 1996	36234	Sheep (<i>Ovis aries</i>)	2	U	OR	14	w	12	mo	JV	F	CHM	GLUC	SR		7140	77
Behavior (BEH)																		
45	Miranda et al, 1981	36240	Rat (<i>Rattus norvegicus</i>)	2	M	FD	5	w	NR	NR	JV	M	FDB	FCNS	WO	3.60		75
46	Anugwa et al, 1984	2010	Rabbit (<i>Oryctolagus cuniculus</i>)	3	M	FD	8	w	8	w	JV	B	FDB	FCNS	WO	3.64	6.67	85
47	Bassuny, 1991	2020	Rabbit (<i>Oryctolagus cuniculus</i>)	5	U	FD	7	w	35	d	JV	M	FDB	FCNS	WO	4.25		74
48	Ward, et al, 1991	1888	Pig (<i>Sus scrofa</i>)	2	M	FD	144	d	31	d	JV	B	FDB	FDNG	WO	4.37		70
49	Allcroft et al, 1961	14387	Pig (<i>Sus scrofa</i>)	4	M	FD	4	w	8-10	w	JV	B	FDB	FCNS	WO	5.60	9.34	84
50	Gershbein et al 1983	136	Rat (<i>Rattus norvegicus</i>)	2	U	FD	80	d	44	d	JV	M	BEH	NMVM	WO	5.89		66
51	Thacker, 1991	2304	Pig (<i>Sus scrofa</i>)	2	U	FD	35	d	NR	NR	LC	F	FDB	FCNS	WO	6.69		74
52	Apgar et al, 1995	25922	Pig (<i>Sus scrofa</i>)	4	M	FD	5	w	31	d	JV	B	FDB	FCNS	WO	6.90		70
53	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	2	M	FD	28	d	29	d	JV	B	FDB	FCNS	WO	7.37		70
54	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	2	M	FD	28	d	29	d	JV	B	FDB	FCNS	WO	7.37		70
55	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	2	M	FD	28	d	30	d	JV	B	FDB	FCNS	WO	8.21		70
56	Allcroft et al, 1961	14387	Pig (<i>Sus scrofa</i>)	4	M	FD	19	w	8-10	w	JV	B	FDB	FCNS	WO	8.43		69
57	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	3	M	FD	28	d	29	d	JV	B	FDB	FCNS	WO	8.50		70
58	Cromwell et al 1989	2061	Pig (<i>Sus scrofa</i>)	5	U	FD	33	d	28	d	JV	B	FDB	FCNS	WO	8.67	13.0	80
59	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	4	M	FD	28	d	30	d	JV	B	FDB	FCNS	WO	8.68		70
60	Cromwell et al 1989	2061	Pig (<i>Sus scrofa</i>)	4	U	FD	28	d	28	d	JV	B	FDB	FCNS	WO	10.0	19.9	80

Table 6.1 Mammalian Toxicity Data Extracted for Wildlife Toxicity Reference Value (TRV)

