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 a hundredfold 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, expert panel peer reviews, and agencywide 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, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MRL WORKSHEET

Chemical Name: 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)
CAS Number: 1746-01-6
Date: December 10, 1998
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [] Chronic
Key to Figure: 78m
Species: Mice

Minimal Risk Level: 0.0002 (2×10^{-4}) [X] µg/kg/day [ ] ppm

Reference: Burleson et al. 1996

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

Groups of 20 female B6C3F1 mice were administered a single gavage dose of 0, 0.001, 0.005, 0.01, 0.05, or 0.1 µg/kg 2,3,7,8-TCDD in corn oil. Seven days after 2,3,7,8-TCDD exposure, the mice were infected intranasally with influenza A/Hong Kong/8/68 (H3N2) virus diluted at 10^{-48}, 10^{-50}, 10^{-52}, or 10^{-54}. In a separate experiment, groups of 18 female mice received a single gavage dose of 0, 0.001, 0.01, or 0.1 µg/kg 2,3,7,8-TCDD and were infected 7 days later with influenza A virus at a dose not known to cause mortality (10^{-54} and 10^{-58}) or were sham-infected. Body weight, thymus weight, and wet lung weights were measured 3, 9, or 12 days postinfection. Pulmonary virus titers were determined in groups of 72 mice exposed to 0, 0.001, 0.01, or 0.01 µg/kg 2,3,7,8-TCDD and infected with influenza A virus seven days later. For the virus titer study, groups mice were killed 2 hours, 1, 4, 6, 7, 8, 9, 10, and 11 days post-infection.

Effects noted in study and corresponding doses:

Statistically significant increases in mortality were observed in the influenza A infected mice exposed to 0.01, 0.05, or 0.1 µg/kg 2,3,7,8-TCDD. However, no between group differences in mortality were observed at these 2,3,7,8-TCDD dosages. Mortality in mice receiving 0.001 or 0.005 µg/kg did not significantly differ from the mortality in the control group. Exposure to 2,3,7,8-TCDD did not enhance the increase in relative lung weight normally seen in mice infected with influenza A virus. As compared to controls, no significant alterations in thymus weights were observed in 2,3,7,8-TCDD-exposed mice sham-infected or those infected with influenza A virus. 2,3,7,8-TCDD exposure did not result in a significant increase in viral titers in the lung, as compared to titers from the control group. The authors noted that the lack of dose-response in mortality and the lack of effect on the relative lung weight, thymus weight, and viral titers suggest that 2,3,7,8-TCDD may be exerting an effect via an indirect mechanism such as through an effect on cytokines.

Dose and end point used for MRL derivation: Impaired resistance to influenza A virus infection, as evidence by the significant increase in mortality, was observed in female $B6C3F_1$ mice administered a single gavage dose of $0.01 µg/kg. No significant effects were observed at lower doses. Thus, 0.005 and 0.01 µg/kg are the NOAEL and LOAEL, respectively, for impaired resistance.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans- A comparison of species sensitivity suggests that even though there are wide ranges of sensitivity for some 2,3,7,8-TCDD-induced health effects, for most health effects, the LOAELs for the majority of animal species cluster within an order of magnitude. Based on the weight of evidence of animal species comparisons and human and animal mechanistic data, it is reasonable to assume that human sensitivity would fall within the range of animal sensitivity.
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

No. A modifying factor of 0.7 was applied to adjust for the difference in higher bioavailability of 2,3,7,8-TCDD from gavage with an oil vehicle than from food. Support for this modifying factor comes from toxicokinetic studies in Sprague Dawley rats. In rats fed 0.35 or 1 µg/kg/day 2,3,7,8-TCDD in the diet for 42 days, approximately 60% of the administered dose was absorbed (Fries and Marrow 1975). In contrast, 70-84% of a single or repeated gavage dose of 0.01-50 µg/kg 2,3,7,8-TCDD in corn oil was absorbed in rats (Piper et al. 1973; Rose et al. 1976). Thus, the ratio of 2,3,7,8-TCDD absorption from the diet to gavage with an oil vehicle is 0.71-0.85.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Was a conversion used from intermittent to continuous exposure?

