APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chromium(VI) aerosols and mists
CAS number: 18540-29-9
Date: October 2008
Profile status: Final Draft Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [X] Chronic
Key to figure: 11, 29
Species: Human

Minimal Risk Level: $5x10^{-6}$ mg chromium(VI)/m^3 for dissolved hexavalent chromium aerosols and mists.

Reference: Lindberg E, Hedenstierna G. 1983. Chrome plating: Symptoms, findings in the upper airways, and effects on lung function. Arch Environ Health 38:367-374.

Experimental design: Eighty-five male and 19 female chrome-plating workers exposed to chromic acid were assessed for nose, throat, and chest symptoms, were inspected for effects in nasal passages, and were given pulmonary function tests. Study participants were compared to a reference group of 119 auto mechanics who were not exposed to chromium. The length of worker exposures to chromic acid ranged from 0.1 to 36 years, spanning intermediate- and chronic-exposure durations. Since the study population included workers exposed for both intermediate and chronic durations, data are considered appropriate for derivation of the intermediate- and chronic-duration inhalation MRLs. Chromium exposures were measured using personal air samplers and stationary equipment positioned close to the baths containing chromic acid. The exposure categories were defined as high average daily concentrations >0.002 mg chromium(VI)/m^3], low (average daily concentrations <0.002 mg chromium(VI)/m^3), and mixed category (chromium(VI) was <0.002 mg chromium(VI)/m^3, with exposure to other acids and metallic salts). Correlations with nasal irritation and respiratory functions were also determined for peak exposures. Statistical analyses were performed using the chi-square test with Yate's correction when comparing nasal findings, and the Student's two tail t-test was used when comparing lung function findings.

Effects noted in study and corresponding doses: Nasal irritation ($p<0.05$), mucosal atrophy ($p<0.05$), and ulceration ($p<0.01$), and decreases in spirometric parameters (forced vital capacity, forced expired volume in 1 second, and forced mid-expiratory flow) were observed in workers occupationally exposed to ≥0.002 mg chromium(VI)/m^3 as chromic acid with a median exposure period of 2.5 years. About 60% of the exposed subjects were smokers, but no consistent association between exposure and cigarette smoking was observed. Short-term peak exposures to chromic acid correlated better with nasal septum damage than with 8-hour mean concentrations.

Dose end point used for MRL derivation: 0.002 mg chromium(VI)/m^3 (nasal irritation, mucosal atrophy, decreased FVC, FEP_1, and FEV)

[ ] NOAEL [X] LOAEL [ ] benchmark concentration (BMC)

The LOAEL of 0.002 mg chromium(VI)/m^3 for upper respiratory effects was selected as the point of departure for derivation of the intermediate- and chronic-duration inhalation MRLs for dissolved hexavalent chromium aerosols and mists. The LOAEL was duration-adjusted to a $LOAEL_{ADJ}$ of 0.0005 mg chromium(VI)/m^3 for continuous exposure. The intermediate- and chronic-duration inhalation MRLs of 0.000005 mg chromium(VI)/m^3 for dissolved hexavalent chromium aerosols and mists were

derived by dividing the $LOAEL_{ADJ}$ of 0.0005 mg chromium(VI)/m^3 by a composite uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Uncertainty factors used in MRL derivation:

[X] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: No. Not applicable.

Was a conversion used from intermittent to continuous exposure? Yes, the LOAEL of 0.002 mg chromium(VI)/m^3 was multiplied by 8 hour/24 hour and by 5 days/7 days to yield a duration-adjusted LOAEL ($LOAEL_{ADJ}$) of 0.0005 mg chromium(VI)/m^3.

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the major target of inhalation exposure to chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. In workers exposed to dissolved hexavalent chromium aerosols and mists (as chromium trioxide mist) for intermediate durations, nasal irritation, ulceration, and mucosal atrophy and rhinorrhea have been reported, with LOAEL values ranging from 0.09 to 0.1 mg chromium(VI)/m^3 (Gibb et al. 2000a; Gomes 1972; Kleinfeld and Rosso 1965). Similarly, studies in rats and mice have shown that the upper respiratory tract is a primary target of exposure to inhaled chromium trioxide mist, with LOAEL values ranging from 0.49 to 3.63 mg chromium(VI)/m^3 (Adachi 1987; Adachi et al. 1986; Kim et al. 2004). In addition, numerous intermediate- and chronic-duration exposure studies of workers to chromium(VI) compounds in general identify the respiratory tract as the primary target of exposure, with reports of epistaxis, chronic rhinorrhea, nasal itching and soreness, nasal mucosal atrophy, perforations and ulceration of the nasal septum, bronchitis, pneumonoconiosis, decreased pulmonary function, and pneumonia (Bovet et al. 1977; Cohen et al. 1974; Davies et al. 1991; Gomes 1972; Greater Tokyo Bureau of Hygiene 1989; Hanslian et al. 1967; Keskinen et al. 1980; Kleinfeld and Rosso 1965; Lee and Goh 1988; Letterer 1939; Lieberman 1941; Lindberg and Hedenstierna 1983; Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950; Novey et al. 1983; Pastides et al. 1991; PHS 1953; Royle 1975b; Sassi 1956; Sluis-Cremer and du Toit 1968; Sorahan et al. 1987; Taylor 1966).

Agency Contact (Chemical Manager): Sharon Wilbur

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chromium(VI) particulates
CAS number: 18540-29-9
Date: October 2008
Profile status: Final Draft Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 14
Species: Rat

Minimal Risk Level: 0.0003 mg chromium (VI)/m^3 for hexavalent chromium particulate compounds

Reference: Glaser U, Hochrainer D, Steinholf D. 1990. Investigation of irritating properties of inhaled CrVI with possible influence on its carcinogenic action. Environ Hyg 2:235-245.

Experimental design: Eight-week-old male Wistar rats (30 animals in each group) were exposed 22 hours/day, 7 days/week to 0, 0.05, 0.1, 0.2, or 0.4 mg chromium(VI)/m^3 as sodium dichromate aerosol particulates. Groups of 10 animals were sacrificed after 30 or 90 days of exposure or after 90 days of exposure and a 30-day recovery period. The respective mass median mean diameters (MMAD) and geometric standard deviation were 0.28 μm and 1.63 for the 0.5 and 0.1 mg chromium(VI)/m^3 concentrations and 0.39 μm and 1.72 for the 0.2 and 0.4 mg chromium(VI)/m^3 concentrations. Hematological, clinical chemistry, and urinalysis tests were performed. Gross and histological examinations were limited to the upper airway epithelia, left lung lobes, and the kidneys. In addition, lung lavage fluid was analyzed for total protein, albumin, lactate dehydrogenase, and β-glucuronidase activities.

Effects noted in study and corresponding doses: No deaths or abnormal clinical signs occurred at any of the exposures. Body weight was significantly ($p<0.001$) decreased at 0.2 and 0.4 mg chromium(VI)/m^3 for 30 days, at 0.4 mg chromium(VI)/m^3 for 90 days ($p<0.05$), and at 0.2 ($p<0.01$) and 0.4 mg chromium(VI)/m^3 ($p<0.05$) in the recovery group. No differences in urinary protein and no exposure-related histopathological lesions were noted. No differences were seen in analysis of serum levels or activities of alanine aminotransferese, alkaline phosphatase, glucose, urea, total bilirubin, total cholesterol, or phospholipids. There were no hematological effects on red blood cells, but the white blood cell counts increased significantly in a dose-related manner at ≥0.1 mg chromium(VI)/m^3 after 30 days and at ≥0.05 mg chromium(VI)/m^3 after 90 days. White blood cells counts were not increased in 90 day exposure plus 30-day observation group.

Obstructive respiratory dyspnea occurred at ≥0.2 mg chromium(VI) chromium(VI)/m^3 after 30 and 90 days. Mean lung weight was increased in all exposure groups and was statistically increased at ≥0.05 mg chromium(VI)/m^3 for 30 days, and at ≥0.1 mg chromium(VI)/m^3 for 90 days and in the 90-day plus recovery period group. Histological examination revealed slight hyperplasia in high incidence at ≥0.05 mg chromium(VI)/m^3 at 30 days. With longer exposure, the incidence declined, indicating repair. Lung fibrosis occurred at ≥0.1 mg chromium(VI)/m^3 for 30 days, but was not seen in rats exposed for 90 days. Accumulation of macrophages was observed in all exposed rats, regardless of exposure concentration or duration. This histiocytosis probably accounts for the increased lung weight. Histology of upper airways revealed focal inflammation. Results of bronchoalveolar lavage (BAL) analysis provided further information of the irritation effect. Total protein in BAL fluid was significantly increased in all exposed groups, but declined in the recovery period. Albumin in BAL fluid increased in a dose-related manner at all concentrations in the 30-day group, but recovery started during 90-day exposure and continued during the 30-day observation period. The activities of lactate dehydrogenase

and β-glucuronidase, measures of cytotoxicity, were elevated at 0.2 and 0.4 mg chromium(VI)/m^3 for 30 and 90 days, but returned to control values during the recovery period. The number of macrophages in the BAL fluid had significantly increased after 30 and 90 days, but normalized during the recovery period. The macrophages were undergoing cell division or were multinucleate and larger. This activation of macrophages was not observed in the recovered rats. The study authors concluded that inflammation is essential for the induction of most chromium inhalation effects and may influence the carcinogenicity of chromium(VI) compounds.

Dose end point used for MRL derivation: 0.016 mg/m^3 (alterations in lactate dehydrogenase levels in bronchoalveolar lavage), converted to a $BMCL_{HEC}$ of 0.010 mg chromium(VI)/m^3

[ ] NOAEL [ ] LOAEL [X] benchmark concentration (BMC)

The Agency adopted the benchmark concentration (BMC) analysis of the Glaser et al. (1990) data conducted by Malsch et al. (1994) for deriving an intermediate-duration inhalation MRL for hexavalent chromium particulate compounds. Using the 90-day exposure data (as described above), Malsch et al. (1994) developed BMCLs for lung weight and BAL fluid levels of lactate dehydrogenase, protein, and albumin. Prior to conducting the benchmark analysis, Malsch et al. (1994) adjusted the dose-response data for intermittent exposure. Duration-adjusted data were then fitted to a polynomial mean response regression model by the maximum likelihood method to derive BMCLs (defined as the 95% lower confidence limit on the concentration corresponding to a 10% relative change in the end point compared to the control). The BMCL values for lung weight, lactate dehydrogenase in the BAL fluid, protein in BAL fluid, and albumin in BAL fluid were 0.067, 0.016, 0.035, and 0.031 mg chromium(VI)/m^3, respectively. The lowest BMCL, 0.016 mg chromium(VI)/m^3 for alterations in lactate dehydrogenase levels in BAL fluid, was selected to derive the intermediate-duration inhalation MRL. The BMCL of 0.016 mg chromium(VI)/m^3 was converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.010 mg chromium(VI)/m^3, as described below. The intermediate-duration inhalation MRL of 0.0003 mg chromium (VI)/m^3 for hexavalent chromium particulate compounds was derived by dividing the $BMCL_{HEC}$ of 0.010 mg chromium(VI)/m^3 by a composite uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Uncertainty factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans, with dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.
Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
The BMCL of 0.016 mg chromium(VI)/m^3 was converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.010 mg chromium(VI)/m^3 using the RDDR (regional deposited dose ratio) program (EPA 1994c) as follows:

$$BMCL_{HEC} = BMCL \times RDDR$$
$$BMCL_{HEC} = 0.016 \text{ mg chromium(VI)/m}^3 \times 0.630 = 0.010 \text{ mg chromium(VI)/m}^3$$

where
RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal to the predicted inhalation particulate exposure concentration for a human. The RDDR

multiplier of 0.630 for the thoracic region tract was determined using the default subchronic body weight of 217 g for male Wistar rats (EPA 1988d) and a particle size MMAD±GSD of 0.5±1.63 μm reported in the Glaser et al. (1984) study. Although the actual mean particle size reported in the critical study was 0.28 μm, the RDDR program (EPA 1994c) can only run be run for particle sizes ranging from 0.5 to 30 μm; therefore, 0.5 μm was used as the default particle size to calculated the RDDR. Since the critical study did not report body weight, the default subchronic body weight of 217 g for male Wistar rats was used.

Was a conversion used from intermittent to continuous exposure? Yes. Animals were exposed for 22 hours/day, 7 days/week. Prior to conducting the benchmark analysis, Malsch et al. (1994) adjusted the dose-response data for intermittent exposure (22 hours/day) by multiplying data points for all outcome measures by 22 hours/24 hours.

Other additional studies or pertinent information that lend support to this MRL: The findings in this study are supported by another 90-day study conducted by the same group (Glaser et al. 1985). In this study, groups of 20 male Wistar rats were exposed to 0, 0.025, 0.05, 0.1, or 0.2 mg chromium(VI)/m^3 as sodium dichromate for 22 hours/day, 7 days/week for 90 days. No deaths occurred at any of the exposures. All exposed animals showed normal histologic findings in lung, kidney, liver, stomach, and gonads. Lung and spleen weights were increased significantly at doses above 0.025 mg chromium(VI)/m^3. Serum levels of triglycerides and phospholipid were increased in rats exposed to 0.2 mg chromium(VI)/m^3. Serum contents of total immunoglobulins were significantly increased in the 0.05 and 0.1 mg chromium(VI)/m^3 groups. At 0.025 and 0.2 mg chromium(VI)/m^3, serum immunoglobulin contents were no different than controls. The SRBC antibody response was increased in all dosed groups over control values. Chromium treatment at 0.2 mg chromium(VI)/m^3 also enhanced the mitogenic-stimulation of splenic Concanavalin T-lymphocytes. At 0.025 mg chromium(VI)/m^3, there were significant increases in polynuclear macrophages and the number of macrophages in telophase, and increases in lymphocytes in bronchoalveolar lavage samples. At 0.05 and 0.2 mg chromium(VI)/m^3, there were significant decreases in total numbers of macrophages. The percentages of polynuclear macrophages, lymphocytes, and granulocytes were increased at chromium exposures of 0.05 mg chromium(VI)/m^3, but at 0.2 mg chromium(VI)/m^3, the percentage of granulocytes cells was lower than control values. At 0.025 and 0.05 mg chromium(VI)/m^3 exposures, phagocytosis of latex particles by alveolar macrophages was increased over controls. However, at 0.2 mg chromium(VI)/m^3, the phagocytic activity was less than controls and there was a decrease in lung clearance of iron oxide particulates.

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chromium(VI)
CAS Numbers: 18540-29-9
Date: October 2008
Profile status: Final Draft Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 45
Species: Rat

Minimal Risk Level: 0.005 [X] mg chromium(VI)/kg/day [ ] ppm

Reference: NTP. 2008a. NTP technical report on the toxicology and carcinogenesis studies of sodium dichromate dihydrate (CAS No. 7789-12-0) in F344/N rats and B6C3F1 mice (drinking water studies). Washington, DC: National Toxicology Program. NTP TR 546. http://ntp.niehs.nih.gov/files/546_web_FINAL.pdf. August 13, 2008.

Experimental design: Male F344/N rats (6–7 weeks old) were exposed to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study. Male rats (50/group) were exposed to drinking water concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L. In a subgroup of 10 male rats, blood was collected from the retroorbital sinus after exposure durations of 4 days, 22 days, 3 months, 6 months, and 1 year and evaluated for hematology (Hct; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte and platelet morphology; MCV; MCH; MCHC; and leukocyte count and differentials) and clinical chemistry (urea nitrogen, creatinine, total protein, albumin, ALT, AP, creatine kinase, SDH, and bile acids). Clinical signs of toxicity were assessed over the course of exposure. NTP calculated mean daily doses of sodium dichromate dihydrate in male rats of 0, 0.6, 2.2, 6, or 17 mg/kg (equivalent to 0, 0.21, 0.77, 2.1, or 5.9 mg chromium(VI)/kg/day, respectively) over the course of the 2-year study. Since observations were made at various time points during the chronic study (e.g., 22 days to 1 year), rather than using different dosage scales for each observation and outcome in the dose-response modeling, time-averaged dosages for the chronic duration (i.e., 101 weeks) were used to represent the dosage received during the intermediate- (i.e., >2–<52 weeks) and chronic- (>2–101 weeks) duration periods. This is an approximation of the actual dosages received, which varied as a function of body weight, and therefore, time of observation, with the differences most pronounced at the earliest periods of the intermediate-duration exposure (e.g., 3–12 weeks). The rationale for this simplification of the dose-response analysis is as follows: (1) outcomes observed at specific time points in the study (e.g., blood effects) after the acute period (>2 weeks) were considered to be relevant to the entire intermediate-duration period (>2–<52 weeks), if observed at multiple observation times during the intermediate-duration period; (2) chronic duration dosages were nearly identical to the time-averaged dosages for intermediate-duration exposure (e.g., <12% difference in the rat study); and (3) the possible bias introduced into estimates of BMDLs as a result of using chronic-duration dosages to represent intermediate-duration dosages is small (<12%) and conservative (i.e., BMDLs based on the chronic-duration dosages may be slightly lower than BMDLs based on actual intermediate-duration dosages).