Copper
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Result #	Reference	Ref No.	Test Organism	# of Conc/Doses	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Type	Effect Measure	Response Site	NOAEL Dose* (mg/kg bw/day)	LOAEL Dose* (mg/kg bw/day)	Total	
61	Edmonds and Baker, 1986	2075	Pig (<i>Sus scrofa</i>)	3	U	FD	28	d	4	w	JV	NR	FDB	FCNS	WO	10.3	26.9	80	
62	Apgar and Kornegay, 1996	25928	Pig (<i>Sus scrofa</i>)	2	M	FD	14	d	NR	NR	JV	M	FDB	FCNS	WO	16.5		73	
63	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	DR	15	d	6	w	JV	B	FDB	WCNS	WO	17.2	51.7	75	
64	Grobner et al, 1986	2113	Rabbit (<i>Oryctolagus cuniculus</i>)	6	M	FD	28	d	28	d	JV	NR	FDB	FCNS	WO	27.7	45.7	85	
65	Bush et al., 1995	2043	Mink (<i>Mustela vison</i>)	3	M	FD	132	d	10	w	JV	B	FDB	FCNS	WO	33.4		69	
66	Hebert, 1993	2126	Mouse (<i>Mus musculus</i>)	6	U	DR	15	d	6	w	JV	B	FDB	WCNS	WO	33.8	101	75	
67	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	FD	13	w	6	w	JV	B	FDB	FCNS	WO	49.7	99.4	80	
68	Grobner et al, 1986	2113	Rabbit (<i>Oryctolagus cuniculus</i>)	6	M	FD	28	d	28	d	JV	NR	FDB	FCNS	WO	59.0		70	
69	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	FD	7	d	6	w	JV	B	FDB	FCNS	WO	179	359	80	
70	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	5	U	DR	2	w	6	w	JV	M	FDB	WCNS	WO	259	400	74	
71	Hebert et al, 1993	2127	Mouse (<i>Mus musculus</i>)	5	U	DR	2	w	6	w	JV	M	FDB	WCNS	WO	589	1365	74	
72	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	6	U	FD	15	d	6	w	JV	M	FDB	FCNS	WO	2050	3360	79	
73	Hebert et al, 1993	2127	Mouse (<i>Mus musculus</i>)	6	U	FD	15	d	6	w	JV	B	FDB	FCNS	WO	12500	18700	79	
74	Ortolani et al, 2003	36759	Sheep (<i>Ovis aries</i>)	2	U	DR	14	d	6	mo	JV	M	FDB	FCNS	WO		3.00	72	
75	Freundt and Ibrahim, 1990	2640	Rat (<i>Rattus norvegicus</i>)	2	U	DR	91	d	NR	NR	JV	F	FDB	WCNS	WO		5.78	68	
76	DeGoey et al, 1971	2064	Pig (<i>Sus scrofa</i>)	2	U	FD	98	d	NR	NR	JV	NR	FDB	FCNS	WO		7.46	74	
77	Onifade and Abu, 1998	2237	Rabbit (<i>Oryctolagus cuniculus</i>)	4	U	FD	70	d	7	w	JV	NR	FDB	FCNS	WO		9.47	73	
78	Boyden, 1938	14653	Rat (<i>Rattus norvegicus</i>)	5	U	FD	4	w	28	d	JV	B	FDB	FCNS	WO		23.5	73	
79	Komulainen, 1983	12079	Rat (<i>Rattus norvegicus</i>)	4	U	DR	3	w	4	w	JV	M	FDB	WCNS	WO		28.0	72	
Physiology (PHY)																			
80	Bailey et al, 2001	25941	Cattle (<i>Bos taurus</i>)	3	M	FD	112	d	NR	NR	JV	NR	PHY	FDCV	WO	1.33		69	
81	Arthur, 1965	2012	Guinea pig (<i>Cavia porcellus</i>)	3	U	FD	8	w	NR	NR	JV	B	PHY	GPHY	HA	1.48		73	
82	Omole et al, 1976	43456	Pig (<i>Sus scrofa</i>)	3	U	FD	127	d	NR	NR	NR	B	PHY	FDCV	WO	2.77	4.43	76	
83	Solaiman et al, 2001	36748	Goat (<i>Capra hircus</i>)	3	U	GV	9	w	7-8	mo	JV	F	PHY	FDCV	WO	3.14		69	
84	Anugwa et al, 1984	2010	Rabbit (<i>Oryctolagus cuniculus</i>)	3	M	FD	8	w	8	w	JV	B	PHY	DIFD	WO	3.64	6.67	85	
85	Ward et al, 1991	1888	Pig (<i>Sus scrofa</i>)	2	M	FD	144	d	31	d	JV	B	PHY	FDCV	WO	4.37		70	
86	Apgar et al, 1995	25922	Pig (<i>Sus scrofa</i>)	4	M	FD	5	w	31	d	JV	B	PHY	FDCV	WO	6.90		70	
87	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	2	M	FD	28	d	29	d	JV	B	PHY	FDCV	WO	7.37		70	
88	Kline et al, 1971	20975	Pig (<i>Sus scrofa</i>)	2	M	FD	88	d	69	d	JV	NR	PHY	FDCV	WO	7.63		69	
89	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	2	M	FD	28	d	30	d	JV	B	PHY	FDCV	WO	8.21		70	
90	Braude and Ryder, 1973	2034	Pig (<i>Sus scrofa</i>)	4	M	FD	112	d	9	w	JV	NR	PHY	FDCV	WO	8.29		69	
91	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	3	M	FD	28	d	29	d	JV	B	PHY	FDCV	WO	8.50		70	
92	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	4	M	FD	28	d	30	d	JV	B	PHY	FDCV	WO	8.68		70	
93	Cromwell et al, 1989	2061	Pig (<i>Sus scrofa</i>)	4	U	FD	28	d	28	d	JV	B	PHY	FDCV	WO	8.89	17.8	80	
94	Grobner et al, 1986	2113	Rabbit (<i>Oryctolagus cuniculus</i>)	6	M	FD	28	d	28	d	JV	NR	PHY	FDCV	WO	9.45	23.6	85	
95	Edmonds and Baker, 1986	2075	Pig (<i>Sus scrofa</i>)	3	U	FD	28	d	4	w	JV	NR	PHY	FDCV	WO	10.3	26.9	80	
96	Grobner et al, 1986	2113	Rabbit (<i>Oryctolagus cuniculus</i>)	6	M	FD	28	d	28	d	JV	NR	PHY	FDCV	WO	33.6	59.0	85	
97	Keen et al, 1982	11928	Rat (<i>Rattus norvegicus</i>)	4	U	FD	7	w	NR	NR	JV	F	PHY	GPHY	PL	189		66	
98	Bassuny, 1991	2020	Rabbit (<i>Oryctolagus cuniculus</i>)	5	U	FD	7	w	35	d	JV	M	PHY	FDCV	WO		0.758	74	
99	Cromwell et al, 1989	2061	Pig (<i>Sus scrofa</i>)	5	U	FD	33	d	28	d	JV	B	PHY	FDCV	WO		4.10	74	
100	Cromwell et al, 1989	2061	Pig (<i>Sus scrofa</i>)	3	U	FD	28	d	28	d	JV	B	PHY	FDCV	WO		4.89	74	
101	DeGoey et al, 1971	2064	Pig (<i>Sus scrofa</i>)	2	U	FD	23	d	NR	mo	JV	NR	PHY	IRRI	SK		15.5	73	
102	Rana and Kumar, 1980	2256	Rat (<i>Rattus norvegicus</i>)	2	U	GV	20	d	90	d	JV	M	PHY	IRRI	FO		39.8	80	
Pathology (PTH)																			
103	Uthus, 2001	36349	Rat (<i>Rattus norvegicus</i>)	2	U	FD	62	d	NR	NR	JV	M	ORW	ORWT	KI	2.07		73	
104	Miranda et al, 1981	36240	Rat (<i>Rattus norvegicus</i>)	2	M	FD	5	w	NR	NR	JV	M	ORW	SMIX	LI	3.60		79	
105	Humann-Ziehank et al, 2001	36762	Sheep (<i>Ovis aries</i>)	2	U	FD	84	d	1	yr	AD	M	ITX	GITX	WO	3.70		70	
106	Ward et al, 1991	1888	Pig (<i>Sus scrofa</i>)	2	M	FD	144	d	31	d	JV	B	HIS	GHS	GT	4.37		70	
107	Adam et al, 1977	3752	Goat (<i>Capra hircus</i>)	4	U	GV	144	d	12	mo	AD	B	HIS	GHS	LI	5.36	10.7	82	
108	Hebert, 1993	2126	Mouse (<i>Mus musculus</i>)	6	U	DR	15	d	6	w	JV	F	ORW	ORWT	TS	5.53	18.4	73	
109	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	FD	13	w	6	w	JV	F	HIS	GLSN	KI	6.01	12.0	80	
110	Thacker, 1991	2304	Pig (<i>Sus scrofa</i>)	2	U	FD	7	d	NR	NR	GE	F	GRS	BDWT	WO	6.51		72	
111	Anugwa et al, 1984	2010	Rabbit (<i>Oryctolagus cuniculus</i>)	3	M	FD	8	w	8	w	JV	B	ORW	SMIX	LI	6.67		70	
112	Ritchie et al, 1963	14402	Pig (<i>Sus scrofa</i>)	2	U	FD	15	w	7	w	JV	NR	ORW	ORWT	LI	8.08		69	
113	Onifade and Abu, 1998	2237	Rabbit (<i>Oryctolagus cuniculus</i>)	4	U	FD	70	d	7	w	JV	NR	ORW	SMIX	BR	9.47	18.9	79	
114	Howell et al, 1991	36230	Sheep (<i>Ovis aries</i>)	2	U	GV	19	w	6-9	mo	JV	M	HIS	CTYP	LI	14.3		73	
115	Prince et al, 1979	2253	Pig (<i>Sus scrofa</i>)	2	U	FD	63	d	53	d	JV	NR	ITX	GITX	WO	16.5		73	
116	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	DR	15	d	6	w	JV	B	ITX	GITX	WO	17.2	51.6	75	
117	Bush et al, 1995	2043	Mink (<i>Mustela vison</i>)	3	M	FD	132	d	10	w	JV	B	HIS	NCRO	LI	33.4		78	
118	Kumar et al, 1987	2186	Rat (<i>Rattus norvegicus</i>)	2	U	GV	45	d	90	d	JV	M	ORW	ORWT	KI	39.8		76	
119	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	FD	15	d	6	w	JV	B	ORW	ORWT	LI	40.9	81.8	80	
120	DeVries et al, 1986	10891	Rat (<i>Rattus norvegicus</i>)	2	U	DR	11	mo	3	w	JV	F	ORW	ORWT	LI	45.8		69	

Table 6.1 Mammalian Toxicity Data Extracted for Wildlife Toxicity Reference Value (TRV)