No

Other additional studies or pertinent information that lend support to this MRL:

2,3,7,8-TCDD is a known immunosuppressant in animals in acute-, intermediate, and chronic-duration studies (Kerkvliet 1995). Suppression of the antibody response to sheep erythrocytes was observed in B6C3F1 mice administered 14 daily doses of 0.1 µg 2,3,7,8-TCDD/kg/day (Holsapple et al. 1986), and a significant increase in mortality was observed in $B6C3F_1$ mice administered 1.0 µg/kg/day 2,3,7,8-TCDD for 14 days and challenged with *Streptococcus pneumoniae* (White et al. 1986). Decreased survival after viral infection was also reported in female B6C3F1 mice after a single intraperitoneal dose of 0.1 µg 2,3,7,8-TCDD/kg (House et al. 1990). A significant suppression of complement hemolytic activity was observed in mice administered 0.01 µg/kg/day via gavage for 14 days (White et al. 1986). Furthermore, 2,3,7,8-TCDD alters the immune system of offspring when exposed through lactation and/or *in utero*. For example, a dose-related decrease in relative thymus weights were seen in offspring of rats dosed at levels of 0.005-0.35 µg 2,3,7,8-TCDD/kg on day 16 of pregnancy (Madsen and Larsen 1979).

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX A

MRL WORKSHEET

Chemical Name: 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)
CAS Number: 1746-01-6
Date: December 10, 1998
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [] Chronic
Key to Figure: 187g
Species: Guinea pig

Minimal Risk Level: 0.00002 (2×10^{-5}) [X] µg/kg/day [ ] ppm

Reference: DeCaprio et al. 1986

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

Groups of weanling Hartley guinea pigs (10/sex) were administered a diet containing 2, 10, 76 or 430 ppt for 90 days. These diets provided an average of 0.0001, 0.0007, 0.005, or 0.028 µg 2,3,7,8-TCDD/kg/day. The average doses were estimated by the investigators. A group of control guinea pigs was fed a diet without added 2,3,7,8-TCDD. Body weights and food consumption were monitored throughout the experiment. At the end of the dosing period the animals were sacrificed and clinical chemistries, hematology, organ weights and histopathology examinations were performed. The recovery following treatment was studied in groups of 10 guinea pigs fed a diet containing 430 ppt 2,3,7,8-TCDD for 11, 21, or 35 days and allowed to recover for 79, 69, or 55 additional days, respectively.

Effects noted in study and corresponding doses:

The highest dietary level of 2,3,7,8-TCDD caused net body weight loss and mortality. Four males and four females died and additional animals had to be sacrificed due to poor health. Food consumption was significantly reduced in the highest dose group only. Body weight gain in the 0.0007 and 0.005 µg/kg/day male groups was reduced by 9% and 20%, respectively. In the corresponding female groups, body weight gain was reduced by 6% and 15%. Gross lesions were observed only in the highest dose group and included thymic atrophy, depletion of body fat, and liver enlargement. Significant changes in organ weights included a decrease in absolute kidney weight and in absolute and relative thymus weight in males dosed with 0.005 µg/kg/day, increase in relative liver weight in males and females at the 0.005 µg/kg/day level, and increase in relative brain weight in males at this same dose level. Organ weights from high dose animals were not monitored. Administration of 2,3,7,8-TCDD did not cause any significant hematological effect (blood was not collected from the highest dose group). In the 0.005 µg/kg/day groups, serum ALT was significantly reduced in females whereas triglycerides were elevated in males. No other significant changes in clinical chemistries were observed. Treatment-related histological alterations were observed only in the two higher dose groups and consisted of hepatocellular cytoplasmic inclusion bodies and atrophy of the thymic cortex. In the recovery study there was 10% mortality in the groups treated for 11 and 21 days and 70% mortality in the group treated for 35 days. Surviving animals in all groups exhibited significantly reduced body weight gain.