Effect noted in study and corresponding doses: No treatment-related clinical signs of toxicity were observed in rats over the course of this study. Hematological effects consistent with microcytic, hypochromic anemia were observed at all intermediate-duration time points (22 days to 6 months) in male rats exposed to sodium dichromate dihydrate in drinking water; severity exhibited dose-dependence. At the 22-day assessment in rats, decreases were observed in Hct, Hgb, MCV, and MCH at ≥0.77 mg chromium(VI)/kg/day; effects at higher doses included decreased MCHC and platelet count at ≥2.1 mg chromium(VI)/kg/day, and decreased erythrocyte and reticulocyte counts, and increased nucleated

erythrocytes at 5.9 mg chromium(VI)/kg/day). At the 3-month assessment in rats, decreases were observed for MCV and MCH at ≥0.77 mg chromium(VI)/kg/day; effects at higher doses included decreased Hgb at ≥2.1 mg chromium(VI)/kg/day and decreased Hct and increased erythrocyte, reticulocyte, platelet, leukocyte, and segmented neutrophil counts at ≥5.9 mg chromium(VI)/kg/day. Increases in cell counts indicate a compensatory hematopoietic response to anemia. At 6 months in rats, decreased MCV, MCH, and MCHC were observed at ≥0.77 mg chromium(VI)/kg/day; at 5.9 mg chromium(VI)/kg/day, decreased Hgb was observed. For all intermediate-duration exposures (22 days to 6 months), NOAEL and LOAEL values in male rats for hematological effects were 0.21 and 0.77 mg chromium(VI)/kg/day, respectively. Although effects in rats were similar at the 22-day and 3-month assessments, NTP (2008a) concluded that effects were more severe at 22 days than at 3 months based on the magnitude of changes and the number of parameters affected in rats exposed to 0.77 mg chromium(VI)/kg/day. Effects at 6 months were less severe than those observed at the 22-day and 3-month assessments. Although the magnitude of the decreases in hematological parameters was small at 0.77 mg chromium(VI)/kg/day compared to the control group (6.1–10.6%), there is clear indication of damage to the hematological system and this dose level was considered a minimal LOAEL. At the next highest dose (2.1 mg chromium(VI)/kg/day), these parameters were 16–25% lower than controls. As defined by ATSDR, an effect that enhances the susceptibility of an organism to the deleterious effects of other chemical, physical, microbiological, or environmental influences should be considered adverse. Thus, the slight, but statistically significant, decrease in hematological parameters at 0.77 mg chromium(VI)/kg/day was considered minimally adverse.

Evaluation of clinical chemistry parameters in male rats showed significant alterations in serum liver enzyme activities, although changes were not consistent over all intermediate-duration exposures. At the 22-day assessment, increases were observed for ALT (≥0.77 mg chromium(VI)/kg/day) and AP (5.9 mg chromium(VI)/kg/day), but no change was observed for SDH. At 3 months, ALT was increased (≥0.77 mg chromium(VI)/kg/day), but AP was decreased (≥0.21 mg chromium(VI)/kg/day) and no change was observed for SDH. At 6 months, increases were observed for ALT and SDH (≥2.1 mg chromium(VI)/kg/day), but AP was decreased (0.77 mg chromium(VI)/kg/day). Due to the inconsistent changes in serum liver enzyme activities, NTP (2008a) concluded that alterations in liver enzymes (specifically ALT) were suggestive of enzyme induction, rather than hepatocellular damage. Thus, altered serum liver enzyme activities were not considered indicative of an adverse effect on the liver.

Dose and end point used for MRL derivation: 0.52 mg chromium(VI)/kg/day (microcytic, hypochromic anemia)

[ ] NOAEL [ ] LOAEL [X] benchmark dose (BMD)

Exposure to sodium dichromate dihydrate in drinking water resulted in microcytic, hypochromic anemia in male rats at all intermediate-duration exposures (22 days to 6 months). The severity was greatest at the 22-day assessment compared to the 3- and 6-month assessments; therefore, microcytic, hypochromic anemia observed at the 22-day assessment was identified as the critical effect for derivation of the intermediate-duration oral MRL. In male rats, decreases in Hct, Hgb, MCV, and MCH were the most sensitive measures of hematological effects, with NOAEL and LOAEL values of 0.21 and 0.77 mg chromium(VI)/kg/day, respectively; data sets for these end points are summarized in Table A-1.

Table A-1. Hematological Effects in Male F/344 Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

	Dose (mg chromium(VI)/kg/day)				
	0	0.21	0.77	2.1	5.9
Male rats					
Hematocrit (percent)	46.0±1.1[a]	44.4±0.4	43.2±0.6[b]	38.7±0.6[c]	33.5±0.8[c]
Hemoglobin (g/dL)	15.5±0.3	15.1±0.2	14.2±0.2[c]	12.0±0.3[c]	10.1±0.2[c]
MCV (fL)	59.5±0.4	58.6±0.5	54.9±0.5[c]	47.4±0.4[c]	45.0±0.7[c]
MCH (pg)	19.8±0.1	19.5±0.2	17.7±0.2[c]	14.8±0.2[c]	16.3±0.5[c]

[a]Mean±standard error: number of rats/group=10; number of mice/group=10
[b]Significantly different ($p \leq 0.05$) from the control group by Dunn's or Shirley's test
[c]Significantly different ($p \leq 0.01$) from the control group by Dunn's or Shirley's test

MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume

Source: NTP 2008a

To determine the point of departure for derivation of the intermediate-duration oral MRL, available continuous-variable models in the EPA BMDs (version 1.4.1) were fit to the data for Hct, Hgb, MCV, and MCH in male rats (NTP 2008a; Table A-1). The BMD and the 95% lower confidence limit (BMDL) calculated is an estimate of the doses associated with a change of 2 standard deviations from the control ($BMDL_{2sd}$); the use of 2 standard deviations takes into consideration of the normal variability in the population and decreases the possibility of misclassifying a small change as anemia. The model-fitting procedure for continuous data is as follows. The simplest model (linear) is applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then the other continuous models (polynomial, power, and Hill models) are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the test for constant variance is negative, the linear model is run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then the other continuous models are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the tests for both constant and nonconstant variance are negative, then the data set is considered not to be suitable for BMD modeling.

A summary of the BMDs and BMDLs for the best fitting models for each hematological end point are shown in Table A-2. For male rats, $BMDL_{2sd}$ values ranged from 0.37 mg chromium(VI)/kg/day for MCH to 0.71 mg chromium(VI)/kg/day for hemoglobin. None of the models provided adequate fit to the data, even with the two highest doses dropped from the analysis, for Hct. Additional details of the benchmark dose analysis for each data set modeled are presented in the last section of this worksheet. Because several hematological parameters are used to define the clinical picture of anemia, the $BMDL_{2sd}$ values for hemoglobin, MCV, and MCH were averaged resulting in a $BMDL_{2sd}$ of 0.52 mg chromium(VI)/kg/day. The intermediate-duration MRL of 0.005 mg chromium(VI)/kg/day was derived by dividing the average $BMDL_{2sd}$ by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Table A-2. Summary of BMDs and BMDLs From the Best Fitting Models for Hematological End Points in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

End point	Model	Number of doses	BMD_{2sd} (mg/kg/day)[b]	$BMDL_{2sd}$ (mg/kg/day)[b]
Hematocrit (percent)[a]	——	——	——	——
Hemoglobin (g/dL)	Polynomial (2-degree)	5	0.88	0.71
MCV (fL)	Hill	4	0.63	0.49
MCH (pg)	Linear	4	0.44	0.37

[a]None of the models provided an adequate fit to the data.
[b]Units of BMD_{1sd} and $BMDL_{1sd}$ are mg chromium(VI)/kg/day.

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; 2sd = a 2 standard deviation change from the control

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Daily doses for each exposure group based on measured body weight and drinking water intake were reported by study authors (NTP 2008a). Additional information on daily doses used for intermediate-duration exposure is discussed in the experimental design section above.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Identification of anemia, as defined by significant alterations in hematocrit, hemoglobin, MCH, and MCV, as the critical end point for deriving an intermediate-duration oral MRL is supported by results of a 22-day study in female mice (NTP 2008a), 3-month drinking water study on sodium dichromate dihydrate in rats and mice (NTP 2007), and dietary studies on potassium dichromate in rats and mice (NTP 1996a, 1996b, 1997). In the 3-month sodium dichromate dihydrate drinking water study in male and female F344/N rats (NTP 2007), blood was collected for hematology assessments after 23 days and after 3 months of exposure; for B6C3F1 mice, hematological assessments were conducted only after 3 months. Dose-dependent hematological effects consistent with microcytic, hypochromic anemia, including decreased Hct, Hgb, MCV, and MCH, were observed in rats at the 23-day and 14-week hematological assessments; the LOAEL value at both time points in males and females was 1.7 mg chromium(VI)/kg/day (a NOAEL was not established). Hematological effects were more severe at the 23-day assessment compared to the 14 week assessment. Similar hematological effects were observed in male and female B6C3F1 mice and male BALB/c and C57BL/6 mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks, with a LOAEL value of 3.1 mg chromium(VI)/kg/day (a NOAEL was not established). Results of the 3-month study in rats and mice (NTP 2007) were not selected as the basis for the

intermediate-duration MRL because a lower LOAEL value (0.77 mg chromium(VI)/kg/day) was observed for intermediate-duration exposures in the 2-year study (NTP 2008a). In a dietary studies on potassium dichromate, microcytic, hypochromic anemia was observed in male and female Sprague-Dawley rats exposed for 9 weeks, with NOAEL and LOAEL values in males of 2.1 and 8.4 mg chromium(VI)/kg/day, respectively, and of 2.5 and 9.8 mg chromium(VI)/kg/day, respectively, in females (NTP 1996b). Similar hematological effects were observed in male and female BALB/c mice exposed to potassium dichromate in the diet for 9 weeks with NOAEL and LOAEL values in males of 7.3 and 32.2 mg chromium(VI)/kg/day, respectively, and in females of 12 and 48 mg chromium(VI)/kg/day, respectively (NTP 1996a). In a multigeneration study on dietary potassium dichromate in BALB/c mice, a LOAEL value of 7.8 for hematological effects was reported (a NOAEL was not established) (NTP 1997). Compared to the LOAEL values for hematological effects at 22 days and 3 months in male rats (0.77 mg chromium(VI)/kg/day) and female mice (0.38 mg chromium(VI)/kg/day) observed in the critical study on sodium dichromate dihydrate in drinking water, higher LOAEL values were reported in the 9-week dietary study on potassium dichromate in rats (8.4 and 9.8 mg chromium(VI)/kg/day in males and females, respectively) (EPA 1996b) and mice (32.2 and 48 mg chromium(VI)/kg/day in males and females, respectively) (NTP 1996a). The reason for the differences in LOAEL values has not been established, but could be due to different exposure media (drinking water versus feed) or differences in strain sensitivity (rats).

The erythrocyte has a high capacity for chromium(VI) uptake and binding. Chromium(VI) enters the erythrocyte though a sulfate ion channel; once inside the cell, it is rapidly reduced to reactive intermediates (chromium(V) and chromium(IV)) and binds to hemoglobin and other ligands. The chromium-hemoglobin complex is stable and remains sequestered within the cell over the life-span of the erythrocyte (Paustenbach et al. 2003). Thus, chromium(VI) uptake and subsequent sequestration as a chromium-Hgb complex by erythrocytes provides supporting information regarding the plausibility of adverse hematological effects following intermediate-duration oral exposure to chromium(VI).

Details of Benchmark Dose Analysis for the Intermediate-duration Oral MRL

Hematocrit in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data (Table A-3). The linear model was applied to the data again while applying the power model integrated into the BMDS to account for nonhomogenous variance. The nonconstant variance model also did not provide an adequate fit (as assessed by the p-value for variance). In an attempt to achieve an adequate fitting model, the highest doses were dropped from the data set. As with the full data set, statistical tests indicated that the variances were not constant across exposure groups without the highest doses. Similar to the full data set, applying the nonhomogenous variance model also did not provide an adequate fit (as assessed by the p-value for variance); therefore, the data set is considered not suitable for benchmark dose modeling.

Table A-3. Model Predictions for Changes in Hematocrit (Percent) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

Model	Variance p-value[a]	p-Value for the means[a]	AIC	BMD_{2sd} (mg/kg/day)	$BMDL_{2sd}$ (mg/kg/day)
All doses					
Linear[b,c]	0.03	0.02	145.49	—	—
Linear[c,d]	0.01	0.02	147.49	—	—
Polynomial (1-degree)[c,d]	0.01	0.02	147.49	—	—
Polynomial (2-degree)[c,d]	0.01	0.02	147.49	—	—
Polynomial (3-degree)[c,d]	0.01	0.02	147.49	—	—
Polynomial (4-degree)[c,d]	0.01	0.02	147.49	—	—
Power[d]	0.01	0.02	147.49	—	—
Hill[d]	0.01	0.28	142.76	—	—
Highest dose dropped					
Linear[b,c]	0.01	0.64	109.33	—	—
Linear[c,d]	0.02	0.43	109.21	—	—
Polynomial (1-degree)[c,d]	0.02	0.43	109.21	—	—
Polynomial (2-degree)[c,d]	0.02	0.43	109.21	—	—
Polynomial (3-degree)[c,d]	0.02	0.43	109.21	—	—
Power[d]	0.02	0.43	109.21	—	—
Hill[d]	0.02	0.21	111.09	—	F[e]
Two highest doses dropped					
Linear[b,c]	0.01	0.37	86.65	—	—
Linear[c,d]	0.02	0.15	85.61	—	—
Polynomial (1-degree)[c,d]	0.02	0.15	85.61	—	—
Polynomial (2-degree)[c,d]	0.02	0.15	85.61	—	—
Power[d]	0.02	0.15	85.61	—	—
Hill[d]	NA[f]				

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance
[c]Restriction = non-positive
[d]Nonconstant variance
[e]F = BMDL computation failed
[f]NA = model failed to generate output

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

Hemoglobin in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did provide an adequate fit (as assessed by the p-value for variance) to the data. The polynomial, power, and Hill models were then fit to the data with constant variance assumed. Only the Hill model provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-4); however, the model failed to generate a figure. Without a visual representation of the model, an assessment of model fit is not complete. In order to obtain an appropriate

assessment for model fit adequacy, the highest dose was dropped from the dataset. After dropping the highest dose from the dataset, all models provided an adequate fit to the constant variance model and to the means (as assessed by the p-values for variance and means). Most models, with the exception of the Hill model, took the form of a linear model. Comparing across models, the best fitting model is generally determined by the lowest AIC. As assessed by the AIC, the linear model provides the best fit to the data. The predicted BMD_{2sd} and $BMDL_{2sd}$ for the data are 0.88 and 0.71 mg chromium(VI)/kg/day (Figure A-1).

Table A-4. Model Predictions for Changes in Hemoglobin (g/dL) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

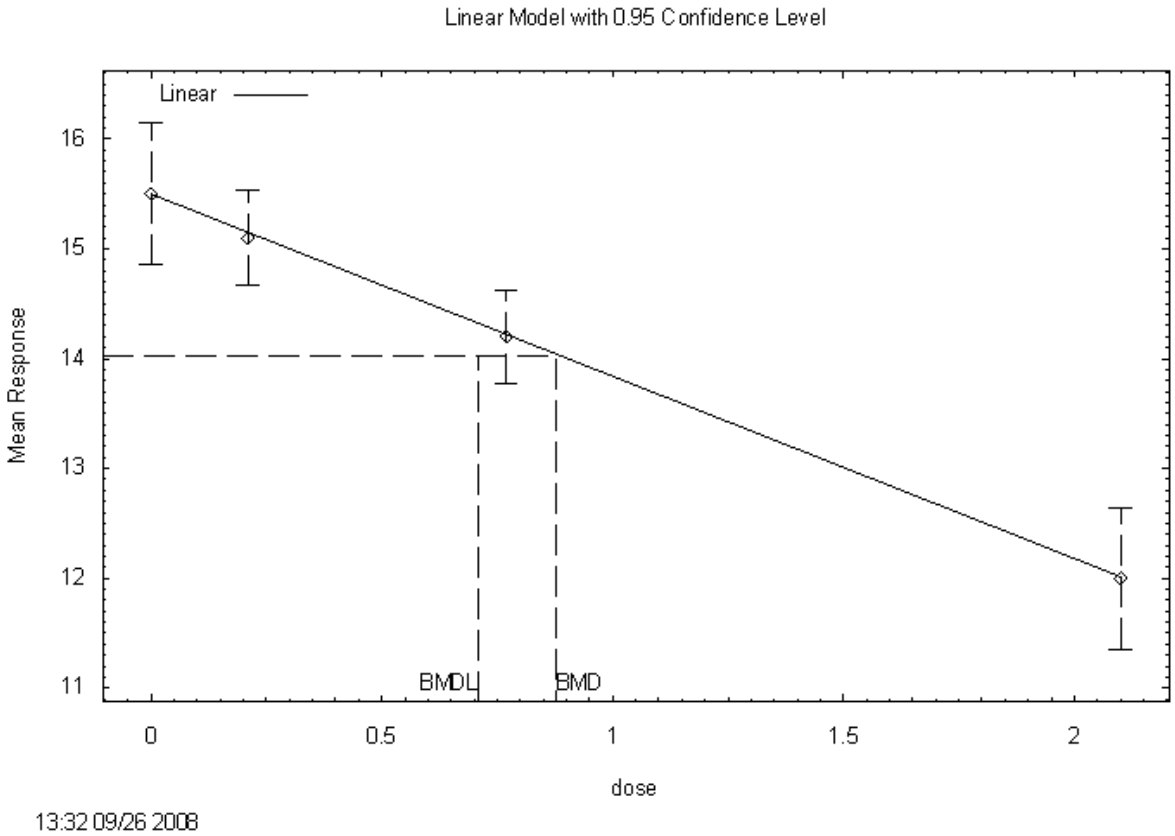
Model[a]	Variance p-value[b]	p-Value for the means[b]	AIC	BMD_{2sd} (mg/kg/day)	$BMDL_{2sd}$ (mg/kg/day)
Linear[c]	0.40	<0.0001	46.98	—	—
Polynomial (1-degree)[c]	0.40	<0.0001	46.98	—	—
Polynomial (2-degree)[c]	0.40	<0.0001	46.98	—	—
Polynomial (3-degree)[c]	0.40	<0.0001	46.98	—	—
Polynomial (4-degree)[c]	0.40	<0.0001	46.98	—	—
Power	0.40	<0.0001	46.98	—	—
Hill	0.40	0.51	24.37	0.83	0.55
Highest dose dropped					
Linear	**0.36**	**0.99**	**20.37**	**0.88**	**0.71**
Polynomial (1-degree)[c]	0.36	0.99	20.37	0.88	0.71
Polynomial (2-degree)[c]	0.36	0.99	20.37	0.88	0.71
Polynomial (3-degree)[c]	0.36	0.99	20.37	0.88	0.71
Power	0.36	0.99	20.37	0.88	0.71
Hill	0.36	0.99	22.36	0.87	0.57

[a]Constant variance assumed for all models
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Restriction = non-positive

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

Figure A-1. Predicted and Observed Changes in Hemoglobin in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days*



*BMDs and BMDLs indicated are associated with a 2 standard deviation change from the control, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Mean Cell Volume in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did provide an adequate fit (as assessed by the p-value for variance) to the data. The polynomial, power, and Hill models were then fit to the data with constant variance assumed. The Hill model was the only model which provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-5). Using the constant-variance Hill model, the BMD_{2sd} and $BMDL_{2sd}$ are 0.63 mg chromium(VI)/kg and 0.49 mg chromium(VI)/kg, respectively (Figure A-2).