Copper
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Result #	Reference	Ref No.	Test Organism	# of Conc/Doses	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Type	Effect Measure	Response Site	NOAEL Dose* (mg/kg bw/day)	LOAEL Dose* (mg/kg bw/day)	Total
121	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	5	U	FD	92	d	6	w	JV	M	HIS	HYPL	SH	70.4	142	79
122	Hebert, 1993	2126	Mouse (<i>Mus musculus</i>)	6	U	FD	13	w	6	w	JV	B	ORW	ORWT	LI	82.8	166	80
123	Keen et al, 1982	11928	Rat (<i>Rattus norvegicus</i>)	4	U	FD	7	w	NR	NR	JV	F	HIS	GHIS	MT	91.7	183	79
124	Hebert, 1993	2126	Mouse (<i>Mus musculus</i>)	6	U	FD	15	d	6	w	JV	M	ORW	ORWT	LI	97.2	194	80
125	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	6	U	FD	15	d	6	w	JV	B	HIS	HYPL	SH	197	385	79
126	Dodds-Smith et al, 1992	2069	Common shrew (<i>Sorex araneus</i>)	2	U	FD	12	w	NR	NR	JV	B	ORW	ORWT	KI	251		69
127	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	5	U	DR	2	w	6	w	JV	B	ITX	GITX	WO	259	400	74
128	Haywood, 1985	2121	Rat (<i>Rattus norvegicus</i>)	5	U	FD	1	w	NR	NR	JV	M	HIS	NCRO	LI	274	365	73
129	Hebert et al, 1993	2127	Mouse (<i>Mus musculus</i>)	5	U	DR	2	w	6	w	JV	B	ITX	GITX	WO	1430	3400	74
130	Hebert et al, 1993	2127	Mouse (<i>Mus musculus</i>)	5	U	FD	92	d	6	w	JV	B	ITX	GITX	WO	48300		73
131	Grobner et al, 1986	2113	Rabbit (<i>Oryctolagus cuniculus</i>)	6	M	FD	28	d	28	d	JV	NR	ORW	ORWT	DT		3.40	79
132	Howell et al, 1974	2148	Sheep (<i>Ovis aries</i>)	3	U	GV	37	w	6-12	mo	JV	B	HIS	GHIS	BR		5.09	80
133	Gopinath et al, 1974	36202	Sheep (<i>Ovis aries</i>)	2	U	DR	10	w	6	mo	JV	F	HIS	GHIS	KI		5.09	72
134	King, 1975	2179	Rabbit (<i>Oryctolagus cuniculus</i>)	2	U	FD	6	w	5	w	JV	B	ORW	SMIX	IN		5.43	72
135	Ishmael et al, 1971	2155	Sheep (<i>Ovis aries</i>)	2	U	OR	88	d	6	mo	JV	F	ORW	SMIX	LI		7.57	70
136	King, 1975	2179	Rabbit (<i>Oryctolagus cuniculus</i>)	2	U	FD	6	w	5	w	JV	B	ORW	SMIX	IN		10.9	72
137	Radecki et al, 1992	2255	Pig (<i>Sus scrofa</i>)	2	U	FD	14	d	21	d	JV	B	HIS	GHIS	GT		12.0	73
138	DeGoey et al, 1971	2064	Pig (<i>Sus scrofa</i>)	2	U	FD	23	d	NR	mo	JV	NR	HIS	NCRO	LI		15.5	73
139	Boyden, 1938	14653	Rat (<i>Rattus norvegicus</i>)	5	U	FD	4	w	28	d	JV	B	ORW	ORWT	SP		23.5	73
140	Rana and Kumar, 1980	2256	Rat (<i>Rattus norvegicus</i>)	2	U	GV	20	d	90	d	JV	M	HIS	NCRO	LI		39.8	80
141	Rana and Kumar, 1985	2257	Rat (<i>Rattus norvegicus</i>)	2	U	GV	20	d	90	d	AD	M	HIS	GHIS	LI		39.8	80
142	Aburto et al, 2001	25964	Rat (<i>Rattus norvegicus</i>)	2	U	FD	12	mo	10	w	JV	M	HIS	GHIS	LI		48.7	73
143	Chesta et al, 1989	2047	Guinea pig (<i>Cavia porcellus</i>)	2	U	DR	45	d	NR	NR	GE	F	HIS	GHIS	LI		73.7	67
144	Rana et al, 1985	13236	Rat (<i>Rattus norvegicus</i>)	2	U	GV	30	d	90	d	JV	M	ORW	SMIX	LI		100	80
145	Fuentealba et al, 2000	36364	Rat (<i>Rattus norvegicus</i>)	2	U	FD	12	w	21	d	JV	B	HIS	NCRO	LI		122	72
146	Fuentealba et al, 2000	36364	Rat (<i>Rattus norvegicus</i>)	2	U	FD	18	w	NR	NR	GE	F	HIS	NCRO	LI		132	72
147	Fuentealba et al, 1989	2095	Rat (<i>Rattus norvegicus</i>)	2	U	FD	4	w	6	w	JV	M	HIS	USTR	LI		135	66
148	Fuentealba et al, 1989	2096	Rat (<i>Rattus norvegicus</i>)	2	U	FD	16	w	NR	mo	JV	M	HIS	HYPL	BI		135	66
149	Fuentealba et al, 1993	2097	Rat (<i>Rattus norvegicus</i>)	2	U	FD	10	w	NR	mo	JV	M	HIS	HYPL	BI		135	72
150	Fuentealba et al, 1989	2098	Rat (<i>Rattus norvegicus</i>)	2	U	FD	3	w	6	w	JV	M	HIS	GHIS	KI		135	66
151	Fuentealba and Haywood, 1988	2094	Rat (<i>Rattus norvegicus</i>)	2	U	FD	1	w	6	w	JV	M	HIS	GHIS	LI		135	66
152	Haywood, 1980	2122	Rat (<i>Rattus norvegicus</i>)	2	U	FD	15	w	NR	mo	JV	M	HIS	HYPL	BI		157	72
153	Haywood et al, 1985	2125	Rat (<i>Rattus norvegicus</i>)	2	U	FD	5	w	NR	mo	AD	M	HIS	NCRO	KI		233	66
154	Haywood and Loughran, 1985	2124	Rat (<i>Rattus norvegicus</i>)	5	U	FD	6	w	NR	mo	JV	M	HIS	NCRO	LI		285	73
155	Gooneratne and Howell, 1980	36200	Sheep (<i>Ovis aries</i>)	2	U	DR	63	d	6-9	mo	JV	M	HIS	GHIS	MU		1817	72
Reproduction (REP)																		
156	Aulerich et al, 1982	2013	Mink (<i>Mustela vison</i>)	5	U	FD	357	d	NR	mo	JV	F	REP	PROG	WO	3.40	6.79	85
157	Thacker, 1991	2304	Pig (<i>Sus scrofa</i>)	2	U	FD	7	d	NR	NR	GE	F	REP	PROG	WO	6.51		79
158	Webster, 1979	823	Mouse (<i>Mus musculus</i>)	4	U	FD	19	d	4	mo	GE	F	REP	PRWT	WO	50.7		79
159	Lecyk, 1980	2193	Mouse (<i>Mus musculus</i>)	7	U	FD	49	d	NR	NR	GE	B	REP	PROG	WO	90.9	136	84
160	Lecyk, 1980	2193	Mouse (<i>Mus musculus</i>)	7	U	FD	49	d	NR	NR	GE	B	REP	PROG	WO	90.9	136	84
161	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	FD	13	w	6	w	JV	M	REP	SPCL	SM	107		80
162	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	4	U	FD	92	d	6	w	JV	M	REP	SPCL	SM	304		70
163	Hebert, 1993	2126	Mouse (<i>Mus musculus</i>)	6	U	FD	13	w	6	w	JV	M	REP	SPCL	SM	358		76
164	Hebert et al, 1993	2127	Mouse (<i>Mus musculus</i>)	4	U	FD	92	d	6	w	JV	M	REP	SPCL	SM	48300		70
165	Cromwell et al, 1993	2062	Pig (<i>Sus scrofa</i>)	2	U	FD	783	d	10	mo	GE	F	REP	RSUC	WO		5.51	80
166	Bataineh et al, 1998	1717	Rat (<i>Rattus norvegicus</i>)	2	U	DR	12	w	NR	NR	AD	M	REP	TEWT	TE		41.2	67
Growth (GRO)																		
167	Engle and Spears, 2001	25940	Cattle (<i>Bos taurus</i>)	2	U	FD	239	d	NR	NR	JV	M	GRO	BDWT	WO	0.812		69
168	Engle et al, 2000	25935	Cattle (<i>Bos taurus</i>)	2	U	FD	154	d	NR	NR	JV	M	GRO	BDWT	WO	0.852		69
169	Bailey et al, 2001	25941	Cattle (<i>Bos taurus</i>)	3	M	FD	112	d	NR	NR	JV	NR	GRO	BDWT	WO	1.33		73
170	Arthur, 1965	2012	Guinea pig (<i>Cavia porcellus</i>)	3	U	FD	8	w	NR	NR	JV	B	GRO	BDWT	WO	1.48		70
171	Uthus, 2001	36349	Rat (<i>Rattus norvegicus</i>)	2	U	FD	62	d	NR	NR	JV	M	GRO	BDWT	WO	2.07		77
172	Miranda et al, 1981	36240	Rat (<i>Rattus norvegicus</i>)	2	M	FD	5	w	NR	NR	JV	M	GRO	BDWT	WO	3.60		81
173	Bassuny, 1991	2020	Rabbit (<i>Oryctolagus cuniculus</i>)	5	U	FD	7	w	35	d	JV	M	GRO	BDWT	WO	4.25		78
174	Ward et al, 1991	1888	Pig (<i>Sus scrofa</i>)	2	M	FD	144	d	31	d	JV	B	GRO	BDWT	WO	4.37		74
175	King, 1975	2179	Rabbit (<i>Oryctolagus cuniculus</i>)	2	U	FD	8	w	5	w	JV	B	GRO	BDWT	WO	5.43		76
176	Cromwell et al, 1993	2062	Pig (<i>Sus scrofa</i>)	2	U	FD	783	d	10.3	mo	GE	F	GRO	BDWT	WO	5.51		69
177	Allcroft et al, 1961	14387	Pig (<i>Sus scrofa</i>)	4	M	FD	4	w	8-10	w	JV	B	GRO	BDWT	WO	5.60	9.34	88
178	Gershbein et al, 1983	136	Rat (<i>Rattus norvegicus</i>)	2	U	FD	80	d	44	d	JV	M	GRO	BDWT	WO	5.89		68
179	Anugwa et al, 1984	2010	Rabbit (<i>Oryctolagus cuniculus</i>)	3	M	FD	8	w	8	w	JV	B	GRO	BDWT	WO	6.67		74
180	Apgar et al, 1995	25922	Pig (<i>Sus scrofa</i>)	4	M	FD	5	w	31	d	JV	B	GRO	BDWT	WO	6.90		74