Dose and end point used for MRL derivation: The dose of 0.0007 µg/kg/day represents a NOAEL for decreased thymus weight, whereas the 0.005 µg/kg/day is a LOAEL.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans-A comparison of species sensitivity suggests that even though there are wide ranges of sensitivity for some 2,3,7,8-TCDD-induced health effects, for most health effects, the LOAELs for the majority of animal species cluster within an order of magnitude. Based on the weight of evidence of animal species comparisons and human and animal mechanistic data, it is reasonable to assume that human sensitivity would fall within the range of animal sensitivity.
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

No. The doses were estimated by the investigators.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Was a conversion used from intermittent to continuous exposure?

No

Other additional studies or pertinent information that lend support to this MRL:

2,3,7,8-TCDD is a known immunosuppressant in animals in acute-, intermediate, and chronic-duration studies (Kerkvliet 1995). Reduction of thymus weight was also observed in intermediate-duration oral studies in rats (Van Birgelen et al. 1995; Viluksela et al. 1994). Another sensitive species for immunological effects of 2,3,7,8-TCDD is the marmoset monkey in which alterations in lymphocyte subsets have been reported after subcutaneous application of an average 0.0015 µg 2,3,7,8-TCDD/kg/day for 26 weeks (Neubert et al. 1992). Furthermore, 2,3,7,8-TCDD alters the immune system of offspring when exposed through lactation and/or *in utero*. For example, a dose-related decrease in relative thymus weights were seen in offspring of rats dosed at levels of 0.005-0.35 µg 2,3,7,8-TCDD/kg on day 16 of pregnancy (Madsen and Larsen 1979).

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX A

MRL WORKSHEET

Chemical Name: 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)
CAS Number: 1746-01-6
Date: December 10, 1998
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 226k
Species: Monkey

Minimal Risk Level: 0.000001 (1×10^{-6}) [X] µg/kg/day [ ] ppm

Reference: Schantz et al. 1992

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

Groups of 8 female rhesus monkeys were fed a diet containing 0, 5, or 25 ppt 2,3,7,8-TCDD for a total of 16.2 ± 0.4 months. After 7 months of exposure, the monkeys were mated with unexposed males. (Only 1 monkey in the 25 ppt group delivered a viable offspring; this offspring was not studied behaviorally). The monkeys were fed the 2,3,7,8-TCDD diet throughout the mating period, gestation, and lactation. The authors estimated that the total 2,3,7,8-TCDD intake over the course of the study was 59.6 ± 5.0 ng/kg for the 5 ppt group. The offspring were weaned at 4 months and individually housed. Mesenteric fat samples were collected from the offspring at age 5 months; the average 2,3,7,8-TCDD levels in the fat samples was 377 ±141 ppt (range of 290-950) for the 5 ppt group and below the detection limit of 2-200 ppt for the controls. When the offspring were 8.6 months of age, they were placed in peer groups of 4 monkeys and allowed to play for 1.5 hours without interference. The peer groups consisted of two 2,3,7,8-TCDD-exposed monkeys and two control monkeys. Behavioral patterns (social interactions and other behaviors such as vocalization, locomotion, self-directed behavior and environmental exploration) were monitored 4 days/week for 9 weeks.

Effects noted in study and corresponding doses:

No overt signs of toxicity were observed in the mothers or offspring, and birth weights and growth were not adversely affected by 2,3,7,8-TCDD exposure. Significant alterations were observed in play behavior, displacement, and self-directed behavior in the 2,3,7,8-TCDD -exposed offspring. 2,3,7,8-TCDD-exposed monkeys tended to initiate more rough-tumble play bouts and retreated less from play bouts than controls, were less often displaced from preferred positions in the playroom than the controls, and engaged in more self-directed behavior than controls. No other significant alterations in behavior were observed.