Table A-5. Model Predictions for Changes in MCV (fL) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

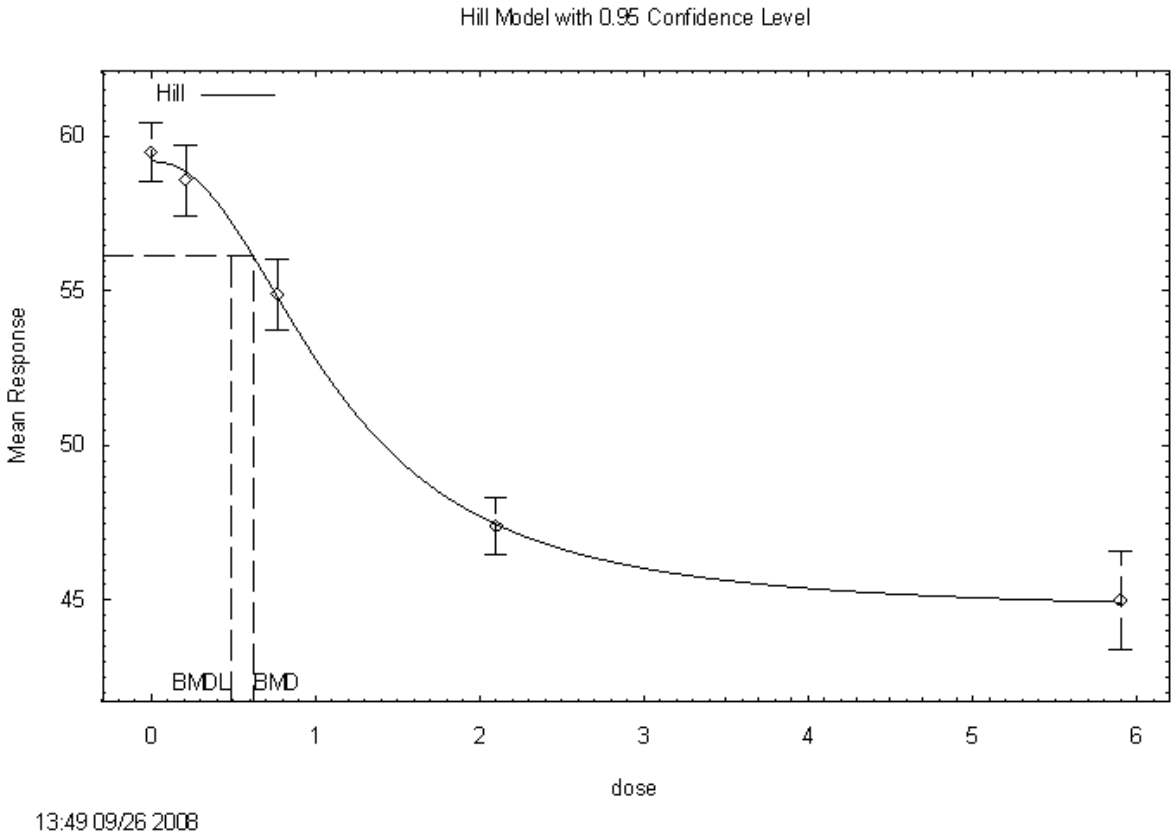
Model[a]	Variance p-value[b]	p-Value for the means[b]	AIC	BMD_{2sd} (mg/kg/day)	$BMDL_{2sd}$ (mg/kg/day)
Linear[c]	0.41	<0.0001	168.50	—	—
Polynomial (1-degree)[c]	0.41	<0.0001	168.50	—	—
Polynomial (2-degree)[c]	0.41	<0.0001	168.50	—	—
Polynomial (3-degree)[c]	0.41	<0.0001	168.50	—	—
Polynomial (4-degree)[c]	0.41	<0.0001	168.50	—	—
Power	0.41	<0.0001	168.50	—	—
Hill	**0.41**	**0.41**	**104.52**	**0.63**	**0.49**

[a]Constant variance assumed for all models
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Restriction = non-positive

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

Figure A-2. Predicted and Observed Changes in MCV in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days*



*BMDs and BMDLs indicated are associated with a 2 standard deviation change from the control, and are in units of mg chromium(VI)/kg/day

Source: NTP 2008a

Mean Cell Hemoglobin in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data. The linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. The nonconstant variance model also did not provide an adequate fit (as assessed by the p-value for variance). In an attempt to achieve an adequate fitting model, the highest dose was dropped from the data-set. Unlike the full data-set, statistical tests indicated that the variances were constant across exposure groups without the highest dose. All of the models reverted to the linear model and provided an adequate fit to the means (Table A-6). Using the constant-variance Linear model (without the highest dose), the BMD_{2sd} and $BMDL_{2sd}$ are 044 and 0.37 mg chromium(VI)/kg, respectively (Figure A-3).

Table A-6. Model Predictions for Changes in MCH (pg) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

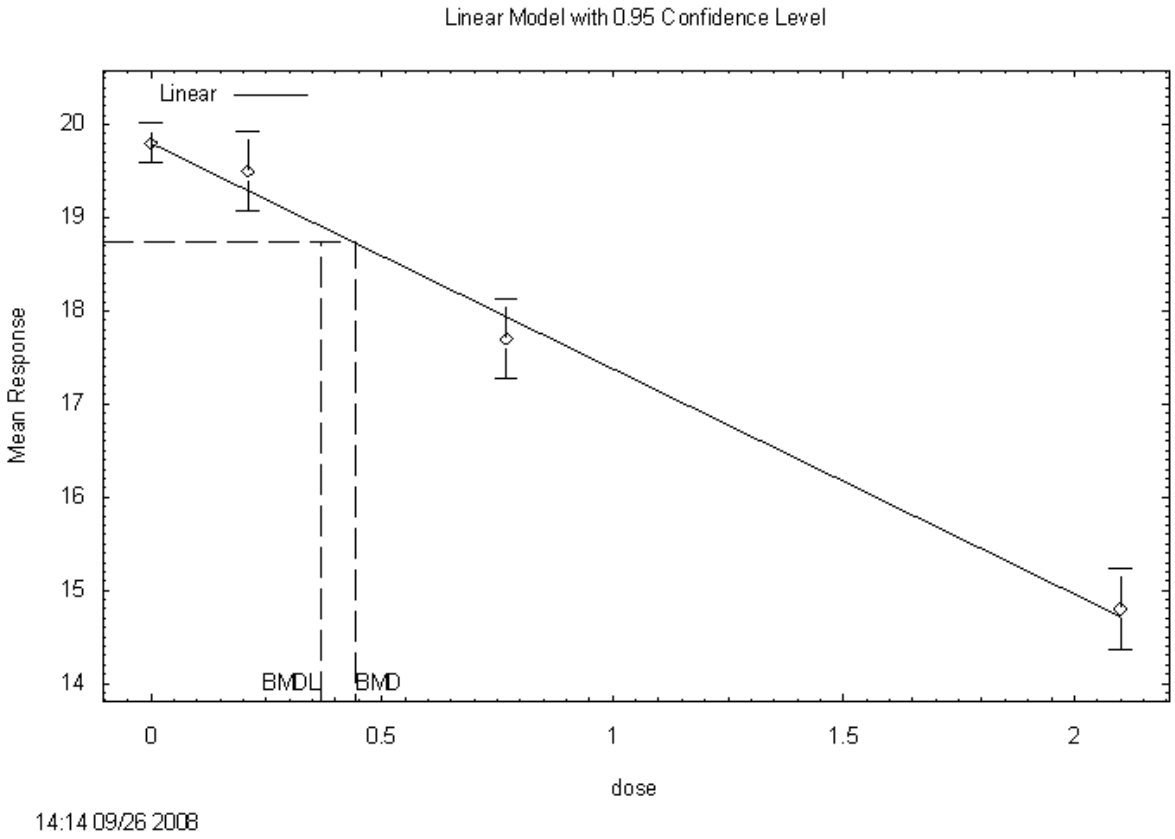
Model	Variance p-value[b]	p-Value for the means[b]	AIC	BMD_{2sd} (mg/kg/day)	$BMDL_{2sd}$ (mg/kg/day)
All doses					
Linear[b,c]	<0.0001	<0.0001	107.27	—	—
Linear[c,d]	0.00	<0.0001	57.60	—	—
Polynomial (1-degree)[c,d]	0.00	<0.0001	57.60	—	—
Polynomial (2-degree)[c,d]	0.00	<0.0001	57.60	—	—
Polynomial (3-degree)[c,d]	0.00	<0.0001	57.60	—	—
Polynomial (4-degree)[c,d]	0.00	<0.0001	57.60	—	—
Power[d]	0.00	<0.0001	57.60	—	—
Hill[d]	0.00	0.02	34.64	—	—
Highest dose dropped (four doses)					
Linear[b,c]	**0.14**	**0.15**	**-3.57**	**0.44**	**0.37**
Polynomial (1-degree)[b,c]	0.14	0.15	-3.57	0.44	0.37
Polynomial (2-degree)[b,c]	0.14	0.15	-3.57	0.44	0.37
Polynomial (3-degree)[b,c]	0.14	0.15	-3.57	0.44	0.37
Power[b]	0.14	0.15	-3.57	0.44	0.37
Hill[b]	0.14	NA[e]	-3.39	0.46	0.32

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance
[c]Restriction = non-positive
[d]Nonconstant variance
[e]NA = degrees of freedom are ≤0; the Chi-Square test for fit is not valid.

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

Figure A-3. Predicted and Observed Changes in MCH in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days*



*BMDs and BMDLs indicated are associated with a 2 standard deviation change from the control, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Agency Contact (Chemical Manager): Sharon Wilbur

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chromium(VI)
CAS Numbers: 18540-29-9
Date: October 2008
Profile status: Final Draft Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 95
Species: Mouse

Minimal Risk Level: 0.001 [X] mg chromium(VI)/kg/day [ ] ppm

Reference: NTP. 2008a. NTP technical report on the toxicology and carcinogenesis studies of sodium dichromate dihydrate (CAS No. 7789-12-0) in F344/N rats and B6C3F1 mice (drinking water studies). Washington, DC: National Toxicology Program. NTP TR 546. http://ntp.niehs.nih.gov/files/546_web_FINAL.pdf. August 13, 2008.

Experimental design: Groups of F344/N rats (50/sex/group) and B6C3F1 mice (50/sex/group) were exposed to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study. Rats and female mice were exposed to drinking water concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L. NTP (2008a) calculated mean daily doses of sodium dichromate dihydrate in male rats of 0, 0.6, 2.2, 6, or 17 mg/kg (equivalent to 0, 0.21, 0.77, 2.1, or 5.9 mg chromium(VI)/kg/day, respectively), in female rats of 0, 0.7, 2.7, 7, or 20 mg/kg (equivalent to 0, 0.24, 0.94, 2.4, and 7.0 mg chromium(VI)/kg/day, respectively), and in female mice of 0, 1.1, 3.9, 9, or 25 mg/kg (equivalent to 0, 0.38, 1.4, 3.1, or 8.7 mg chromium(VI)/kg/day, respectively) over the course of the 2-year study. Male mice were exposed to 0, 14.3, 28.6, 85.7, or 257.4 mg sodium dichromate dihydrate/L. NTP (2008a) calculated mean daily doses of sodium dichromate dihydrate in male mice of 1.1, 2.6, 7, or 17 mg/kg (equivalent to 0, 0.38, 0.91, 2.4, and 5.9 mg chromium(VI)/kg/day, respectively). Mortality, clinical signs of toxicity, body weight, and water intake were assessed over the course of exposure. In a subgroup of 10 male rats and 10 female mice, blood was collected from the retroorbital sinus after exposure durations of 4 days (rats only), 22 days, 3 months, 6 months, and 1 year and evaluated for hematology (Hct; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte and platelet morphology; MCV; MCH; MCHC; and leukocyte count and differentials) in rats and mice and clinical chemistry (urea nitrogen, creatinine, total protein, albumin, ALT, AP, creatine kinase, SDH, and bile acids) in rats only. Blood for hematology and clinical chemistry was not obtained at the end of the 2-year treatment period. At the end of the 2-year treatment period, necropsies and histopathological assessment of comprehensive tissues, gross lesions and tissue masses were performed on all animals. No data on organ weights were presented in the study report (NTP 2008a).

Effect noted in study and corresponding doses: Study results presented in the following discussion are noncancer findings associated with chronic-duration exposures only; results of hematological and clinical chemistry assessments conducted at 4 days and from 22 days to 6 months are described in the acute- and intermediate-duration MRL worksheets, respectively; carcinogenic effects are reviewed in Section 3.2.2.7 (Oral Exposure, Cancer). In rats, no treatment-related effects were observed on survival and no clinical signs of toxicity were observed. Final body weight was significantly decreased by 12% in male and 11% in females exposed to the highest drinking water concentration. Study authors attributed alterations in body weight to decreased water intake (due to decreased palatability) rather than to a toxicological effect. Hematological assessments conducted in male rats at 1-year showed dose-dependent effects indicative of microcytic, hypochromic anemia: decreased MCH (≥0.77 mg chromium(VI)/kg/day), decreased MCV and MCHC (≥2.1 mg chromium(VI)/kg/day), and decreased Hgb (5.9 mg chromium(VI)/kg/day). No

hematological effects were observed at 2.1 mg chromium(VI)/kg/day. Other hematological effects observed were decreased leukocyte (5.9 mg chromium(VI)/kg/day) and segmented neutrophil counts (≥0.77 mg chromium(VI)/kg/day). Alterations in clinical chemistry parameters observed after 1 year of exposure were increased ALT and decreased AP (≥0.77 mg chromium(VI)/kg/day), increased BUN and creatine kinase (≥2.1 mg chromium(VI)/kg/day), and decreased total protein (5.9 mg chromium(VI)/kg/day). Regarding the toxicological significance of elevated ALT, as discussed below, histopathological assessment of the liver showed minimal-to-mild chronic inflammation in males (≥2.1 mg chromium(VI)/kg/day) and females (≥0.24 mg chromium(VI)/kg/day). However, since serum activities of AP, SDH, or bile acids were not increased, elevated serum ALT activity may have resulted from enzyme induction rather than hepatocellular injury. Histopathological evaluations revealed an increased incidence of nonneoplastic lesions in the liver (males and females), small intestine (males and females), mesenteric lymph nodes (males and females), pancreatic lymph nodes (females only) and salivary gland (females only). Hepatic lesions observed in male rats included minimal-to-mild chronic inflammation (≥0.77 mg chromium(VI)/kg/day) and histiocytic cellular infiltration (5.9 mg chromium(VI)/kg/day); hepatic lesions in females included chronic inflammation (≥0.24 mg chromium(VI)/kg/day), histiocytic cellular infiltration (≥0.94 mg chromium(VI)/kg/day) and fatty change (≥0.94 mg chromium(VI)/kg/day). Although chronic hepatic inflammation is commonly observed in aging rats, the incidence was significantly enhanced by exposure. Histiocytic cellular infiltration (minimal-to-mild) of the duodenum, was observed in males (≥0.77 mg chromium(VI)/kg/day) and females (≥2.4 mg chromium(VI)/kg/day). Nonneoplastic lesions of lymph nodes included the following: histocytic cellular infiltration of mesenteric lymph nodes in males and females at ≥0.77 and ≥2.4 mg chromium(VI)/kg/day, respectively; hemorrhage of mesenteric lymph nodes in males and females at ≥0.77 and ≥7.0 mg chromium(VI)/kg/day, respectively; and histocytic cellular infiltration of pancreatic lymph nodes in females at ≥2.4 mg chromium(VI)/kg/day only. The incidence of salivary gland atrophy was significantly in female rats at 2.4 mg chromium(VI)/kg/day; although the incidence was also increased at 7.0 mg chromium(VI)/kg/day, the change was not significantly different from control. Salivary atrophy was not observed in male rats. No data on organ weights were presented in the study report (NTP 2008a).