Table 6.1 Mammalian Toxicity Data Extracted for Wildlife Toxicity Reference Value (TRV)

Copper
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Result #	Reference	Ref No.	Test Organism	# of Conc/Doses	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Type	Effect Measure	Response Site	NOAEL Dose* (mg/kg bw/day)	LOAEL Dose* (mg/kg bw/day)	Total
181	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	4	U	FD	28	d	26-32	d	JV	B	GRO	BDWT	WO	7.19		69
182	Omole, 1977	12977	Rabbit (<i>Oryctolagus cuniculus</i>)	4	U	FD	8	w	6	w	JV	B	GRO	BDWT	WO	7.34		69
183	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	2	U	FD	28	d	26-32	d	JV	B	GRO	BDWT	WO	7.36		69
184	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	2	M	FD	28	d	29	d	JV	B	GRO	BDWT	WO	7.37		74
185	Kline et al, 1971	20975	Pig (<i>Sus scrofa</i>)	4	M	FD	88	d	69	d	JV	NR	GRO	BDWT	WO	7.63		73
186	Gipp et al, 1973	14396	Pig (<i>Sus scrofa</i>)	2	U	FD	12	w	NR	NR	JV	F	GRO	BDWT	WO	7.66		68
187	Cromwell et al, 1989	2061	Pig (<i>Sus scrofa</i>)	3	U	FD	28	d	28	d	JV	B	GRO	BDWT	WO	7.68		69
188	Luo and Dove, 1996	25929	Pig (<i>Sus scrofa</i>)	2	U	FD	15	d	26	d	JV	M	GRO	BDWT	WO	7.72		69
189	Myres and Bowland, 1973	12809	Pig (<i>Sus scrofa</i>)	2	U	FD	10	w	70	d	JV	B	GRO	BDWT	WO	7.84		69
190	Ritchie et al, 1963	14402	Pig (<i>Sus scrofa</i>)	2	U	FD	15	w	7	w	JV	NR	GRO	BDWT	WO	8.08		68
191	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	2	M	FD	28	d	30	d	JV	B	GRO	BDWT	WO	8.21		74
192	Braude and Ryder, 1973	2034	Pig (<i>Sus scrofa</i>)	4	M	FD	112	d	9	w	JV	NR	GRO	BDWT	WO	8.29		73
193	Allcroft et al, 1961	14387	Pig (<i>Sus scrofa</i>)	4	M	FD	19	w	8-10	w	JV	B	GRO	BDWT	WO	8.43		73
194	Prince et al 1979	2253	Pig (<i>Sus scrofa</i>)	2	U	FD	59	d	64	d	JV	NR	GRO	BDWT	WO	8.44		68
195	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	3	M	FD	28	d	29	d	JV	B	GRO	BDWT	WO	8.50		74
196	Cromwell et al, 1998	25930	Pig (<i>Sus scrofa</i>)	4	M	FD	28	d	30	d	JV	B	GRO	BDWT	WO	8.68		74
197	Cromwell et al 1989	2061	Pig (<i>Sus scrofa</i>)	3	U	FD	28	d	28	d	JV	B	GRO	BDWT	WO	9.60		69
198	Gipp et al, 1974	14397	Pig (<i>Sus scrofa</i>)	2	U	FD	35	d	3	w	JV	B	GRO	BDWT	WO	9.93		69
199	Brandt, 1983	2033	Mink (<i>Mustela vison</i>)	3	M	FD	4	mo	90	d	JV	M	GRO	BDWT	WO	10.2	19.6	88
200	Edmonds and Baker, 1986	2075	Pig (<i>Sus scrofa</i>)	3	U	FD	28	d	4	w	JV	NR	GRO	BDWT	WO	10.3	26.9	84
201	Radecki et al, 1992	2255	Pig (<i>Sus scrofa</i>)	2	U	FD	14	d	21	d	JV	B	GRO	BDWT	WO	12.0		68
202	Aulerich et al, 1982	2013	Mink (<i>Mustela vison</i>)	5	U	FD	20	w	NR	mo	JV	B	GRO	BDWT	WO	12.4		68
203	Felsman et al, 1973	3760	Cattle (<i>Bos taurus</i>)	4	U	FD	98	d	6	w	JV	M	GRO	BDWT	WO	12.7		68
204	Smith et al, 1975	3756	Horse - Shetland pony (<i>Equus caballus</i>)	4	M	FD	84	d	NR	NR	JV	NR	GRO	BDWT	WO	13.8		74
205	Suttle and Mills, 1966	3757	Pig (<i>Sus scrofa</i>)	3	U	FD	14	d	NR	NR	JV	F	GRO	BDWT	WO	16.2	27.6	84
206	Cromwell et al, 1989	2061	Pig (<i>Sus scrofa</i>)	5	U	FD	33	d	28	d	JV	B	GRO	BDWT	WO	16.4		69
207	Apgar and Kornegay, 1996	25928	Pig (<i>Sus scrofa</i>)	2	M	FD	14	d	NR	NR	JV	M	GRO	BDWT	WO	16.5		77
208	Cromwell et al, 1989	2061	Pig (<i>Sus scrofa</i>)	4	U	FD	28	d	28	d	JV	B	GRO	BDWT	WO	16.7		69
209	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	DR	15	d	6	w	JV	B	GRO	BDWT	WO	17.2	51.6	79
210	Lalich et al, 1965	2189	Rat (<i>Rattus norvegicus</i>)	2	U	FD	42	d	NR	NR	JV	M	GRO	BDWT	WO	17.5		68