Dose and end point used for MRL derivation:

Although the mothers were exposed to 5 or 25 ppt 2,3,7,8-TCDD, only the offspring from the 5 ppt group underwent behavioral testing. The 5 ppt dietary concentration is equivalent to a daily dose of 1.2×10^{-4} µg/kg/day. This dose is a LOAEL for altered social behavior.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 3 for extrapolation from animals to humans A comparison of species sensitivity suggests that even though there are wide ranges of sensitivity for some 2,3,7,8-TCDD-induced health effects, for most health effects, the LOAELs for the majority of animal species cluster within an order of magnitude. Based on the weight of evidence of animal species comparisons and human and animal mechanistic data, it is reasonable to assume that human sensitivity would fall within the range of animal sensitivity.
[X] 10 for human variability.

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

Monkeys were exposed to a dietary concentration of 5 ppt 2,3,7,8-TCDD; the authors estimated that the total maternal intake during the 16.2 months of exposure (492 days) was 59.6 ng/kg.

Daily dose = (59.6 ng/kg) / (492 days) = 0.12 ng/kg/day (1.2×10^{-4} µg/kg/day)

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Was a conversion used from intermittent to continuous exposure?

No

Other additional studies or pertinent information that lend support to this MRL:

A behavioral teratology test battery was performed in monkey infants exposed to 2,3,7,8-TCDD during gestation and lactation; the results of this test battery was published in a series of papers (Bowman et al. 1989a; Schantz and Bowman 1989; Schantz et al. 1992). No significant alterations in reflex development, visual exploration, locomotor activity, or fine motor control were found (Bowman et al. 1989a). In tests of cognitive function, object learning was significantly impaired, but no effect on spatial learning was observed (Schantz and Bowman 1989). When the monkey infants were placed in social groups, altered social behavior was observed (Bowman et al. 1989a; Schantz et al. 1992). Additional data on the neurodevelopmental toxicity of 2,3,7,8-TCDD are limited to a study in which prenatal exposure to 2,3,7,8-TCDD resulted in masculinized behavior in female rats (Schantz et al. 1991). No chronic duration animal neurotoxicity studies were located, decreased motor activity was reported in rats acutely exposed to 2 (Giavini et al. 1983) or 5 (Seefeld et al. 1984a) µg/kg/day. The Schantz and Bowman studies are the only available chronic developmental toxicity studies. Acute and intermediate duration studies provide evidence that 2,3,7,8-TCDD is a potent developmental toxicant. Other sensitive developmental effects that have been observed included cleft palate [lowest LOAEL- 0.1 µg/kg/day (Giavini et al. 1982)], hydronephrosis [lowest LOAEL- 1 µg/kg (Moore et al. 1973)], immunosuppression [lowest LOAEL- 0.005 µg/kg (Madsen and Larsen 1979)], impaired development of the reproductive system [lowest LOAEL- 0.064 µg/kg (Mably et al. 1992a, 1992b, 1992c)], and increased newborn mortality [lowest LOAEL-0.7 µg/kg (Bjerke et al. 1994a)]; NOAELs were not identified for these effects in the most sensitive species or strain.

Some human studies have reported effects on the central and peripheral nervous systems shortly after exposure to high levels of 2,3,7,8-TCDD (Filippini et al. 1981; Moses et al. 1984; Pazderova-Vejlupkova et al. 1981; Pocchiari et al. 1979; Suskind 1977). However, follow-up studies did not find neurological effects years after exposure termination (Barbieri et al. 1988), suggesting that the effects may be transient. No human studies examined the effect of 2,3,7,8-TCDD on the developing neurologic system.