In mice, no treatment-related effects on survival or signs of toxicity were observed. Final body weight was significantly decreased by 15% in male and 8% in females exposed to the highest drinking water concentration. The study authors attributed the alterations in body weight to decreased water intake (due to decreased palatability) rather than to a toxicological effect. Hematological assessments conducted in female mice at 1 year showed dose-dependent effects indicative of microcytic, hypochromic anemia and compensatory erythropoiesis: decreased MCV and MCH (≥3.1 mg chromium(VI)/kg/day) and increased erythrocyte count at ≥3.1 mg chromium(VI)/kg/day. Platelet count and segmented neutrophil count were decreased at 8.7 mg chromium(VI)/kg/day. Severity of hematological effects on mice was less than in rats. Clinical chemistry was not evaluated in male or female mice. Histopathological evaluations revealed an increased incidence of nonneoplastic lesions in the liver (females), small intestine (male and females), and mesenteric and pancreatic lymph nodes (males and females). Histiocytic cellular infiltration of the liver was observed in all treatment groups, with incidence and severity exhibiting dose-dependence. Chronic inflammation of the liver was also observed in females at ≥3.1 mg chromium(VI)/kg/day. In males, only pre-neoplastic (clear cell and eosinophilic foci) lesions were observed at the highest dose tested. Diffuse epithelial hyperplasia of the duodenum was observed in all treatment groups in males and females (≥0.38 mg chromium(VI)/kg/day), with histiocytic cellular infiltration of the duodenum in males and females at ≥2.4 and 3.1 mg chromium(VI)/kg/day, respectively. Histiocytic cellular infiltration was observed in mesenteric lymph nodes in all treatment groups in males and females (≥0.38 mg chromium(VI)/kg/day) and in pancreatic lymph nodes at ≥2.4 and ≥3.1 mg chromium(VI)/kg/day in males and females, respectively. Increased incidence of cytoplasm alteration of the pancreas (depletion of zymogen granules from acinar epithelial cells) was observed in males at

≥2.4 mg chromium(VI)/kg/day and in females in all treatment groups (≥0.38 mg chromium(VI)/kg/day); the toxicological significance of this finding is not clear.

Dose and end point used for MRL derivation: 0.09 mg chromium(VI)/kg/day (diffuse epithelial hyperplasia of the duodenum)

[ ] NOAEL [ ] LOAEL [X] benchmark dose (BMD)

Chronic-duration exposure of rats and mice to sodium dichromate dihydrate in drinking water resulted in microcytic, hypochromic anemia and nonneoplastic lesions of the liver, duodenum, mesenteric and pancreatic lymph nodes, pancreas and salivary gland. Based on comparison of LOAEL values (Table A-7), the lowest LOAELs were observed for histopathological changes of the liver (chronic inflammation in female rats and histiocytic cellular infiltration in female mice), duodenum (diffuse epithelial hyperplasia in male and female mice), mesenteric lymph node (histiocytic cellular infiltration in male and female mice) and pancreas (cytoplasm cellular alteration of acinar epithelial cells in female mice), with effects occurring in all treatment groups. Therefore, all effects with LOAEL values of the lowest dose tested were considered as the possible the critical effect for derivation of the chronic-duration oral MRL. Incidence data for these lesions are summarized in Table A-8.

Table A-7. NOAEL and LOAEL Values for Effects in Rats and Mice Exposed to Sodium Dichromate Dihydrate in Drinking Water for 1–2 Years

	NOAEL/LOAEL value (mg chromium(VI)/kg/day)			
Effect or tissue with lesion	Male rats	Female rats	Male mice	Female mice
Hematological effects	0.21/0.77	N/A	N/A	1.4/3.1
Liver	0.21/0.77	0.24[a]	2.4/5.9[c]	0.38[a]
Duodenum	0.21/0.77	0.94/2.4	0.38[a]	0.38[a]
Mesenteric lymph node	0.21/0.77	0.94/2.4	0.38[a]	0.38[a]
Pancreatic lymph node	N/O	0.94/2.4	0.91/2.4	1.4/3.1
Pancreas	N/O	N/O	0.91/2.4	0.38[a]
Salivary gland	N/O	2.4[b]	N/O	N/O

[a]No NOAEL value was identified; effects occurred in all treatment groups
[b]Not observed at other doses
[c]Pre-neoplastic lesions

LOAEL = lowest-observed-adverse-effect level; N/A = not assessed; N/O = effect not observed; NOAEL = no-observed-adverse-effect level

Source: NTP 2008a

Table A-8. Incidence Data for Nonneoplastic Lesions[a] Occurring in All Treatment Groups of Female F/344 Rats and Male and Female B6C3F1 Mice Exposed to Sodium Dichromate Dihydrate in Drinking Water for 2 Years

	Dose (mg chromium(VI)/kg/day)				
	0	0.24	0.94	2.4	7.0
Female rats					
Liver, chronic inflammation	12/50[b] (1.3)	21/50[c] (1.2)	28/50[d] (1.3)	35/50[d] (1.6)	39/50[d] (2.1)
	Dose (mg chromium(VI)/kg/day)				
	0	0.38	0.91	2.4	5.9
Male mice					
Duodenum: diffuse epithelial hyperplasia	0/50	11/50[d] (2.0)	18/50[d] (1.6)	42/50[d] (2.1)	32/50[c] (2.1)
Mesenteric lymph node: histiocytic cellular infiltration	14/47 (1.2)	38/47[d] (1.1)	31/49[d] (1.2)	32/49[d] (1.5)	42/46[c] (2.5)
	Dose (mg chromium(VI)/kg/day)				
	0	0.38	1.4	3.1	8.7
Female mice					
Duodenum: diffuse epithelial hyperplasia	0/50	16/50[d] (1.6)	35/50[d] (1.7)	31/50[d] (1.6)	42/50[d] (2.2)
Mesenteric lymph node: histiocytic cellular infiltration	3/46 (1.0)	29/48[d] (1.3)	26/46[d] (1.1)	40/50[d] (1.9)	42/50[d] (2.7)
Liver: histiocytic cellular infiltration	2/49 (1.0)	15/50[d] (1.1)	23/50[d] (1.0)	32/50[d] (1.0)	45/50[d] (1.9)
Pancreas: acinus, cytoplasmic alteration	0/48	6/50[c] (2.5)	6/49[c] (2.0)	14/50[d] (2.4)	32/50[d] (2.6)

[a]Lesion severity (1=minimal, 2=mild, 3=moderate, 4=marked)
[b]Number of animals with lesions/number of animals examined
[c]Significantly different (p≤0.05) from the control group by Dunn's or Shirley's test
[d]Significantly different (p≤0.01) from the control group by Dunn's or Shirley's test

Source: NTP 2008a

To determine the specific end point for derivation of the chronic-duration oral MRL, all available dichotomous models in the EPA (version 1.4.1) were fit to the incidence data for selected end points in female rats and male and female mice exposed to sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a) (Table A-8). To provide potential points of departure for MRL derivation, 10% extra risk was selected as the benchmark response in accordance with U.S. EPA (2000) technical guidance for benchmark dose analysis to select a response level near the lower range of detectable observations. The BMD_{10s} and $BMDL_{10s}$ from the best fitting models for nonneoplastic lesions of the liver (female rats and mice), duodenum (male and female mice), mesenteric lymph nodes (male and female mice), and pancreas (female mice) are shown in Table A-9. For chronic inflammation of the liver in female rats, the log-logistic model provided the best fit, with BMD_{10} and $BMDL_{10}$ values of 0.22 and 0.14 mg chromium(VI)/kg/day, respectively. For diffuse epithelial hyperplasia in male mice, the multistage and quantal linear models provided the best fit, with BMD_{10} and $BMDL_{10}$ values of 0.16 and 0.13 mg chromium(VI)/kg/day, respectively. For diffuse epithelial hyperplasia in female mice, the best

fit was provided by several models (gamma, multistage, quantal linear, and weibull) with BMD_{10} and $BMDL_{10}$ values of 0.12 and 0.09 mg chromium(VI)/kg/day, respectively. For histiocytic alteration of the liver and cytoplasm alteration of the pancreas in female mice, the log-logistic model provided the best fit, with BMD_{10} and $BMDL_{10}$ values of 0.17 and 0.12 mg chromium(VI)/kg/day, respectively, for liver lesions and of 0.68 and 0.52 mg chromium(VI)/kg/day, respectively, for pancreas lesions. For lesions of the mesenteric lymph nodes in male and female mice, none of the models provided adequate fit to the data, even with the two highest doses dropped from the analysis; thus, data sets for these lesions were considered not suitable for BMD analysis. Additional details of the benchmark dose analysis for each data set modeled are presented in the last section of this worksheet. Based on the lowest $BMDL_{10}$ value of 0.09 mg chromium(VI)/kg/day, diffuse epithelial hyperplasia of the duodenum in female mice was selected as the point of departure for derivation of the chronic-duration oral MRL. The chronic-duration oral MRL based on nonneoplastic lesions of the duodenum in female mice is expected to be protective for all other adverse effects observed in the 2-year drinking water study (e.g., hematological effects and lesions of the liver, lymph nodes, pancreas, and salivary gland). The chronic-duration MRL of 0.001 mg chromium(VI)/kg/day was derived by dividing the $BMDL_{10}$ by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Table A-9. Summary of BMD_{10} and $BMDL_{10}$ from the Best Fitting Models for Nonneoplastic Lesions of the Liver, Duodenum, Mesenteric Lymph Nodes, and Pancreas in Female Rats and Male and Female Mice After Exposure to Sodium Dichromate Dihydrate in Drinking Water for 2 Years

End point	Species/sex	Model	Number of doses	BMD[a] (mg/kg/day)	BMDL[a] (mg/kg/day)
Liver, chronic inflammation	Rat/female	Log-logistic	5	0.22	0.14
Duodenum: diffuse epithelial hyperplasia	Mouse/male	1-Degree polynomial multistage/quantal linear	4	0.16	0.13
Mesenteric lymph node: histiocytic cellular infiltration[b]	Mouse/male	—	—	—	—
Duodenum: diffuse epithelial hyperplasia	**Mouse/female**	**Gamma/Multistage/quantal linear/weibull**	**3**	**0.12**	**0.09**
Mesenteric lymph node: histiocytic cellular infiltration[b]	Mouse/female	—	—	—	—
Liver: histiocytic cellular infiltration	Mouse/female	Log-logistic	5	0.17	0.12
Pancreas: acinus, cytoplasmic alteration	Mouse/female	Log-logistic	5	0.68	0.52

[a]BMDs and BMDLs from dichotomous data are associated with a 10% extra risk; doses are in terms of mg chromium(VI)/kg/day.
[b]None of the models provided an adequate fit to the data.

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Daily doses for each treatment group were reported by study authors (NTP 2008a) based on body weights and water intake over the 2-year exposure period.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Selection of nonneoplastic lesions of the duodenum in female mice is as the critical effect for the chronic-duration oral MRL is supported by observations from the same study showing adverse gastrointestinal effects in male mice (diffuse epithelial hyperplasia at ≥0.38 mg chromium(VI)/kg/day and histiocytic cellular infiltration at 5.9 mg chromium(VI)/kg/day) and in male and female rats (histiocytic cellular infiltration at ≥0.77 and ≥0.94 mg chromium(VI)/kg/day, respectively) exposed to sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a). Although no other chronic-duration studies on oral chromium(VI) in animals were identified, a 3-month study on sodium dichromate dihydrate in drinking water revealed adverse gastrointestinal effects in rats and mice (including a comparative study in 3 mouse strains) (NTP 2007). Epithelial hyperplasia and histiocytic cellular infiltration of the duodenum was observed at ≥3.1 and ≥5.9 mg chromium(VI)/kg/day, respectively, in male and female B6C3F1 mice. Similar nonneoplastic lesions of the duodenum were also reported in the 3-month comparative study in male B6C3F1, BALB/c, and C57BL/6 mice, with epithelial hyperplasia at ≥2.8 mg chromium(VI)/kg/day in B6C3F1 and BALB/c strains and ≥5.2 in the C57BL/6 strain, and histiocytic cellular infiltration at ≥2.8 mg chromium(VI)/kg/day in B6C3F1 and C57BL/6 strains and ≥5.2 mg chromium(VI)/kg/day in the BALB/c strain. In male and female F344/N rats, histiocytic cellular infiltration was observed at ≥3.5 mg chromium(VI)/kg/day. At a higher daily dose (20.9 mg chromium(VI)/kg/day), ulcer, epithelial regenerative focal hyperplasia, and epithelial focal squamous metaplasia of the glandular stomach were observed.

Details of Benchmark Dose Analysis for the Chronic-duration Oral MRL

Chronic Inflammation of the Liver in Female Rats. As assessed by the chi-square goodness-of-fit statistic, only the log-logistic model provided an adequate fit (X^2 p-value ≥0.1) to the data (Table A-10). Based on the log-logistic model, the BMD associated with a 10% extra risk was 0.22 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.14 mg chromium(VI)/kg/day (Figure A-4).

Table A-10. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Chronic Inflammation of the Liver in Female Rats Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

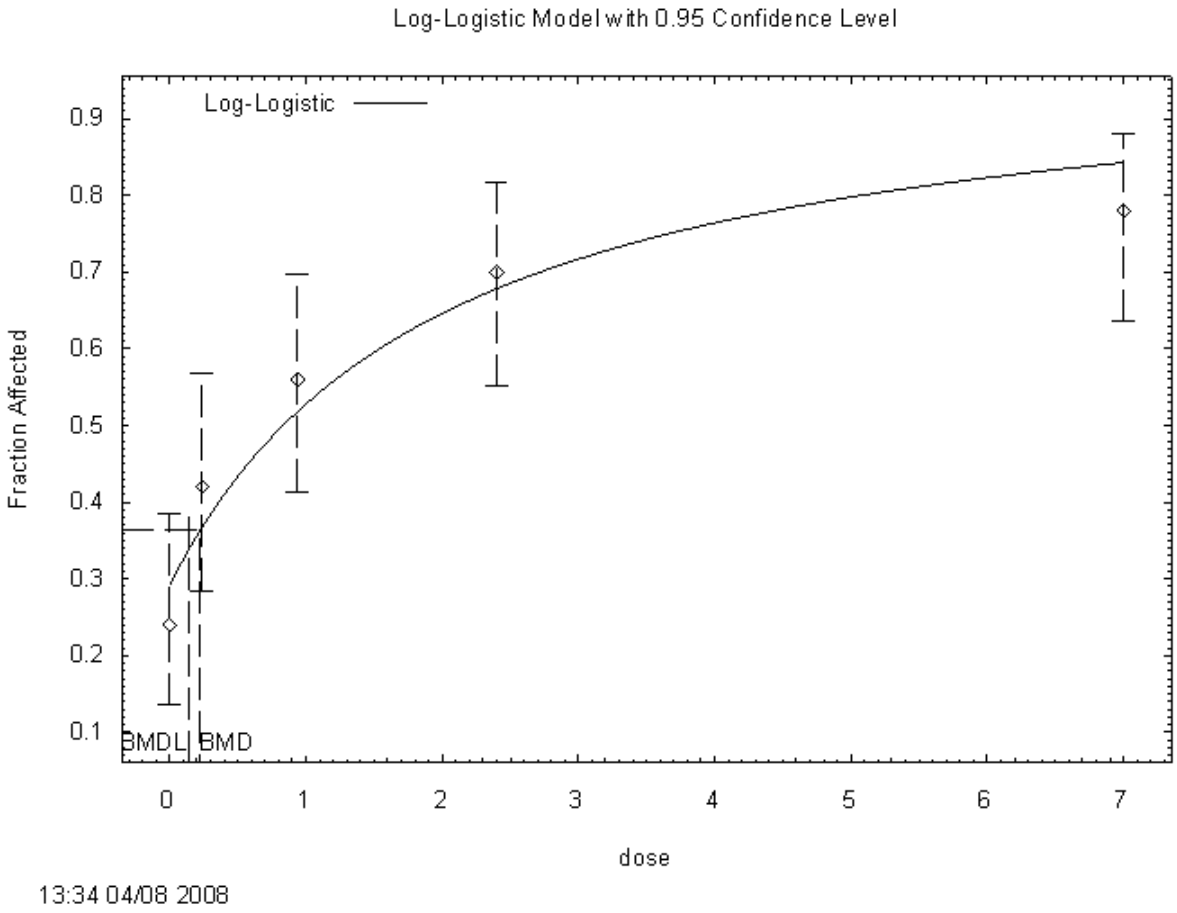
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
Gamma[a]	0.51	0.37	0.04	317.97
Logistic	0.84	0.65	0.01	321.45
Log-logistic[b]	**0.22**	**0.14**	**0.37**	**312.57**
Multi-stage[c]	0.51	0.37	0.04	317.97
Probit	0.88	0.70	0.01	321.80
Log-probit[b]	0.89	0.61	0.01	320.86
Quantal linear	0.51	0.37	0.04	317.97
Weibull[a]	0.51	0.37	0.04	317.97

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Figure A-4. Predicted and Observed Incidence of Chronic Inflammation of the Liver in Female Rats Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Diffuse Epithelial Hyperplasia of the Duodenum in Male Mice. As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit (X^2 p-value $\geq$0.1) to the full dataset (Table A-11). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. After dropping the highest dose, the gamma, log-logistic, multistage, log-probit, quantal linear, and weibull models provided adequate fits to the data (X^2 p-value >0.1). Comparing across models, a better fit is generally indicated by a lower AIC (EPA 2000). As assessed by AIC, the 1-degree polynomial multistage model provided the best fit to the data (Figure A-5). Based on the multistage model, the BMD associated with a 10% extra risk was 0.16 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.13 mg chromium(VI)/kg/day.