211	Cromwell et al, 1989	2061	Pig (<i>Sus scrofa</i>)	4	U	FD	28	d	28	d	JV	B	GRO	BDWT	WO	17.8		69
212	Felsman et al, 1973	3760	Cattle (<i>Bos taurus</i>)	4	U	FD	98	d	6	w	JV	M	GRO	BDWT	WO	22.9		68
213	Grobner et al, 1986	2113	Rabbit (<i>Oryctolagus cuniculus</i>)	6	M	FD	28	d	28	d	JV	NR	GRO	BDWT	WO	27.7	45.7	89
214	Onifade and Abu, 1998	2237	Rabbit (<i>Oryctolagus cuniculus</i>)	4	U	FD	70	d	7	w	JV	NR	GRO	BDWT	WO	28.4		77
215	Bush et al, 1995	2043	Mink (<i>Mustela vison</i>)	3	M	FD	132	d	10	w	JV	B	GRO	BDWT	WO	33.4		82
216	Hebert, 1993	2126	Mouse (<i>Mus musculus</i>)	6	U	DR	8	d	6	w	JV	B	GRO	BDWT	WO	33.8	101	78
217	King, 1975	2179	Rabbit (<i>Oryctolagus cuniculus</i>)	2	U	FD	6	w	5	w	JV	B	GRO	BDWT	WO	37.1		67
218	White et al, 1985	2324	Rat (<i>Rattus norvegicus</i>)	2	U	FD	50	d	21	d	JV	M	GRO	BDWT	WO	43.1		68
219	DeVries et al, 1986	10891	Rat (<i>Rattus norvegicus</i>)	2	U	DR	11	mo	3	w	JV	F	GRO	BDWT	WO	45.8		73
220	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	FD	13	w	6	w	JV	B	GRO	BDWT	WO	49.8	99.6	84
221	Komulainen, 1983	12079	Rat (<i>Rattus norvegicus</i>)	4	U	DR	1	w	4	w	JV	M	GRO	BDWT	WO	50.0	64.0	82
222	Grobner et al, 1986	2113	Rabbit (<i>Oryctolagus cuniculus</i>)	6	M	FD	28	d	28	d	JV	NR	GRO	BDWT	WO	59.0		74
223	Myers et al, 1993	2225	Rat (<i>Rattus norvegicus</i>)	2	U	DR	6	w	NR	mo	JV	M	GRO	BDWT	WO	73.4		67
224	Tatum et al, 2000	36389	Rat (<i>Rattus norvegicus</i>)	2	U	FD	6	w	NR	NR	JV	F	GRO	BDWT	WO	75.7		68
225	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	FD	15	d	6	w	JV	B	GRO	BDWT	WO	82.5	165	84
226	Keen et al, 1982	11928	Rat (<i>Rattus norvegicus</i>)	4	U	FD	7	w	NR	NR	JV	F	GRO	BDWT	WO	91.7	183	83
227	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	6	U	FD	92	d	6	w	JV	M	GRO	BDWT	WO	146	293	83
228	Hebert, 1993	2126	Mouse (<i>Mus musculus</i>)	6	U	FD	13	w	6	w	JV	B	GRO	BDWT	WO	179	358	84
229	Dodds-Smith et al, 1992	440	Common shrew (<i>Sorex araneus</i>)	2	U	FD	12	w	NR	NR	JV	B	GRO	BDWT	WO	229		77
230	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	5	U	DR	2	w	6	w	JV	M	GRO	BDWT	WO	259	400	78
231	Pettersen et al, 2002	36374	Mouse (<i>Mus musculus</i>)	3	U	FD	3	w	4	w	JV	B	GRO	BDWT	WO	494	988	83
232	Hebert, 1993	2126	Mouse (<i>Mus musculus</i>)	6	U	FD	15	d	6	w	JV	B	GRO	BDWT	WO	690		69
233	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	6	U	FD	15	d	6	w	JV	M	GRO	BDWT	WO	812	1740	83
234	Hebert et al, 1993	2127	Mouse (<i>Mus musculus</i>)	5	U	DR	2	w	6	w	JV	M	GRO	BDWT	WO	1430	3400	78
235	Hebert et al, 1993	2127	Mouse (<i>Mus musculus</i>)	6	U	FD	92	d	6	w	JV	M	GRO	BDWT	WO	2110	4670	83
236	Hebert et al, 1993	2127	Mouse (<i>Mus musculus</i>)	6	U	FD	15	d	6	w	JV	F	GRO	BDWT	WO	19500	47500	83
237	Solaiman et al, 2001	36748	Goat (<i>Capra hircus</i>)	3	U	GV	9	w	7-8	mo	JV	F	GRO	BDWT	WO		1.47	80
238	Ortolani et al, 2003	36759	Sheep (<i>Ovis aries</i>)	2	U	DR	35	d	6	mo	JV	M	GRO	BDWT	WO		3.00	76
239	Freundt and Ibrahim, 1990	2640	Rat (<i>Rattus norvegicus</i>)	2	U	DR	91	d	NR	NR	JV	F	GRO	BDWT	WO		5.78	72
240	DeGoey et al, 1971	2064	Pig (<i>Sus scrofa</i>)	2	U	FD	98	d	NR	NR	JV	B	GRO	BDWT	WO		7.46	78
241	DeGoey et al, 1971	2064	Pig (<i>Sus scrofa</i>)	2	U	FD	23	d	NR	NR	JV	NR	MPH	MUSC	MU		15.5	77
242	Boyden, 1938	14653	Rat (<i>Rattus norvegicus</i>)	5	U	FD	4	w	28	d	JV	B	GRO	BDWT	WO		23.5	77

Table 6.1 Mammalian Toxicity Data Extracted for Wildlife Toxicity Reference Value (TRV)