It should be also noted that 10 years after termination of 2,3,7,8-TCDD exposure in the Schantz et al. (1992) study, Rier et al. (1993) reported a dose-related increase in the incidence and severity of endometriosis in these same rhesus monkeys. Rier et al. (1993) identified a less serious LOAEL of 5 ppt (0.00012 μg/kg/day) for moderate endometriosis. However, monkeys appear to be more susceptible to endometriosis, based on a background incidence of endometriosis in monkeys of 30% (Rier et al. 1993) compared to a background incidence of 10% in humans (Wheeler et al. 1992). Thus, derivation of a chronic oral MRL based on endometriosis would necessitate using an uncertainty factor of less than 1 (or at most, 1) to account for the increased sensitivity of monkeys to endometriosis as compared to humans. If the Rier et al. (1993) study was used to calculate an oral MRL, the LOAEL of 0.00012 μg/kg/day would be divided by an uncertainty factor of 100 (10 to extrapolate from a LOAEL, 10 for human variability and 1 for interspecies differences). This would result in a computed MRL essentially the same as the chronic oral MRL of 1 pg/kg/day based on developmental toxicity as described in the preceding paragraph. Moreover, (1) the clinical history for these rhesus monkeys during the 10 year period between the Schantz et al. (1992) study and examination by Rier et al. (1993) is unknown (not reported); (2) Boyd et al. (1995) did not find an association between exposure to CDDs, CDFs, or PCBs and endometriosis in a clinical study in women; and (3) the EPA (1997) concluded that "the evidence for supporting the hypothesis that CDDs and PCBs are causally related to human endometriosis via an endocrine-disruption mechanism is very weak." So, even though there is information to indicate that endometriosis may also be a sensitive toxicological end point for 2,3,7,8-TCDD exposure, the developmental end point (altered social behavior) reported in the Schantz et al. (1992) study was determined to be the most appropriate end point for derivation of an MRL for chronic oral 2,3,7,8-TCDD exposure.

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX B

Update to the ATSDR Policy Guideline for Dioxins and Dioxin-Like Compounds in Residential Soil

Purpose

The Agency for Toxic Substances and Disease Registry (ATSDR) is updating its *Policy Guideline for Dioxins and Dioxin-Like Compounds in Residential Soil*.

The primary objective of this update is to ensure that ATSDR health assessors evaluate dioxin levels that exceed the ATSDR established screening level of 0.05 ppb as described in the ATSDR Public Health Assessment Guidance Manual (PHAGM) (ATSDR 2005). The 0.05 ppb value should be used as the comparison value when following the PHAGM. The comparison value is not a threshold for toxicity and should not be used to predict adverse health effects (ATSDR 2005).

This update replaces Appendix B in the Toxicological Profile for Chlorinated Dibenzo-p-dioxins (CDDs) (December, 1998). It does not reflect a change in ATSDR's scientific assessment on dioxin toxicity or a change in the ATSDR Minimal Risk Level (MRL). The update does not change the assessment of risk associated with dioxin soil levels up to 1 ppb, the level used by EPA as a preliminary remediation goal for residential soils (EPA 1998).

History of the Dioxin Policy Guideline

In 1998, ATSDR adopted a Policy Guideline for Dioxin and Dioxin-like Compounds (ATSDR, 1998). The policy was developed to guide health assessors in evaluating the public health implications of dioxin and dioxin-like compounds (including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and other structurally related halogenated aromatic hydrocarbons) in residential soils near or on hazardous waste sites. The guideline established three levels as criteria for comparing dioxin levels in residential soil:

- a **screening level**,
- an **evaluation level**, and
- an **action level**.

The guideline also recommended specific considerations for public health actions within each of these levels.

Since the release of the Policy Guidance, ATSDR has issued the PHAGM. ATSDR would like to ensure that health assessors use the screening level as the appropriate comparison value for following the PHAGM, rather than the "action level" described in the earlier version of this policy guidance. This does not reflect a change in dioxin science; it is simply a reiteration to

ensure that the appropriate value is used as a starting point when following the procedures described in the PHAGM.

If health assessors follow the PHAGM, the evaluation and action levels values, as set in 1999, are no longer necessary.