Table A-11. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Diffuse Epithelial Hyperplasia in the Duodenum in Male Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

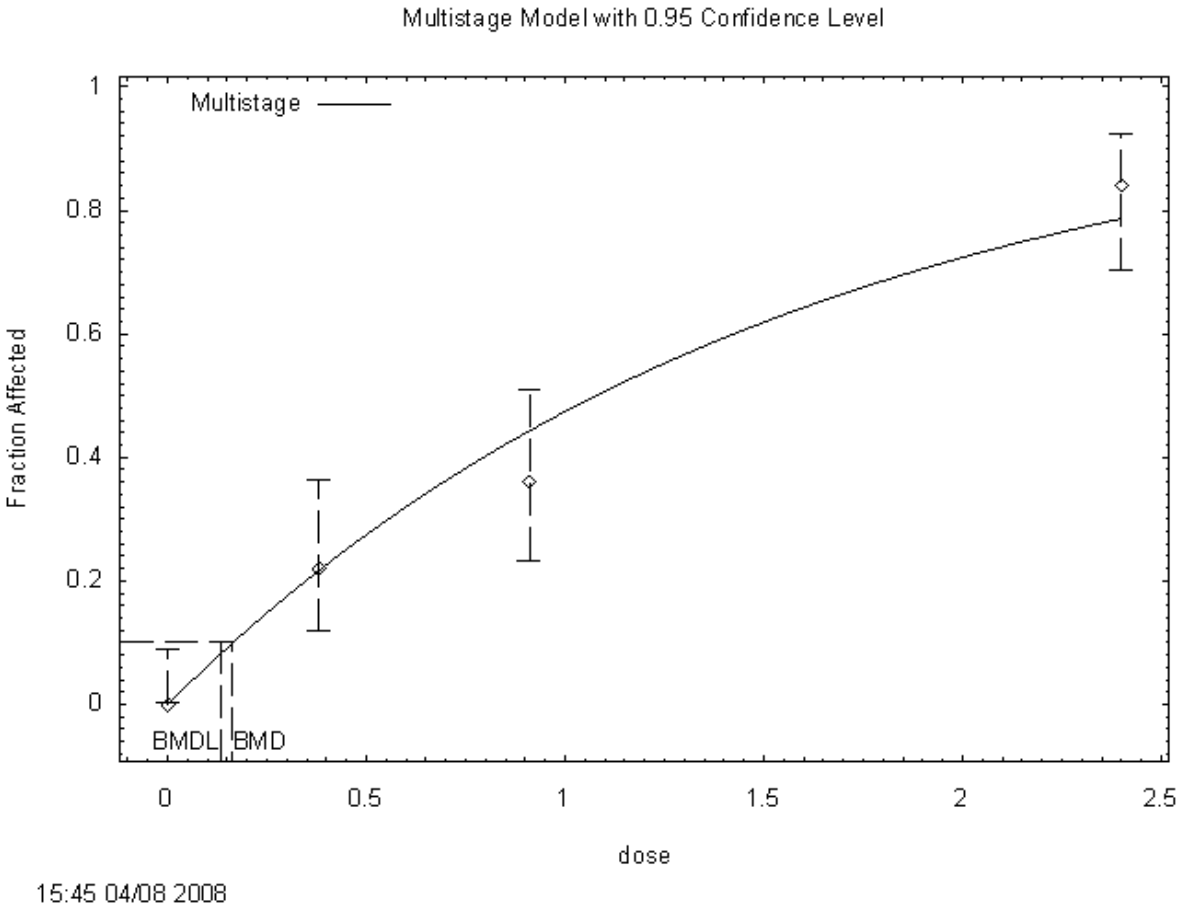
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
All doses				
Gamma[a]	0.31	0.25	0.00	270.99
Logistic	0.90	0.74	0.00	296.25
Log-logistic[b]	0.15	0.12	0.00	247.93
Multi-stage[c]	0.31	0.25	0.00	270.99
Probit	0.90	0.76	0.00	296.18
Log-probit[b]	0.48	0.36	0.00	274.38
Quantal linear	0.31	0.25	0.00	270.99
Weibull[a]	0.31	0.25	0.00	270.99
Highest dose dropped (four doses modeled)				
Gamma[a]	0.22	0.14	0.43	167.67
Logistic	0.47	0.39	0.03	177.09
Log-logistic[b]	0.26	0.15	0.20	169.23
Multi-stage[d]	0.16	**0.13**	**0.52**	**166.34**
Probit	0.45	0.37	0.04	176.19
Log-probit[b]	0.28	0.23	0.33	167.41
Quantal linear	0.16	**0.13**	**0.52**	**166.34**
Weibull[a]	0.22	0.14	0.47	167.50

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.
[d]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; degree polynomial =1.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Figure A-5. Predicted and Observed Incidence of Diffuse Epithelial Hyperplasia in the Duodenum of Male Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Histiocytic Cellular Infiltration of the Mesenteric Lymph Nodes in Male Mice. As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit (X^2 p-value ≥ 0.1) to the full dataset (Table A-12). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. Dropping the highest dose did not result in adequately fitting models, nor did dropping the two highest doses. This dataset is considered not suitable for benchmark dose modeling.

Table A-12. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Histiocytic Cellular Infiltration in Mesenteric Lymph Nodes of Male Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
All doses				
Gamma[a]	0.38	0.26	0.00	285.94
Logistic	0.53	0.39	0.00	286.38
Log-logistic[b]	0.16	0.08	0.00	284.48
Multi-stage[c]	0.43	0.26	0.00	287.88
Probit	0.56	0.43	0.00	286.35
Log-probit[b]	0.83	0.52	0.00	289.36
Quantal linear	0.38	0.26	0.00	285.94
Weibull[a]	0.38	0.26	0.00	285.94
Highest dose dropped (four doses modeled)				
Gamma[a]	0.47	0.24	0.00	258.50
Logistic	0.61	0.35	0.00	259.04
Log-logistic[b]	0.21	0.08	0.00	256.81
Multi-stage[d]	0.47	0.24	0.00	258.50
Probit	0.63	0.37	0.00	259.08
Log-probit[b]	1.24	0.56	0.00	261.28
Quantal linear	0.47	0.24	0.00	258.50
Weibull[a]	0.47	0.24	0.00	258.50
Two highest doses dropped (three doses modeled)				
Gamma[a]	0.11	0.07	0.00	187.77
Logistic	0.17	0.12	0.00	189.97
Log-logistic[b]	0.05	0.03	0.00	183.77
Multi-stage[e]	0.11	0.07	0.00	187.77
Probit	0.17	0.12	0.00	190.12
Log-probit[b]	0.17	0.11	0.00	190.37
Quantal linear	0.11	0.07	0.00	187.77
Weibull[a]	0.11	0.07	0.00	187.77

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.
[d]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 2-degree polynomial is reported.
[e]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Diffuse Epithelial Hyperplasia of the Duodenum in Female Mice. As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit (X^2 p-value $\geq$0.1) to the data (Table A-13). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. After dropping the highest dose, an adequate fit was still not achieved. After dropping the two highest doses, all of the models except for the logistic and probit models provided an adequate fit (X^2 p-value $\geq$0.1) to the data. Comparing across models, a better fit is generally indicated by a lower AIC (EPA 2000). As assessed by AIC, the gamma, multistage, quantal linear, and weibull models generated identical goodness of fit statistics and benchmark doses, as these models all took the form of a 1-degree polynomial multistage model which provides the best fit (Figure A-6). Based on these models, the BMD associated with a 10% extra risk was 0.12 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.09 mg chromium(VI)/kg/day.

Table A-13. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Diffuse Epithelial Hyperplasia in the Duodenum of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

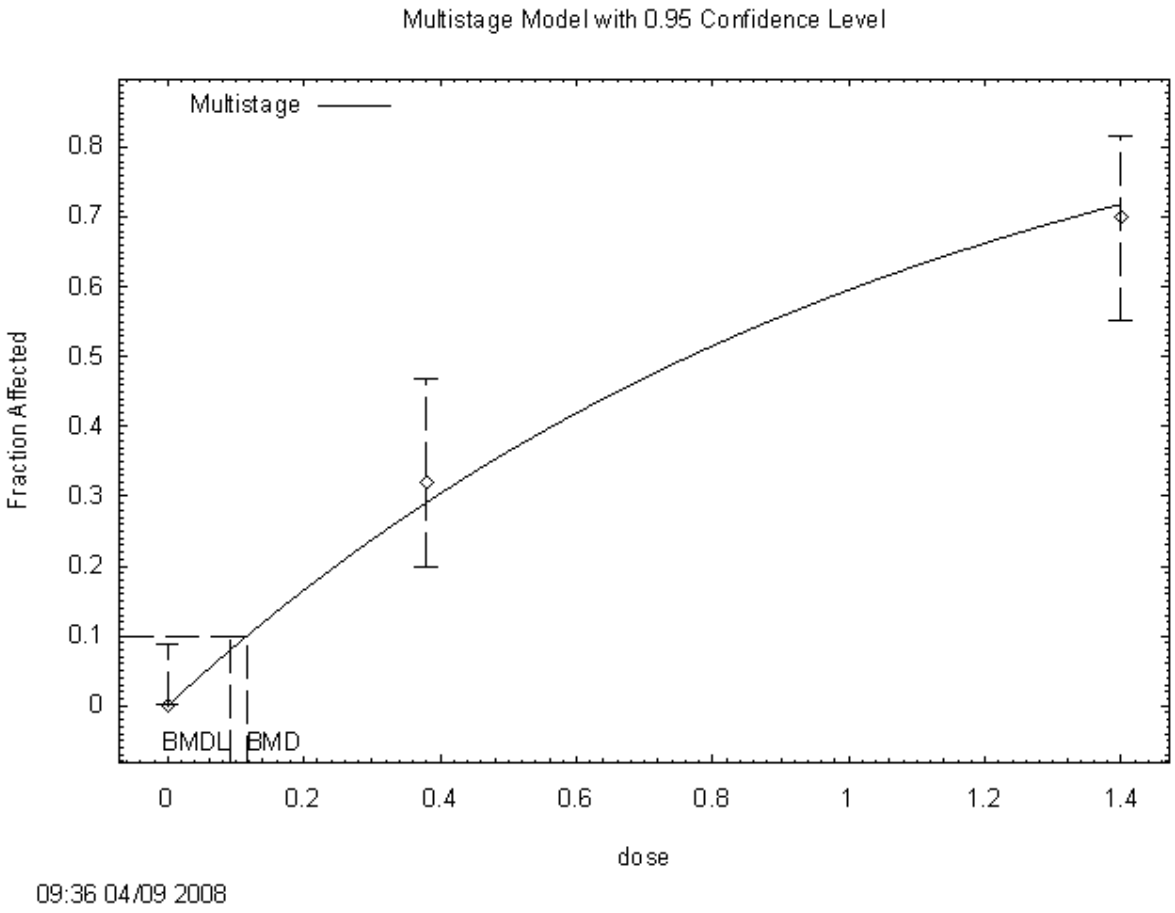
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
All doses				
Gamma[a]	0.34	0.27	0.00	275.34
Logistic	0.88	0.72	0.00	293.17
Log-logistic[b]	0.12	0.09	0.04	245.54
Multi-stage[c]	0.34	0.27	0.00	275.34
Probit	0.93	0.78	0.00	294.03
Log-probit[b]	0.52	0.38	0.00	279.54
Quantal linear	0.34	0.27	0.00	275.34
Weibull[a]	0.34	0.27	0.00	275.34
Highest dose dropped (four doses modeled)				
Gamma[a]	0.20	0.16	0.00	213.41
Logistic	0.55	0.46	0.00	236.10
Log-logistic[b]	0.11	0.08	0.04	200.07
Multi-stage[d]	0.20	0.16	0.00	213.41
Probit	0.54	0.45	0.00	235.61
Log-probit[b]	0.29	0.24	0.00	220.04
Quantal linear	0.20	0.16	0.00	213.41
Weibull[a]	0.20	0.16	0.00	213.41
Two highest doses dropped (three doses modeled)				
Gamma[a]	**0.12**	**0.09**	**0.87**	**126.06**
Logistic	0.34	0.27	0.00	141.77
Log-logistic[b]	0.12	0.06	1.00	127.77
Multi-stage[e]	**0.12**	**0.09**	**0.87**	**126.06**
Probit	0.32	0.26	0.00	140.65
Log-probit[b]	0.20	0.16	0.48	127.17
Quantal linear	**0.12**	**0.09**	**0.87**	**126.06**
Weibull[a]	**0.12**	**0.09**	**0.87**	**126.06**

[a]Restrict power >=1
[b]Slope restricted to >1
[c]Restrict betas >=0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.
[d]Restrict betas >=0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 2-degree polynomial is reported.
[e]Restrict betas >=0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Figure A-6. Predicted and Observed Incidence of Diffuse Epithelial Hyperplasia in the Duodenum of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium (VI)/kg/day.

Source: NTP 2008a

Histiocytic Cellular Infiltration of the Mesenteric Lymph Nodes in Female Mice. As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit (X^2 p-value ≥ 0.1) to the full dataset (Table A-14). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. Dropping the highest dose did not result in adequately fitting models, nor did dropping the two highest doses. This dataset is not suitable for benchmark dose modeling.

Table A-14. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Histiocytic Cellular Infiltration in Mesenteric Lymph Nodes of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
All doses				
Gamma[a]	0.41	0.30	0.00	282.46
Logistic	0.77	0.61	0.00	290.18
Log-logistic[b]	0.09	0.06	0.00	263.55
Multi-stage[c]	0.41	0.30	0.00	282.46
Probit	0.85	0.69	0.00	291.41
Log-probit[b]	0.68	0.47	0.00	285.85
Quantal linear	0.41	0.30	0.00	282.46
Weibull[a]	0.41	0.30	0.00	282.46
Highest dose dropped (four doses modeled)				
Gamma[a]	0.20	0.15	0.00	224.84
Logistic	0.40	0.33	0.00	230.81
Log-logistic[b]	0.07	0.05	0.00	215.19
Multi-stage[d]	0.20	0.15	0.00	224.84
Probit	0.40	0.34	0.00	230.85
Log-probit[b]	0.37	0.24	0.00	231.76
Quantal linear	0.20	0.15	0.00	224.84
Weibull[a]	0.20	0.15	0.00	224.84
Two highest doses dropped (three doses modeled)				
Gamma[a]	0.14	0.10	0.00	172.32
Logistic	0.31	0.24	0.00	178.99
Log-logistic[b]	0.07	0.04	0.00	164.47
Multi-stage[e]	0.14	0.10	0.00	172.32
Probit	0.30	0.23	0.00	178.74
Log-probit[b]	0.21	0.15	0.00	178.11
Quantal linear	0.14	0.10	0.00	172.32
Weibull[a]	0.14	0.10	0.00	172.32

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.
[d]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 2-degree polynomial is reported.
[e]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Histiocytic Cellular Infiltration of the Liver in Female Mice. As assessed by the chi-square goodness-of-fit statistic, only the log-logistic model provided an adequate fit (X^2 p-value ≥ 0.1) to the data (Table A-15). Based on the log-logistic model, the BMD associated with a 10% extra risk was 0.17 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.12 mg chromium(VI)/kg/day (Figure A-7).