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Result #	Reference	Ref No.	Test Organism	# of Conc/Doses	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Type	Effect Measure	Response Site	NOAEL Dose* (mg/kg bw/day)	LOAEL Dose* (mg/kg bw/day)	Total
243	Rana and Kumar, 1980	2256	Rat (<i>Rattus norvegicus</i>)	2	U	GV	20	d	90	d	JV	M	GRO	BDWT	WO		39.8	84
244	Kumar et al, 1987	2186	Rat (<i>Rattus norvegicus</i>)	2	U	GV	45	d	90	d	JV	M	GRO	BDWT	WO		39.8	84
245	Llewellyn et al, 1985	2203	Rat (<i>Rattus norvegicus</i>)	2	U	FD	21	w	NR	NR	JV	M	GRO	BDWT	WO		106	71
246	Fuentealba et al, 2000	36364	Rat (<i>Rattus norvegicus</i>)	2	U	FD	12	w	21	d	JV	B	GRO	BDWT	WO		122	76
247	Haywood, 1985	2121	Rat (<i>Rattus norvegicus</i>)	5	U	FD	15	w	NR	NR	JV	M	GRO	BDWT	WO		274	71
248	Haywood and Loughran, 1985	2124	Rat (<i>Rattus norvegicus</i>)	5	U	FD	6	w	NR	mo	JV	M	GRO	BDWT	WO		285	77
Survival (MOR)																		
249	Bassuny, 1991	2020	Rabbit (<i>Oryctolagus cuniculus</i>)	5	U	FD	7	w	35	d	JV	M	MOR	MORT	WO	4.25		79
250	Cromwell et al, 1993	2062	Pig (<i>Sus scrofa</i>)	2	U	FD	783	d	10.3	mo	GE	F	MOR	MORT	WO	5.51		70
251	Allcroft et al, 1961	14387	Pig (<i>Sus scrofa</i>)	4	M	FD	4	w	8-10	w	JV	B	MOR	MORT	WO	5.60	9.34	89
252	Brandt, 1983	2033	Mink (<i>Mustela vison</i>)	3	M	FD	4	mo	90	d	JV	M	MOR	MORT	WO	10.2	19.6	89
253	Jenkins, 1989	48117	Cattle (<i>Bos taurus</i>)	5	U	FD	6	w	3	d	JV	M	MOR	MORT	WO	16.3	32.5	77
254	Boyden, 1938	14653	Rat (<i>Rattus norvegicus</i>)	5	U	FD	1	w	28	d	JV	B	MOR	MORT	WO	23.3	35.0	84
255	Edmonds and Baker, 1986	2075	Pig (<i>Sus scrofa</i>)	3	U	FD	28	d	4	w	JV	NR	MOR	MORT	WO	25.9		79
256	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	DR	15	d	6	w	JV	B	MOR	MORT	WO	33.3	111	78
257	Bush et al, 1995	2043	Mink (<i>Mustela vison</i>)	3	M	FD	132	d	10	w	JV	B	MOR	MORT	WO	33.4		83
258	Hebert, 1993	2126	Mouse (<i>Mus musculus</i>)	6	U	DR	15	d	6	w	JV	F	MOR	MORT	WO	33.8	101	80
259	Grobner et al, 1986	2113	Rabbit (<i>Oryctolagus cuniculus</i>)	6	M	FD	28	d	28	d	JV	NR	MOR	MORT	WO	45.5		75
260	Grobner et al, 1986	2113	Rabbit (<i>Oryctolagus cuniculus</i>)	6	M	FD	28	d	28	d	JV	NR	MOR	MORT	WO	59.0		75
261	Keen et al, 1982	11928	Rat (<i>Rattus norvegicus</i>)	4	U	FD	7	w	NR	NR	JV	F	MOR	MORT	WO	91.7	183	84
262	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	FD	13	w	6	w	JV	B	MOR	MORT	WO	107		79
263	Dodds-Smith et al, 1992	440	Common shrew (<i>Sorex araneus</i>)	2	U	FD	12	w	NR	NR	JV	B	MOR	MORT	WO	229		78
264	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	5	U	DR	2	w	6	w	JV	M	MOR	MORT	WO	259	400	79
265	Hebert, 1993	2126	Rat (<i>Rattus norvegicus</i>)	6	U	FD	15	d	6	w	JV	B	MOR	MORT	WO	307		79
266	Haywood, 1985	2121	Rat (<i>Rattus norvegicus</i>)	5	U	FD	2	w	NR	NR	JV	M	MOR	MORT	WO	457	548	78
267	Hebert, 1993	2126	Mouse (<i>Mus musculus</i>)	6	U	FD	15	d	6	w	JV	B	MOR	MORT	WO	690		70
268	Hebert, 1993	2126	Mouse (<i>Mus musculus</i>)	6	U	FD	13	w	6	w	JV	B	MOR	MORT	WO	760		79
269	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	6	U	FD	92	d	6	w	JV	B	MOR	MORT	WO	798		78
270	Hebert et al, 1993	2127	Mouse (<i>Mus musculus</i>)	5	U	DR	2	w	6	w	JV	B	MOR	MORT	WO	1430	3400	79
271	Hebert et al, 1993	2127	Rat (<i>Rattus norvegicus</i>)	6	U	FD	15	d	6	w	JV	M	MOR	MORT	WO	4160		78
272	Hebert et al, 1993	2127	Mouse (<i>Mus musculus</i>)	6	U	FD	15	d	6	w	JV	B	MOR	MORT	WO	47500		78
273	Hebert et al, 1993	2127	Mouse (<i>Mus musculus</i>)	6	U	FD	92	d	6	w	JV	B	MOR	MORT	WO	48300		78
274	Gopinath et al, 1974	36202	Sheep (<i>Ovis aries</i>)	2	U	DR	10	w	6	mo	JV	F	MOR	MORT	WO		5.09	77
275	Ishmael et al, 1971	2155	Sheep (<i>Ovis aries</i>)	2	U	OR	31	d	6	mo	JV	F	MOR	MORT	WO		7.57	75
276	Ritchie et al, 1963	14402	Pig (<i>Sus scrofa</i>)	2	U	FD	15	w	7	w	JV	NR	MOR	MORT	WO		8.08	78
277	DeGoey et al, 1971	2064	Pig (<i>Sus scrofa</i>)	2	U	FD	23	d	NR	NR	JV	NR	MOR	MORT	WO		15.5	78
278	McNatt et al, 1971	2216	Rat (<i>Rattus norvegicus</i>)	2	U	DR	3	w	4-11	mo	JV	M	MOR	MORT	WO		114	68