Changes Being Made to the ATSDR Policy Guideline for Dioxins and Dioxin-Like Compounds in Residential Soil

The specific changes to the policy guideline, the reason for those changes, and the expected impact of those changes are summarized in the following table:

Change	Reason for Change	Impact of Change
Elimination of the "evaluation level" and the "action level"	Confusion about interpretation of the evaluation and action levels was a barrier to a more consistent evaluation of exposure to dioxin in residential soils.	This change brings the guidelines up-to-date with ATSDR's PHAGM which uses only screening levels
Strengthened emphasis on exposure pathway analysis beyond direct soil contact	Dietary sources and indirect exposure pathways may make a significant contribution to dioxin exposure.	Assessing both direct and indirect exposure pathways should result in a more comprehensive evaluation of exposure conditions at residential sites with dioxin contamination.

Summary

This policy update replaces Appendix B in the Toxicological Profile for Chlorinated Dibenzo-p-dioxins (CDDs) (December, 1998). ATSDR will no longer refer to an Action Level for dioxin in these evaluations. The 0.05 ppb screening level is retained as an initial comparison value for health assessments. The update does not change the assessment of health hazards associated with dioxin exposure, as summarized in the 1998 ATSDR Toxicological Profile and in the derivation of the Minimum Risk Level (MRL). The policy update impacts site-specific health assessments evaluating exposure to dioxin directly from residential soils. The update ensures consistency in the methodology ATSDR uses for site-specific evaluations of health risks for all chemicals.

EPA's preliminary remediation goal for dioxin in soil has not changed and remains at 1 ppb. ATSDR does not establish clean-up goals or preliminary remediation goals, but ATSDR believes that health risks associated with levels of dioxins in soil below 1 ppb would be low under most scenarios where the primary exposure pathway is incidental ingestion through direct exposure to soil. Additional measures to minimize exposure to dioxins may be necessary when dioxin from soil can enter the food chain pathway.

References

ATSDR. 1998. Toxicological profile for Chlorinated Dibenzo-p-Dioxins. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

ATSDR. 2005. Public health assessment guidance manual. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

EPA. 1998. Approach for Addressing Dioxin in Soil at CERCLA and RCRA Sites. Washington, DC: US Environmental Protection Agency. OSWER Directive 9200.4-26; April 13, 1998.

APPENDIX C

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

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) 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, minimal risk levels (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 No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(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. When sufficient data exists, 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 Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) 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 2 "18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "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 regimen 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 1,1,2,2-Tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 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, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (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 Lowest-Observed-Adverse-Effect Level (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 8 of the profile.

(11) CEL A Cancer Effect Level (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 the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

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 intermediate and chronic 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, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. 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 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level 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 6

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

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

[a] The number corresponds to entries in Figure 2-1.

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-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).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section 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 section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, 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 section. If data are located in the scientific literature, a table of genotoxicity information is included.

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 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (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. They 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 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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 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 LSE Tables.

APPENDIX D

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
2,4,5-TCP	2,4,5-trichlorophenol
AAH	arylhydrocarbon hydroxylase
ACGIH	American Conference of Governmental Industrial Hygienists
ACOH	acetanylide-4-hydroxylase
ACTH	adenocorticotropin
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
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
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
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
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CTL	cytotoxic T-lymphocyte
CWA	Clean Water Act
d	day
Derm	dermal
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/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DTH	delayed-type hypersensitivity
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EGF	epidermal growth factor
EPA	Environmental Protection Agency
EROD	ethoxyresorufin-O-deethylase
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
ft	foot
FR	*Federal Register*
FSH	follicle-stimulating hormone
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GGT	gamma-glutamyl transferase
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HDL	high density lipoprotein
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
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_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LDL	low density lipoprotein
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LH	lteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MFO	mxed-function oxidase
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
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
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NK cells	natural killer cells
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
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
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
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
PEPCK	phosphoenolpyruvate carboxykinase
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio

SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
SRBC	sheep red blood cell
STEL	short-term exposure limit
STORET	Storage and Retrieval
T_3	triidothyronine
T_4	thyroxine
TdO	2,3-dioxygenase
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TSH	thyroid-stimulating hormone
TRI	Toxics Release Inventory
TTR	transthyretin
TWA	time-weighted average
UDPGT	UDP-glucuronosyltransferase
U.S.	United States
UF	uncertainty factor
VLDL	very low density lipoprotein
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

>	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