Table A-15. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Histiocytic Cellular Infiltration in the Liver of Female Rats Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

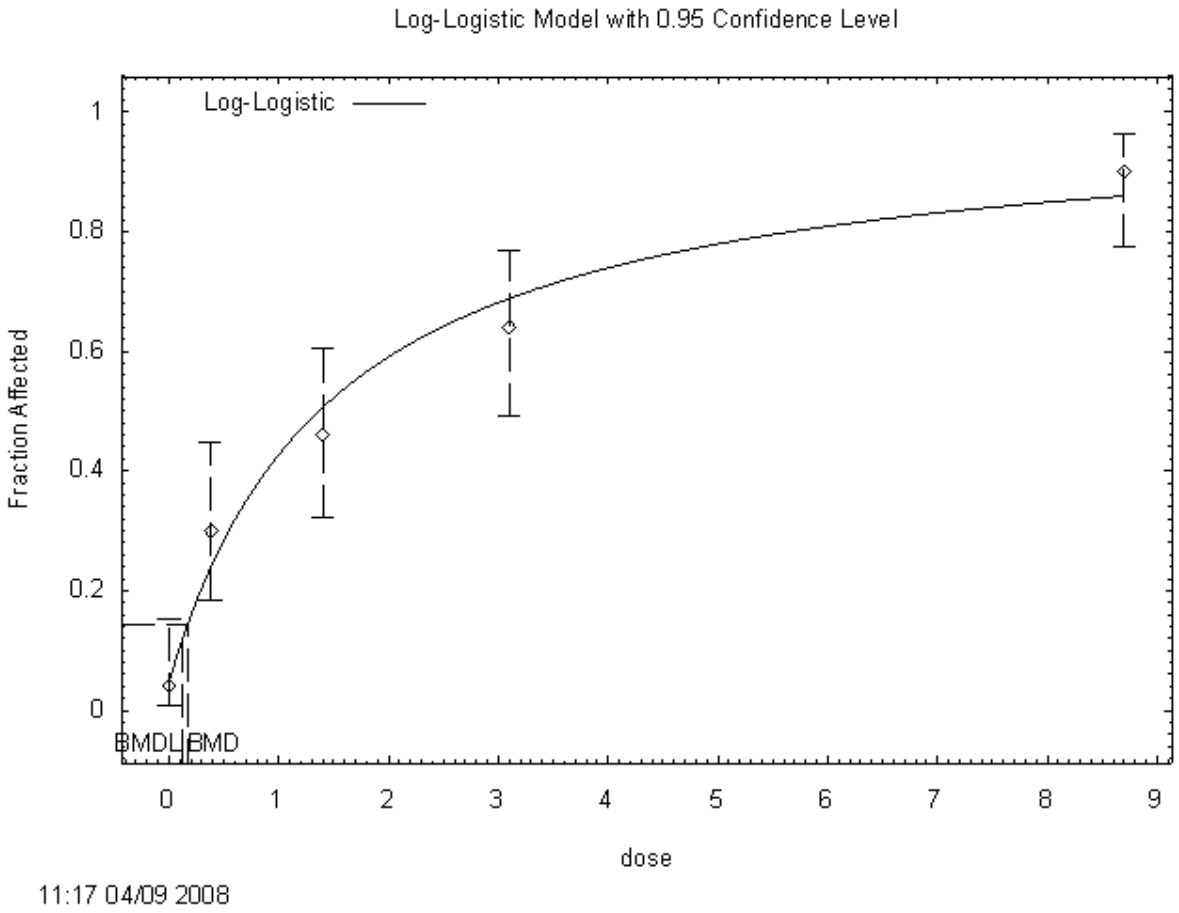
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
Gamma[a]	0.35	0.28	0.08	255.40
Logistic	0.85	0.70	0.00	267.56
Log-logistic[b]	**0.17**	**0.12**	**0.44**	**251.36**
Multi-stage[c]	0.35	0.28	0.08	255.40
Probit	0.88	0.75	0.00	268.64
Log-probit[b]	0.62	0.48	0.01	260.00
Quantal linear	0.35	0.28	0.08	255.40
Weibull[a]	0.35	0.28	0.08	255.40

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Figure A-7. Predicted and Observed Incidence of Histiocytic Cellular Infiltration in the Livers of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium (VI)/kg/day.

Source: NTP 2008a

Cytoplasmic Alteration of Acinar Epithelial Cells of the Pancreas in Female Mice. As assessed by the chi-square goodness-of-fit statistic, all of the models provide adequate fits (X^2 p-value ≥ 0.1) to the data (Table A-16). Comparing across models, a better fit is generally indicated by a lower Akaike's Information Criteria (AIC) (EPA 2000). As assessed by AIC, the log-logistic model provides the best fit (Figure A-8). Based on the log-logistic model, the BMD associated with a 10% extra risk was 0.68 mg chromium (VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.52 mg chromium (VI)/kg/day.

Table A-16. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Pancreas: Acinus, Cytoplasmic Alteration in Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

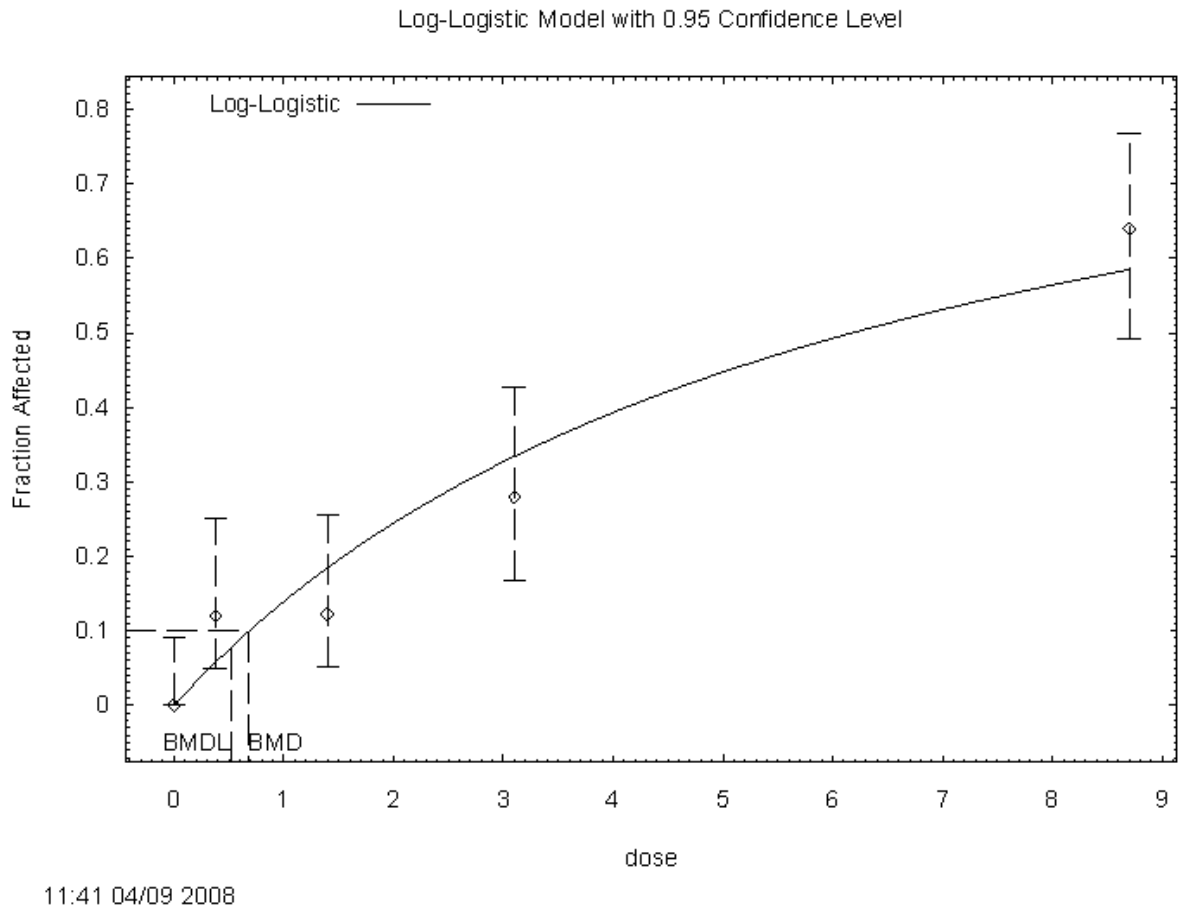
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
Gamma[a]	0.92	0.72	0.13	206.82
Logistic	2.43	2.03	0.09	211.78
Log-logistic[b]	**0.68**	**0.52**	**0.19**	**205.22**
Multi-stage[c]	0.92	0.72	0.13	206.82
Probit	2.24	1.89	0.11	210.99
Log-probit[b]	1.77	1.40	0.11	209.99
Quantal linear	0.92	0.72	0.13	206.82
Weibull[a]	0.92	0.72	0.13	206.82

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Figure A-8. Predicted and Observed Incidence of Pancreas: Acinus, Cytoplasmic Alteration in Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium (VI)/kg/day.

Source: NTP 2008a

Agency Contact (Chemical Manager): Sharon Wilbur

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chromium(III) insoluble particulates
CAS number: 16065-83-1
Date: October 2008
Profile status: Final Draft Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 2
Species: Rat

Minimal Risk Level: 0.005 mg chromium(III)/m^3 for insoluble trivalent chromium particulate compounds

Reference: Derelanko MJ, Rinehart WE, Hilaski RJ, et al. 1999. Thirteen-week subchronic rat inhalation toxicity study with a recovery phase of trivalent chromium compounds, chromic acid and basic chromium sulfate. Toxicol Sci 52(2):278-288.

Experimental design: Groups of 15 male and female CDF (Fisher 344/Crl BR VAF/Plus) rats were exposed to chromic oxide or basic chromium sulfate by nose-only inhalation to 0, 3, 10, or 30 mg chromium(III)/m^3 (measured concentrations) 6 hours/day, 5 days/week for 13 weeks. Mean particle sizes (in microns±GSD, based on 21 samples/test group evaluated over the 13-week exposure period) in the 3, 10, and 30 mg chromium(III)/m^3 groups, were 1.8±1.93, 1.9±1.84, and 1.9±1.78, respectively, for chromic oxide and 4.2±2.48, 4.2±2.37, and 4.5±2.50, respectively, for basic chromium sulfate; no chromium(VI) was detected in samples. Of these 15 rats/sex/group, 10 rats/sex/group were examined and sacrificed after 13 weeks of exposure and 5 rats/sex/group were examined and sacrificed after an additional 13-week recovery (e.g., no exposure) period. Throughout the exposure and recovery periods, rats were examined daily for mortality and clinical signs of toxicity; body weight was recorded weekly, but food consumption was not measured. Ophthamalmoscopic examinations were conducted prior to treatment and before terminal sacrifice. At the end of the treatment and recovery phases, blood was analyzed for "standard" hematology and clinical chemistry, and urinalysis was conducted; specific outcome measures evaluated for these assessments were not reported. In five rats/sex/group, urine was also analyzed for β_2-microglobulin. Gross necropsy was performed on all animals at terminal sacrifice and organ weights were recorded for heart, liver, lungs/trachea (combined), spleen, kidneys, brain, adrenal, thyroid/parathyroid, testes, and ovaries. Bone marrow was examined and differential cell counts of bone marrow were conducted. Microscopic examination of comprehensive tissues (described as "tissues typically harvested for subchronic studies") was conducted for all animals and the control and 30 mg chromium(III)/m^3 groups. For all animals in the 3 and 30 mg chromium(III)/m^3 groups, the following tissues were examined microscopically: kidneys, liver, nasal tissues, trachea, lungs, larynx, mediastinal and mandibular lymph nodes, and all tissues with gross lesions. Histopathological lesions were described, but no incidence data were reported. Sperm morphology, count, and motility were assessed in all males at the end of the 13-week treatment period only.

Effects noted in study and corresponding doses: The following study results are for rats exposed to chromic oxide only; detailed results of animals exposed to basic chromium sulfate are presented in the following intermediate-duration inhalation MRL worksheet for soluble chromium(III) compounds. No mortalities, clinical signs of toxicity, changes in body weight, findings on ophthalmologic examination, or alterations of sperm count, motility, or morphology were observed. Evaluations of hematology, clinical chemistry, and urinalysis did not reveal any treatment-related differences compared to controls; β_2-microglobulin was not detected in urine of rats from any group. Absolute and relative lung/trachea weights were significantly increased by 12 and 13%, respectively, in males in the 30 mg

chromium(III)/m^3 group compared to control. Lung weights were not increased in females. Other significant changes in organ weight changes were limited to small increases in absolute thyroid/parathyroid weight in females in the 10 mg chromium(III)/m^3 group and in relative thyroid/parathyroid weight (combined) in females in the 10 and 30 mg chromium(III)/m^3 groups. The study authors stated that the biological significance of changes in thyroid/parathyroid weight could not be determined; however, no histopathological changes were observed in these tissues in female rats exposed to 30 mg chromium(III)/m^3. On necropsy, most animals (incidence not reported) in the chromic oxide group had green discoloration of the lungs and mediastinal lymph nodes; the degree of discoloration increased with exposure level and was presumed to represent deposition of the test material. Mediastinal lymph node enlargement was noted in the 30 mg chromium(III)/m^3 group. Microscopic examination of the lung revealed foci or aggregates of dark-pigmented (presumably the test material) macrophages within alveolar spaces adjacent to junctions of terminal bronchioles and alveolar ducts; black pigment was observed at the tracheal bifurcation and in periobronchial lymphoid tissue and the medistinal lymph node in all chromic oxide treatment groups. These findings are consistent with normal physiological clearance mechanisms for particulates deposited in the lung and are not considered adverse. Lymphoid hyperplasia of the mediastinal node was observed in rats of all treatment groups (severity not reported). In rats exposed to 10 and 30 mg chromium(III)/m^3, trace-to-mild chronic interstitial inflammation of the lung, characterized by inflammatory cell infiltration, was observed in alveolar septa, and hyperplasia of Type II pneumocytes (severity not reported) were observed. Histopathological changes were isolated to the lungs and respiratory lymphatic tissues and were not observed in other tissues, including nasal tissues and the larynx. Thus, for evaluations conducted at the end of the 13-week treatment period, a LOAEL of 3 mg chromium(III)/m^3 for hyperplasia of the mediastinal node was identified for both males and females; the severity of this effect was not reported. Following the 13-week recovery period, pigmented macrophages and black pigment were observed in peribronchial tissues and the mediastinal lymph node in animals from all treatment groups. Septal cell hyperplasia and chronic interstitial inflammation of the lung, both trace-to-mild in severity, were observed in males of all treatment groups and in females exposed to 10 and 30 mg chromium(III)/m^3. For evaluations conducted at the 13-week posttreatment recovery period, a minimal LOAEL (classified as minimal based on severity) of 3 mg chromium(III)/m^3 for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats was identified.

Dose end point used for MRL derivation: 3 mg chromium(III)/m^3 (trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung), adjusted to 0.54 mg chromium(III)/m^3 for intermittent exposure and converted to a $LOAEL_{HEC}$ of 0.43 mg chromium(III)/m^3

[ ] NOAEL [X] LOAEL

The LOAEL of 3 mg chromium(III)/m^3 for hyperplasia of the mediastinal node in males and females (observed at the end of the 13-week treatment period) and the minimal LOAEL (based on severity) of 3 mg chromium(III)/m^3 for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in males (observed at the end of the 13-week recovery period) were further evaluated as potential critical effects for derivation of the intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds. A BMCL for these effects could not be determined since incidence data for lesions of the lung and respiratory lymphatic tissue were not reported; thus, a NOAEL/LOAEL approach was used. Following adjustment of LOAELs for intermittent exposure ($LOAEL_{ADJ}$) and human equivalent concentrations ($LOAEL_{HEC}$), as described below, trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats was selected as the critical effect, based on the lowest $LOAEL_{HEC}$ of 0.43 mg chromium(III)/m^3 (Table A-17). The intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds of 0.005 mg chromium(III)/m^3 was derived by dividing the minimal $LOAEL_{HEC}$ of 0.43 mg chromium(III)/m^3 by a composite uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

Table A-17. LOAEL Values (Expressed in Terms Of HEC) for Nonneoplastic Lesions in Rats Exposed to Chromic Oxide by Inhalation For 13 Weeks

Species/sex	Lesion type (RDDR location)	RDDR multiplier	$LOAEL_{ADJ}$ (mg chromium(III)/m^3)[a]	$LOAEL_{HEC}$ (mg chromium(III)/m^3)[b]
Rat/male	Septal cell hyperplasia and chronic interstitial inflammation of the lung (thoracic)	0.789	0.54	0.43
Rat/male	Hyperplasia of the mediastinal node (tracheobronchial)	1.225	0.54	0.66
Rat/female	Hyperplasia of the mediastinal node (tracheobronchial)	1.084	0.54	0.59

[a]Duration-adjusted for intermittent exposure ($LOAEL_{ADJ}$ = LOAEL x 6 hours/24 hours x 5 days/7 days = 3 mg chromium(III)/m^3 x 6 hours/24 hours x 5 days/7 days = 0.54 mg chromium(III)/m^3)
[b]$LOAEL_{HEC}$ = $LOAEL_{ADJ}$ x RDDR

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; RDDR = regional deposited dose ratio

Source: Derelanko et al. 1999

Uncertainty factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 3 for extrapolation from animals to humans, with dosimetric adjustment
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: To determine the $LOAEL_{HEC}$, the $LOAEL_{ADJ}$ in rats was multiplied by the RDDR multiplier determined for lesions in various areas of the respiratory tract in male and female rats (Table A-17). The RDDR computer program was used to determine the RDDR multipliers as follows.

For interstitial inflammation of the lung in male rats (specific location of lesion within the lung was not reported by study authors) observed after the 13-week recovery period, the thoracic region for the RDDR program was selected since the observed effect could occur in the both the tracheobronchial and pulmonary regions of the lung. The RDDR multiplier of 0.789 for the thoracic region of the respiratory tract in male rats was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study (data for body weights of male rats in the chromic oxide portion of the study were not reported) and the average particle size (MMAD±GSD) of 1.9±1.85 reported in the Derelanko et al. (1999) study.