AAT = alanine aminotransferase; AD = adult; AHDX = aniline hydroxylase; ASAT = aspartate aminotransferase; B = both; BDWT = body weight changes; BEH = behavior; BI = bile; BIO = biochemical; BL = blood; BLPR = blood pressure; BR = brain; bw = body weight; CALC = calcium; CHM = chemical changes; CTYP = percent cell type; d = day; DIFD = digestibility of food; DR = Drinking water; DT - digestive tract; ENZ = enzyme level changes; F = female; FCNS = food consumption; FD = food; FDB = feeding behavior; FDCV = food conversion efficiency; FDNG = feeding behavior; FFTA = fatty acids, free; FO = foot; G6PD = glucose-6-phosphate dehydrogenase; GBCM = general biochemical changes; GE = gestation; GENZ = general enzyme changes; GGTR = (gamma) Y-glutamyltransferase; GHIS = general histology; GHRM = general hormone; GITX = general intoxication; GLPX = glutathione peroxidase; GLTH = glutathione; GLUC = glucose; GLYC = glycogen; GPHY = general physiology changes; GRO = growth; GRS = gross body weight changes; GT = gastrointestinal tract; GV = gavage; HA = hair; HE = heart; HIS = histological changes; HMGL = hemoglobin; HRM = hormone changes; HYPL = hyperplasia; IN = intestinal tract; IRR = skin irritation; ITX = intoxication; JV = juvenile; kg = kilograms; KI = kidney; LC = lactation; LD = lipid; LI = liver; LOAEL = lowest observed adverse effect level; mg = milligrams; mo = months; M = male; M = measured; MK = milk, lactating females; MOR = effects on mortality and survival; MORT = mortality; MPH = morphology; MT = multiple; MU = muscle; MUSC = muscle changes; NACO = sodium; NOAEL = No Observed Adverse Effect Level; NCRO = necrosis; NR = Not reported; NMVM = number of movements; OR = other oral; ORW = organ weight changes; ORWT = organ weight changes; PCLV = packed cell volume; PHY = physiology; PL = plasma; PROG = progeny numbers/counts; PRTL = protein, total; PRWT = progeny weight; PTH = pathology; RBCE = red blood cell count; REP = reproduction; RSUC = sperm cell counts; SH = stomach; SK = skin; SM = sexually mature; SMIX = weight relative to body weight; SP = spleen; SPCL = sperm cell counts; SR = serum; SURV = survival; TE = testes; TEWT = testes weight; TS = thymus; TWBC = white blood cell count, total; U = unmeasured; UR = urine; USTR = ultrastructural changes; VTMA = vitamin A; w = weeks; WCON = water consumption; WO = whole organism; yr = year.

*NOAEL and LOAEL values that are equal and from the same reference represent different experimental designs.

These are designated with different Phase numbers in Appendix 6.1.

Within the reviewed papers there are 278 results for biochemical (BIO), behavior (BEH), physiology (PHY), pathology (PTH), reproduction (REP), growth (GRO), and survival (MOR) endpoints with a total Data Evaluation Score >65 that were used to derive the TRV (U.S. EPA 2003; Attachment 4-4). These data are plotted in Figure 6.1 and correspond directly with the data presented in Table 6.1. The NOAEL results for growth and reproduction are used to calculate a geometric mean NOAEL. This geometric mean is examined in relationship to the lowest bounded LOAEL for reproduction, growth, and survival to derive the TRV according to the Eco-SSL guidance (U.S. EPA 2003; Attachment 4-5).

A geometric mean of the NOAEL values for reproduction and growth was calculated at 25 mg copper/kg bw/day. However, this value is higher than the lowest bounded LOAEL for reproduction, growth, or mortality results. Therefore, the TRV is equal to the highest bounded NOAEL below the lowest bounded LOAEL for reproduction, growth, or survival, and is equal to 5.60 mg copper/kg bw/day.

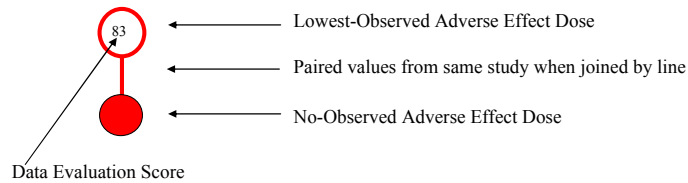
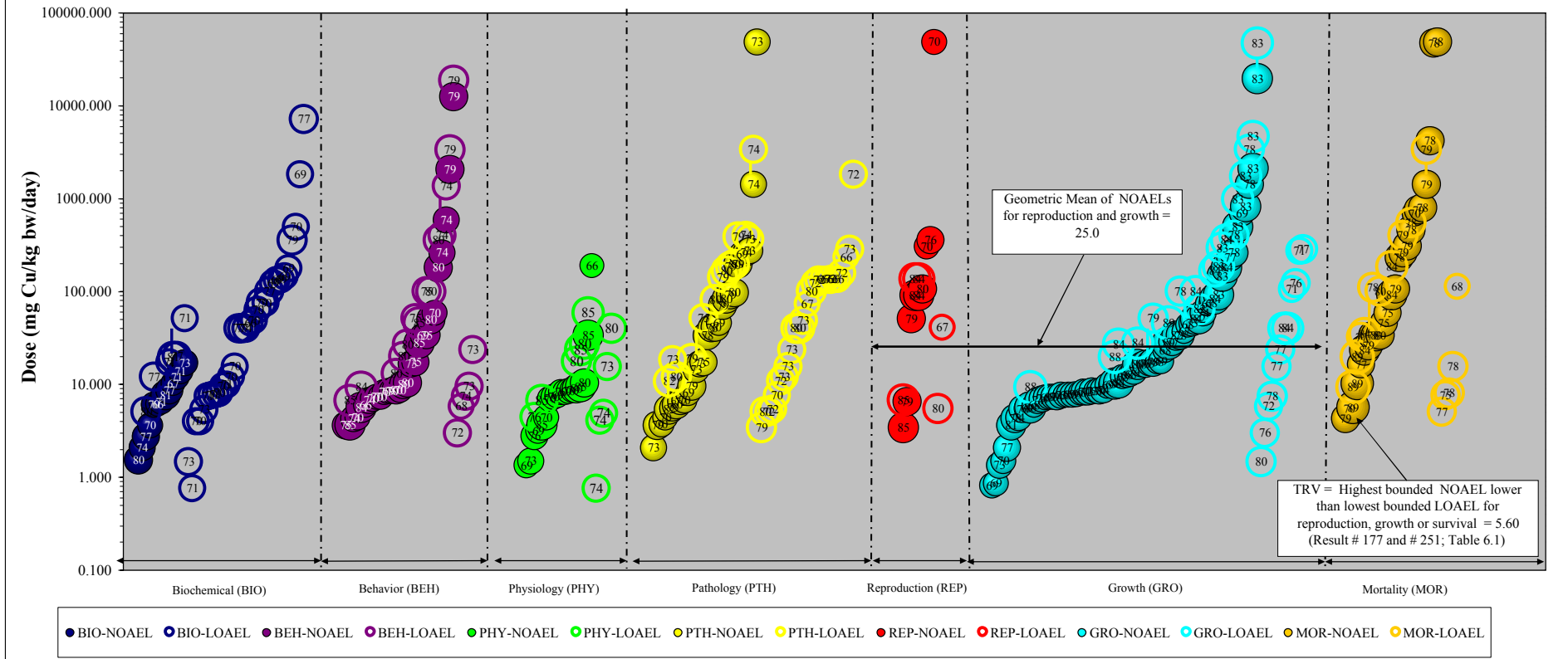
6.2 Estimation of Dose and Calculation of the Eco-SSL

Three separate Eco-SSL values were calculated for mammalian wildlife, one for each of three surrogate receptor groups representing different trophic levels. The mammalian Eco-SSLs derived for copper were calculated according to the Eco-SSL guidance (U.S. EPA, 2003; Attachment 4-5) and are summarized in Table 6.2.