For hyperplasia of the mediastinal node in male and female rats observed at the end of the 13-week treatment period, the tracheobronchial region of the respiratory tract was selected for the RDDR program. Although the mediastinal lymph node is not a respiratory tissue, for the purposes of HEC conversions, it is considered part of the tracheobronchial region of the respiratory system rather than a systemic tissue;

classification of the mediastinal lymph node as a systemic tissue is not appropriate, since the test material reaches the respiratory lymphatic tissues by the pulmonary macrophage clearance system and not by first entering the systemic circulation. For male rats, the RDDR multiplier of 1.225 for the tracheobronchial region of the respiratory tract in male rats was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study (data for body weights of male rats in the chromic oxide portion of the study were not reported) and the average particle size MMAD±GSD of 1.9±1.85 reported in Derelanko et al. (1999). For female rats, the RDDR multiplier of 1.084 for the tracheobronchial region tract was determined using the default subchronic body weight of 124 g for female F344 rats (EPA 1988d) and the average particle size MMAD±GSD of 1.9±1.85 reported in the Derelanko et al. (1999) study; the default value for female body weights was used because female body weights were not reported in the critical study.

Was a conversion used from intermittent to continuous exposure? Rats were exposed for 6 hours/day, 5 days/week for 13 weeks.

$LOAEL_{ADJ}$ = 3 mg chromium(III)/m^3 x 6 hours/24 hours x 5 days/7 days
$LOAEL_{ADJ}$ = 0.54 mg chromium(III)/m^3

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the major target of inhalation exposure to chromium(III) and chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. The available occupational studies for exposure to chromium(III) compounds include, or likely include, concomitant exposure to chromium(VI) compounds and other compounds that may produce respiratory effects (Langård 1980; Mancuso 1951; Osim et al. 1999). Thus, while the available data in humans suggest that respiratory effects occur following inhalation exposure to chromium(III) compounds, the respiratory effects of inhaled chromium(VI) and other compounds are confounding factors. Studies evaluating respiratory effects of intermediate-duration inhalation exposure of animals are limited to the critical study evaluating 13-week exposure to chromic oxide or basic chromium sulfate (Derelanko et al. 1999). Results of this study show that intermediate-duration inhalation exposure to chromic oxide or basic chromium sulfate produced adverse respiratory effects, as indicated by histopathological changes and increased lung weight. However, effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung and respiratory lymph tissues). The authors suggest that differences in the respiratory toxicity of these compounds may be due to differences in chemical-physical properties (e.g., solubility, acidity). Based on the differences in respiratory toxicity between insoluble chromic oxide and soluble basic chromium sulfate, separate intermediate-duration inhalation MRLs were derived for insoluble and soluble trivalent chromium particulate compounds.

Agency Contact (Chemical Manager): Sharon Wilbur

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chromium(III) soluble particulates
CAS number: 16065-83-1
Date: October 2008
Profile status: Final Draft Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 3
Species: Rat

Minimal Risk Level: 0.0001 mg chromium(III)/m^3 for soluble trivalent chromium particulate compounds

Reference: Derelanko MJ, Rinehart WE, Hilaski RJ, et al. 1999. Thirteen-week subchronic rat inhalation toxicity study with a recovery phase of trivalent chromium compounds, chromic acid and basic chromium sulfate. Toxicol Sci 52(2):278-288.

Experimental design: Groups of 15 male and female CDF (Fisher 344/Crl BR VAF/Plus) rats were exposed to chromic oxide or basic chromium sulfate by nose-only inhalation to 0, 3, 10, or 30 mg chromium(III)/m^3 (measured concentrations) 6 hours/day, 5 days/week for 13 weeks. Mean particle sizes (in microns±GSD, based on 21 samples/test group evaluated over the 13-week exposure period) in the 3, 10, and 30 mg chromium(III)/m^3 groups, were 1.8±1.93, 1.9±1.84, and 1.9±1.78, respectively, for chromic oxide and 4.2±2.48, 4.2±2.37, and 4.5±2.50, respectively, for basic chromium sulfate; no chromium(VI) was detected in samples. Of these 15 rats/sex/group, 10 rats/sex/group were examined and sacrificed after 13 weeks of exposure and 5 rats/sex/group were examined and sacrificed after an additional 13-week recovery (e.g., no exposure) period. Throughout the exposure and recovery periods, rats were examined daily for mortality and clinical signs of toxicity; body weight was recorded weekly but food consumption was not measured. Ophthamalmoscopic examinations were conducted prior to treatment and before terminal sacrifice. At the end of the treatment and recovery phases, blood was analyzed for "standard" hematology and clinical chemistry, and urinalysis was conducted; specific outcome measures evaluated for these assessments were not reported. In five rats/sex/group, urine was also analyzed for β_2-microglobulin. Gross necropsy was performed on all animals at terminal sacrifice and organ weights were recorded for heart, liver, lungs/trachea (combined), spleen, kidneys, brain, adrenal, thyroid/parathyroid, testes, and ovaries. Bone marrow was examined and differential cell counts of bone marrow were conducted. Microscopic examination of comprehensive tissues (described as "tissues typically harvested for subchronic studies") was conducted for all animals and the control and 30 mg chromium(III)/m^3 groups. For all animals in the 3 and 30 mg chromium(III)/m^3 groups, the following tissues were examined microscopically: kidneys, liver, nasal tissues, trachea, lungs, larynx, mediastinal and mandibular lymph nodes, and all tissues with gross lesions. Histopathological findings were described, but no incidence data were reported. Sperm morphology, count, and motility were assessed in all males at the end of the 13-week treatment period only.

Effects noted in study and corresponding doses: The following study results are for rats exposed to basic chromium sulfate only; detailed results of animals exposed to chromic oxide are presented in the preceding intermediate-duration inhalation MRL worksheet for insoluble chromium(III) compounds. No treatment-related mortalities were observed; one male rat in the 30 mg chromium(III)/m^3 group died on day 4 of exposure; the study authors did not attribute this death to treatment since no significant signs of toxicity were observed in this animals or in other animals in this treatment group. Females in the 30 mg chromium(III)/m^3 group exhibited sporadic labored breathing; no additional information on this observation was reported. No findings on ophthalmologic examination or alterations of sperm count, motility, or morphology were observed. At the end of the 13-week treatment period, body weight was

significantly decreased in males in the 10 and 30 mg chromium(III)/m^3 groups and females in the 30 mg chromium(III)/m^3 group. The study authors stated that "most" hematological, clinical chemistry, and urinalysis values in all exposure groups were similar to controls, although data were not reported. A significant, dose-related increase in absolute and relative lung/trachea weights was observed in male rats in all treatment groups. Other organ weight changes in males were decreased absolute and increase relative brain weights (30 mg chromium(III)/m^3), increased relative kidney weight (30 mg chromium(III)/m^3), decreased absolute liver weight (30 mg chromium(III)/m^3), increased relative thyroid/parathyroid weight (30 mg chromium(III)/m^3), decreased relative spleen weight (10 and 30 mg chromium(III)/m^3), and increased relative testes weight (30 mg chromium(III)/m^3). In females, absolute and relative lungs weights were increased in a dose-dependent fashion in all treatment groups. Other organ weight changes in females were increased absolute and relative thyroid/parathyroid weight (30 mg chromium(III)/m^3) and decreased absolute spleen weight (30 mg chromium(III)/m^3). With the exception of increased absolute and relative lung weights in males and females, small changes in other organs weights were not considered adverse in the absence of histopathological changes. On necropsy, grey lung discoloration was observed in animals exposed to 10 and 30 mg chromium(III)/m^3; the degree of discoloration increased with exposure level. Microscopic examination of the lung revealed the following changes in all treatment groups: chronic inflammation of the alveoli; alveolar spaces filled with macrophages, neutrophils, lymphocytes and cellular debris; foci of "intense" inflammation and thickened alveolar walls; chronic interstitial inflammation with cell infiltration; hyperplasia of Type II pneumocytes; and granulomatous inflammation, characterized by infiltration of macrophages and multinucleated giant cells. Macrophage infiltration and granulomatous inflammation of the larynx, acute inflammation and suppurative and mucoid exudates of nasal tissues, and histiocytosis and hyperplasia of peribronchial lymphoid tissues and the mediastinal lymph node were also observed in all treatment groups. Following the 13-week recovery period, enlargement of the mediastinal lymph node was observed on gross necropsy in all treatment groups. Microscopic examination of respiratory tissues showed changes to the lung (chronic alveolar inflammation, interstitial inflammation, septal cell hyperplasia, and granulomatous inflammation) in all treatment groups, larynx (granulomatous inflammation) in the 10 and 30 mg chromium(III)/m^3 groups, nasal tissues (trace suppurative exudates) in one to two animals in each groups, and mediastinal lymph node (histiocytosis and hyperplasia) in all treatment groups chromium(III)/m^3 groups. Following the 13-week recovery period, test material was observed in the respiratory tract on necropsy; however, incidence was decreased compared to observations made immediately following treatment (data not presented). In addition, chronic alveolar and interstitial inflammation and septal cell hyperplasia (all trace-to-moderate in severity) were observed in the 10 and 30 mg chromium(III)/m^3 groups, with severity similar to that observed immediately following treatment; in the 3 mg chromium(III)/m^3 group, severity was slightly reduced.

Dose end point used for MRL derivation: 3 mg chromium(III)/m^3 (nasal and larynx lesions), adjusted to 0.54 mg chromium(III)/m^3 for intermittent exposure and converted to a $LOAEL_{HEC}$ of 0.04 mg chromium(III)/m^3

[ ] NOAEL [X] LOAEL

The respiratory tract was identified as the target for inhaled soluble trivalent chromium particulate compounds. Similar effects were observed in male and female rats exposed to inhaled basic chromium sulfate for 13 weeks, with histopathological changes to the nose, larynx, lung, and respiratory lymphatic tissues and increased relative lung weight occurring at ≥3 mg chromium(III)/m^3. Therefore, data for histopathological changes in various regions of the respiratory tract and increased relative lung weights were further evaluated to determine the point of departure for derivation of the intermediate-duration MRL for soluble trivalent chromium particulate compounds.

Benchmark dose analysis could not be conducted for respiratory tract lesions, since incidence data were not reported by Derelanko et al. (1999); therefore, a NOAEL/LOAEL approach was used. The LOAEL value of 3 mg chromium(III)/m^3 for lesions in different regions of the respiratory tract was further evaluated as a potential point of departure. LOAEL values were adjusted for intermittent exposure ($LOAEL_{ADJ}$) and converted to a human equivalent concentration ($LOAEL_{HEC}$), as shown in (Table A-18).

Table A-18. LOAEL Values (Expressed in Terms of HEC) for Nonneoplastic Lesions in Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks

Species/sex	Lesion type (RDDR location)	RDDR multiplier	$LOAEL_{ADJ}$ (mg chromium(III)/m^3)[a]	$LOAEL_{HEC}$ (mg chromium(III)/m^3)[b]
Rat/male	Granulomatous inflammation of larynx; inflammation of nasal tissue (extrathoracic)	0.129	0.54	0.07
Rat/male	Interstitial and alveolar inflammation; alveolar hyperplasia (thoracic)	0.470	0.54	0.25
Rat/female	Granulomatous inflammation of larynx; inflammation of nasal tissue (extrathoracic)	0.078	0.54	0.04
Rat/female	Interstitial and alveolar inflammation; alveolar hyperplasia (thoracic)	0.483	0.54	0.26

[a]Duration-adjusted for intermittent exposure ($LOAEL_{ADJ}$ = LOAEL x 6 hours/24 hours x 5 days/7 days = 3 mg chromium(III)/m^3 x 6 hours/24 hours x 5 days/7 days = 0.54 mg chromium(III)/m^3)
[b]$LOAEL_{HEC}$ = $LOAEL_{ADJ}$ x RDDR

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; RDDR = regional deposited dose ratio

Soucre: Derelanko et al. 1999

To determine the BMC for increased lung weights, available continuous-variable models in the EPA Benchmark Dose (version 1.4.1) were fit to the data for relative lung weights in male and female rats (Derelanko et al. 1999; Table A-19). The BMC and the 95% lower confidence limit (BMCL) calculated is an estimate of the concentrations associated with a change of 1 standard deviation from the control ($BMCL_{1sd}$). The model-fitting procedure for continuous data is as follows. The simplest model (linear) is applied to the data while assuming constant variance. If the data are consistent with the assumption of

constant variance ($p \geq 0.1$), then the other continuous models (polynomial, power, and Hill models) are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest Akaike's Information Criteria (AIC) for the fitted model is selected for BMC derivation. If the test for constant variance is negative, then the linear model is run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then the other continuous models are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMC derivation. If the tests for both constant and nonconstant variance are negative, then the data set is considered not to be suitable for BMC modeling. For male rats, the best model fit (Hill model) did not provide graphic output of the model; since model fit could not be evaluated by visual inspection, the $BMDL_{1sd}$ from the Hill model was not selected. All other models took the form of a linear model (nonconstant variance), yielding predicted BMC_{1sd} and $BMCL_{1sd}$ values of 2.89 and 2.05 mg chromium(III)/m^3, respectively. For female rats, the linear model (nonconstant variance) provided the best fit, with predicted BMC_{1sd} and $BMCL_{1sd}$ values of 6.33 and 3.96 mg/m^3, respectively. Additional details of the benchmark dose analysis for each data set modeled are presented in the last section of this worksheet. The $BMCL_{1sd}$ values for the best fitting models in male and female rats were adjusted for intermittent exposure ($BMCL_{1sd, ADJ}$) and human equivalent concentrations ($BMCL_{1sd, HEC}$), yielding $BMCL_{1sd, HEC}$ values of 0.17 and 0.34 mg chromium(III)/m^3 in males and females, respectively, as shown below (Table A-20).

Table A-19. Relative Lung Weights[a] of CDF Rats[b] Exposed to Basic Chromium Sulfate by Nose-Only Inhalation 6 Hours/Day, 5 Days/Week for 13 Weeks

	Concentrations (mg chromium(III)m^3)			
Relative weight (percent x 10)	0	3	10	30
Basic chromium sulfate, males	4.42±0.187[c]	5.60±0.271[d]	7.1 5± 0.252[d]	10.69±0.688[d]
Basic chromium sulfate, females	5.65±0.418	6.99±0.619[d]	9.24±1.036[d]	12.89±1.134[d]

[a]Combined lung and trachea
[b]10 rat in all groups except male rats in the basic chromium sulfate 30 mg/m^3 group (n=9)
[c]mean±Standard deviation
[d]$p<0.01$

Source: Derelanko et al. 1999

Table A-20. $BMCL_{1sd}$ Values (Expressed in Terms of HEC) for Increased Relative Lung Weight in Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks

Species/sex	RDDR multiplier[a]	Duration-adjusted $BMCL_{1sd, ADJ}$ (mg chromium(III)/m^3)[b]	$BMCL_{1sd, HEC}$ (mg chromium(III)/m^3)[c]
Rat/male	0.470	0.37	0.17
Rat/female	0.483	0.71	0.34

[a]For thoracic region
[b]Duration-adjusted for continuous exposure ($BMCL_{1sd, ADJ}$ = $BMCL_{1sd}$ x 6 hours/24 hours x 5 days/7 days); $BMCL_{1sd}$ for the best fitting models for male and female rats were 2.05 and 3.96 mg chromium(III)/m^3, respectively.
[c]$BMCL_{1sd, HEC}$ = $BMCL_{1sd, ADJ}$ x RDDR

BMCL = lower confidence limit (95%) on the benchmark concentration; HEC = human equivalent concentration; RDDR = regional deposited dose ratio

Source: Derelanko et al. 1999

Based on comparison of $LOAEL_{HEC}$ values for respiratory tract lesions and $BMCL_{1sd, HEC}$ values for increased lung weight, the lowest value of 0.04 mg chromium(III)/m^3 (the $LOAEL_{HEC}$ for lesions of the larynx and nose in female rats) was selected as the point of departure. The intermediate-duration inhalation MRL for soluble trivalent chromium particulate compounds of 0.0001 mg chromium(III)/m^3 was derived by dividing the $LOAEL_{HEC}$ of 0.04 mg chromium(III)/m^3 by a composite uncertainty factor of 300 (10 for use of a LOAEL, 3 for pharmacodynamic variability between animals to humans, and 10 for human variability).

Uncertainty factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: To determine human equivalent concentrations, $LOAEL_{ADJ}$ values for lesions in various areas of the respiratory tract (Table A-18) and $BMCL_{1sd, ADJ}$ values for changes in changes in lung weights (Table A-20) were multiplied by the RDDR multiplier determined for lesions in various areas of the respiratory tract as follows.

For histopathological changes to the nose and larynx, the extrathoracic region for the RDDR program was selected. For male rats, the RDDR multiplier of 0.129 for the extrathoracic region of the respiratory tract was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study and the average particle size (MMAD±GSD) of 4.3±2.45 reported in Derelanko et al. (1999). For female rats, the RDDR multiplier of 0.078 for the extrathoracic region of the respiratory tract was determined using the default subchronic body weight of 124 g for female F344 rats (EPA 1988d) and the average particle size MMAD±GSD of 4.3±2.45 reported in Derelanko et al. (1999); the default value for female body weights was used because female body weights were not reported in Derelanko et al. (1999).