Table 6.2 Calculation of the Mammalian Eco-SSLs for Copper					
Surrogate Receptor Group	TRV for Copper (mg dw/kg bw/d) ¹	Food Ingestion Rate (FIR) ² (kg dw/kg bw/d)	Soil Ingestion as Proportion of Diet (P _s) ²	Concentration of Copper in Biota Type (i) ^{2,3} (B _i) (mg/kg dw)	Eco-SSL (mg/kg dw) ⁴
Mammalian herbivore (vole)	5.60	0.0875	0.032	$\ln(B_i) = 0.394 * \ln(\text{Soil}_i) + 0.688$ where i = plants	1100
Mammalian ground insectivore (shrew)	5.60	0.209	0.030	$B_i = 0.515 * \text{Soil}_i$ where i = earthworms	49
Mammalian carnivore (weasel)	5.60	0.130	0.043	$\ln(B_i) = 0.1444 * \ln(\text{Soil}_i) + 2.042$ where i = mammals	560

¹ The process for derivation of wildlife TRVs is described in Attachment 4-5 of U.S. EPA (2003).
² Parameters (FIR, P_s, B_i values, regressions) are provided in U.S. EPA (2003) Attachment 4-1 (revised February 2005).
³ B_i = Concentration in biota type (i) which represents 100% of the diet for the respective receptor.
⁴ $HQ = [\text{FIR} * (\text{Soil}_i * P_s + B_i)] / \text{TRV}$ solved for $HQ=1$ where $\text{Soil}_i = \text{Eco-SSL}$ (Equation 4-2; U.S. EPA, 2003).

Figure 6.1 Mammalian TRV Derivation for Copper



Wildlife TRV Derivation Process

- 1) There are at least three results available for two test species within the growth, reproduction, and mortality effect groups. There are enough data to derive a TRV.
- 2) There are three NOAEL results available within the growth and reproduction effect groups for calculation of a geometric mean.
- 3) The geometric mean is equal to 25.0 mg copper/kg bw/d and is higher than the lowest bounded LOAEL for results within the reproduction, growth, and survival (MOR) effect groups.
- 4) The mammalian wildlife TRV for copper is equal to 5.60 mg copper/kg bw/day which is the highest NOAEL value lower than the lowest LOAEL value for reproduction and growth.

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CAS Number	Chemical Name	Species Scientific Name	Species Common Name	Species Group	Endpoint	Effect	Effect Measurement	Response Site	Response Site Description	Exposure Duration (Days)	Min Duration (Days)	Max Duration (Days)	Exposure Type	Chemical Analysis	Trend	Effect Percent	Effect Percent Min	Effect Percent Max	Statistical Significance	Significance Level	Conc 1 Type (ug/L)	Conc 1 (ug/L)	Conc Min 1 (ug/L)	Conc 1 Max (ug/L)	Media Type	Test Location	Reference Number	Author	Title	Source	Publication Year
91203	Naphthalene	Procambarus clarkii	Red swamp crayfish	Crustaceans	NR	MPH	SMIX	OV	Ovaries	NR	1	15	R	U	DEC	NR	NR		NR	NR	F	10000	NR	NR	FW	LAB	15236	Sarjini, R. R. Nagabhushanam and M. Fingerman	Naphthalene-Induced Atresia in the Ovary of the Crayfish Procambarus clarkii	Ecotoxicol Environ Saf. 31(1):76-83	1995
91203	Naphthalene	Dicentrarchus labrax	Sea bass	Fish	LOEL	MPH	SMIX	LI	Liver	0.08333	NR	NR	S	U	NC	NR	NR	NR	<0.05	SIG	A	0.9	NR	NR	SW	LAB	66389	Gravato, C., and M.A. Santos	Juvenile Sea Bass Liver P450, EROD Induction, and Erythrocytic Genotoxic Responses to PAH and PAH-Like Compounds	Ecotoxicol Environ Saf. 51(2):115-127	2002
91203	Naphthalene	Dicentrarchus labrax	Sea bass	Fish	NOEL	MPH	SMIX	LI	Liver	0.08333	NR	NR	S	U	NC	NR	NR	NR	<0.05	NOSIG	A	0.3	NR	NR	SW	LAB	66389	Gravato, C., and M.A. Santos	Juvenile Sea Bass Liver P450, EROD Induction, and Erythrocytic Genotoxic Responses to PAH and PAH-Like Compounds	Ecotoxicol Environ Saf. 51(2):115-127	2002
91203	Naphthalene	Micropogonias undulatus	Atlantic croaker	Fish	NOEL	REP	MOTL	NR	Not Reported	0.01389	NR	NR	S	U	NC	NR	NR	NR	<0.05	ANOSIG	F	0.1	NR	NR	SW	LAB	83758	Thomas, P., and K. Doughty	Disruption of Rapid, Nongenomic Steroid Actions by Environmental Chemicals: Interference with Progesterin Stimulation of Sperm Motility in Atlantic Croaker	Environ. Sci. Technol. 38(23):6328-6332	2004
91203	Naphthalene	Micropogonias undulatus	Atlantic croaker	Fish	NR	DVP	GDVP	NR	Not Reported	NR	35	56	S	U	DEC	44	NR		NR	NR	F	500	NR	NR	SW	LAB	16906	Thomas, P., and L. Budiantara	Reproductive Life History Stages Sensitive to Oil and Naphthalene in Atlantic Croaker	Mar. Environ. Res. 39(1-4):147-150	1995
91203	Naphthalene	Micropogonias undulatus	Atlantic croaker	Fish	NR	MPH	SMIX	OV	Ovaries	NR	35	56	S	U	DEC	NR	NR		P<0.01	SIG	F	500	NR	NR	SW	LAB	16906	Thomas, P., and L. Budiantara	Reproductive Life History Stages Sensitive to Oil and Naphthalene in Atlantic Croaker	Mar. Environ. Res. 39(1-4):147-150	1995
91203	Naphthalene	Micropogonias undulatus	Atlantic croaker	Fish	NR	REP	GREP	NR	Not Reported	NR	35	56	S	U	DEC	NR	NR		P<0.02	SIG	F	500	NR	NR	SW	LAB	16906	Thomas, P., and L. Budiantara	Reproductive Life History Stages Sensitive to Oil and Naphthalene in Atlantic Croaker	Mar. Environ. Res. 39(1-4):147-150	1995
91203	Naphthalene	Spirostomum ambiguum	Protozoa	Invertebrates	EC50	DVP	DFRM	NR	Not Reported	1	NR	NR	S	U	INC	NR	NR	NR	NA	NA	F	0.293	NR	NR	FW	LAB	19880	Nalecz-Jawicki, G., and J. Sawicki	Spirotox - A new Tool for Testing the Toxicity of Volatile Compounds	Chemosphere 38(14):3211-3218	1999
91203	Naphthalene	Spirostomum ambiguum	Protozoa	Invertebrates	EC50	DVP	DFRM	NR	Not Reported	2	NR	NR	S	U	INC	NR	NR	NR	NA	NA	F	0.284	NR	NR	FW	LAB	19880	Nalecz-Jawicki, G., and J. Sawicki	Spirotox - A new Tool for Testing the Toxicity of Volatile Compounds	Chemosphere 38(14):3211-3218	1999