For histopathological changes to the lung and increased relative lung weight, the thoracic region (a combination of tracheobronchial and pulmonary regions) was selected. For male rats, the RDDR multiplier of 0.470 for the thoracic region of the respiratory tract was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study and the average particle size (MMAD±GSD) of 4.3±2.45 reported in Derelanko et al. (1999). For female rats, the RDDR multiplier of 0.483 for the thoracic region of the respiratory tract was determined using the default subchronic body weight of 124 g for female F344 rats (EPA 1988d) and the average particle size MMAD±GSD of 4.3±2.45 reported in Derelanko et al. (1999); the default value for female body weights was used because female body weights were not reported in Derelanko et al. (1999).

Was a conversion used from intermittent to continuous exposure? Rats were exposed for 6 hours/day, 5 days/week for 13 weeks. The LOAEL and $BMCL_{1sd}$ values were adjusted for continuous exposure as follows:

$$LOAEL_{ADJ} \text{ or } BMCL_{1sd,\ ADJ} = LOAEL \text{ or } BMCL_{1sd} \text{ x 6 hours/24 hours x 5days/7 days}$$

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the major target of inhalation exposure to chromium(III) and chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. The available occupational studies for exposure to chromium(III) compounds include, or likely include, concomitant exposure to chromium(VI) compounds and other compounds that may produce respiratory effects (Langård 1980; Mancuso 1951; Osim et al. 1999). Thus, while the available data in humans suggest that respiratory effects occur following inhalation exposure to chromium(III) compounds, the respiratory effects of inhaled chromium(VI) and other compounds are confounding factors. Studies evaluating respiratory effects of intermediate-duration inhalation exposure of animals are limited to the critical study evaluating 13-week exposure to chromic oxide or basic chromium sulfate (Derelanko et al. 1999). Results of this study show that intermediate-duration inhalation exposure to chromic oxide or basic chromium sulfate produced adverse respiratory effects, as indicated by histopathological changes and increased lung weight. However, effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung and respiratory lymph tissues). The authors suggest that differences in the respiratory toxicity of these compounds may be due to differences in chemical-physical properties (e.g., solubility, acidity). Based on the differences in respiratory toxicity between insoluble chromic oxide and soluble basic chromium sulfate, separate intermediate-duration inhalation MRLs were derived for insoluble and soluble trivalent chromium particulate compounds.

Details of Benchmark Dose Analysis for the Intermediate-duration Inhalation MRL for Soluble Trivalent Chromium Particulates

Lung Weights in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data. The linear model was applied to the data again while applying the power model integrated into the BMCs to account for nonhomogenous variance. The nonconstant variance model did provide an adequate fit (as assess by the p-value for variance). The polynomial, power, and Hill models were then fit to the data with nonconstant variance assumed. All of the models provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-21). Comparing across models, a better fit is generally indicated by a lower AIC. As assessed by AIC, the Hill model provides the best fit to the data; however, the BMDS software did not generate the graph output needed to assess visual fit of the model to the data. All other models took the form of a linear model, so the

nonconstant variance-linear model is selected for BMC derivation. The predicted BMC_{1sd} and $BMCL_{1sd}$ for the data are 2.89 and 2.05 mg chromium(III)/m^3, respectively (Figure A-9).

Table A-21. Model Predictions for Changes in Relative Lung Weights of Male CDF Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks

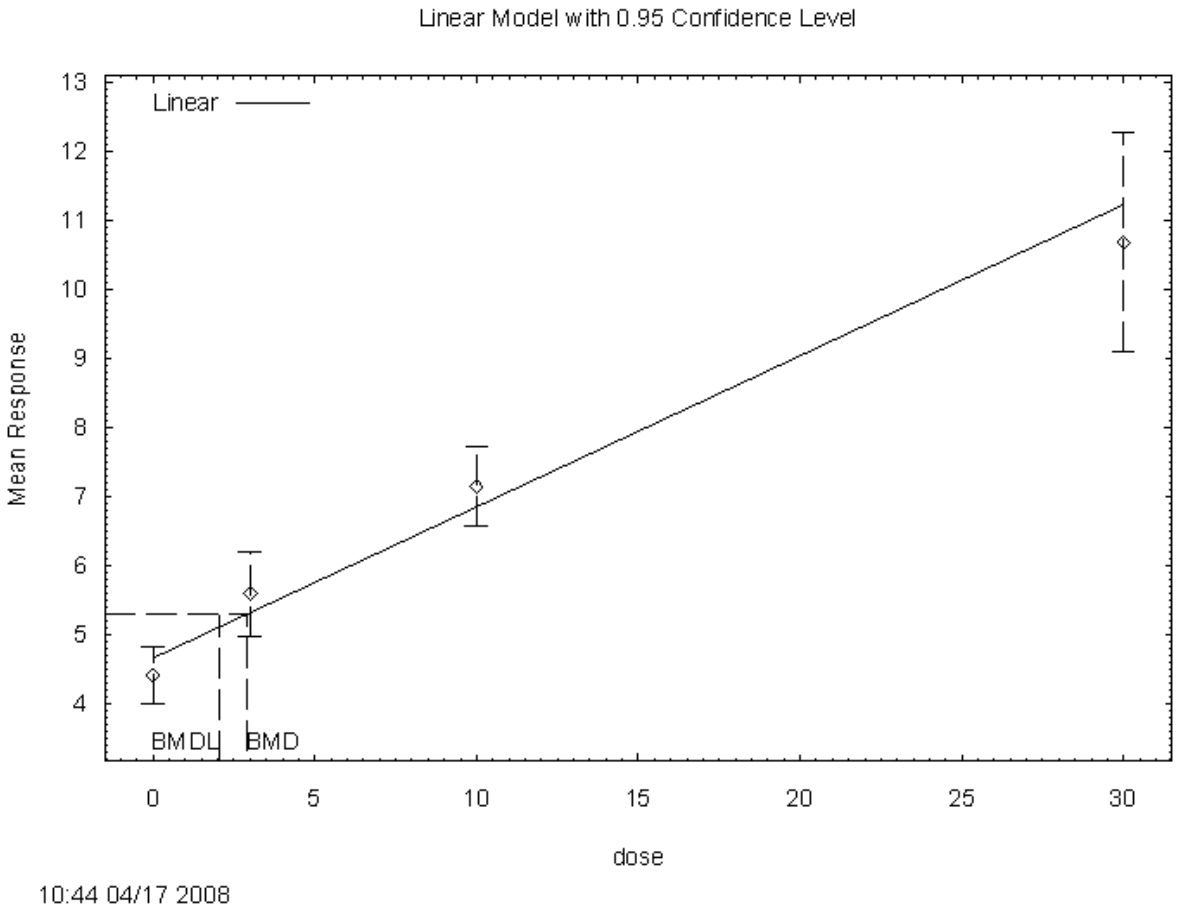
Model	Variance p-value[a]	p-Value for the means[a]	AIC	BMC_{1sd} (mg chromium(III)/m^3)	$BMCL_{1sd}$ (mg chromium(III)/m^3)
Linear[b,c]	0.00	0.30	56.75	5.79	4.70
Linear [c,d]	**0.40**	**0.10**	**44.09**	**2.89**	**2.05**
Polynomial (1-degree)[c,d]	0.40	0.10	44.09	2.89	2.05
Polynomial (2-degree)[c,d]	0.40	0.10	44.09	2.89	2.05
Polynomial (3-degree)[c,d]	0.40	0.10	44.09	2.89	2.05
Power[d]	0.40	0.10	44.09	2.89	2.05
Hill[d]	0.40	0.26	42.79	1.74	1.07

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = non-negative
[d]Nonconstant variance model applied

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; 1sd = a 1 standard deviation change from the control

Source: Derelanko et al. 1999

Figure A-9. Predicted and Observed Changes in Relative Lung Weights in Male Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks*



*BMD=BMC; BMDL=BMCL; BMCs and BMCLs indicated are associated with a 1 standard deviation change from the control, and are in units of mg chromium(III)/m^3.

Source: Derelanko et al. 1999

Lung Weights in Female Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data. The linear model was applied to the data again while applying the power model integrated into the BMDS to account for nonhomogenous variance. The nonconstant variance model did provide an adequate fit (as assess by the p-value for variance). The polynomial, power, and Hill models were then fit to the data with nonconstant variance assumed. All of the models provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-22). Comparing across models, a better fit is generally indicated by a lower AIC. As assessed by AIC, the linear model provides the best fit to the data. The predicted BMC_{1sd} and $BMCL_{1sd}$ for the data are 6.33 and 3.96 mg chromium(III)/m^3, respectively (Figure A-10).

Table A-22. Model Predictions for Changes in Relative Lung Weights of Female CDF Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks

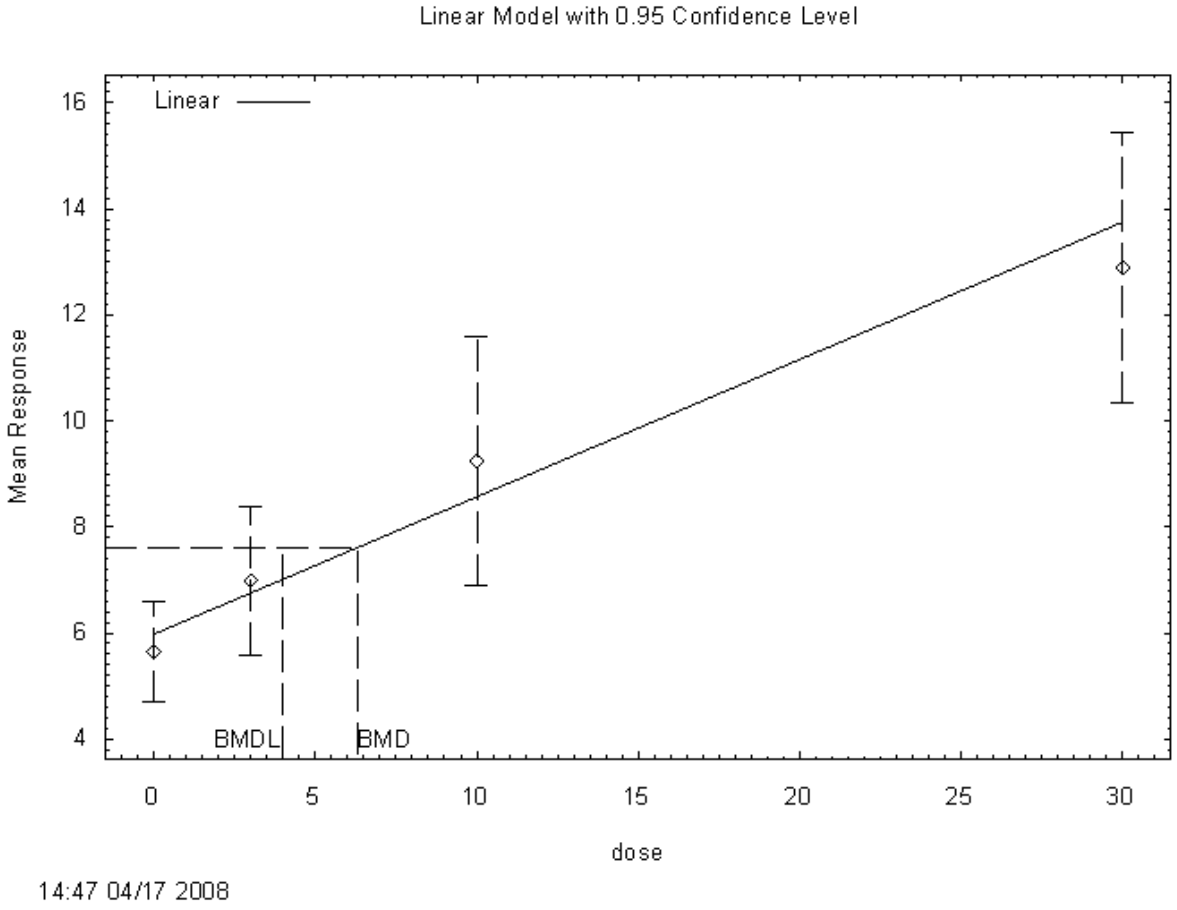
Model	Variance p-value[a]	p-Value for the means[a]	AIC	BMC $_{1sd}$ (mg chromium(III)/m^3)	BMCL $_{1sd}$ (mg chromium(III)/m^3)
Linear[b,c]	0.01	0.51	122.61	11.28	8.59
Linear [c,d]	**0.59**	**0.14**	**117.05**	**6.33**	**3.96**
Polynomial (1-degree)[c,d]	0.59	0.14	117.05	6.33	3.96
Polynomial (2-degree)[c,d]	0.59	0.14	117.05	6.33	3.96
Polynomial (3-degree)[c,d]	0.59	0.14	117.05	6.33	3.96
Power[d]	0.59	0.14	117.05	6.33	3.96
Hill[d]	0.59	NA[e]	117.13	2.84	1.32

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = non-negative
[d]Nonconstant variance model applied
[e]NA = degrees of freedom are ≤0; the Chi-Square test for fit is not valid.

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; 1sd = a 1 standard deviation change from the control

Source: Derelanko et al. 1999

Figure A-10. Predicted and Observed Changes in Relative Lung Weights in Female Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks*



*BMD=BMC; BMDL=BMCL; BMCs and BMCLs indicated are associated with a 1 standard deviation change from the control, and are in units of mg chromium(III)/m^3.

Source: Derelanko et al. 1999

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system,

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

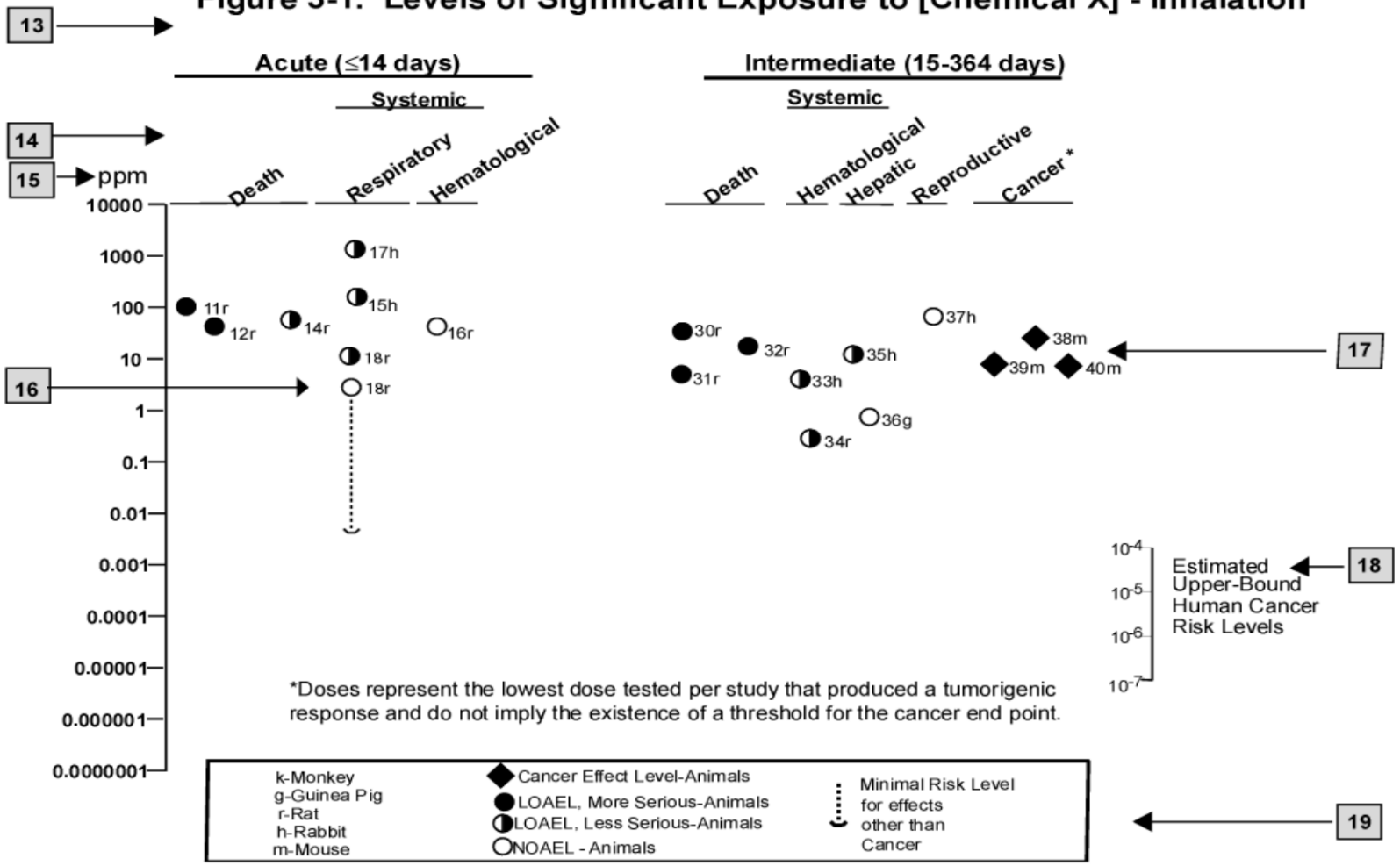
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMDX	dose that produces a X% change in response rate of an adverse effect
BMDLX	95% lower confidence limit on the BMDX
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense

DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid

MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration

OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX