APPENDIX 3 - MRLs AND EMEGs FOR TCDD

CURRENT MRLs

ATSDR published the *Toxicological Profile for TCDD* (ATSDR, 1989). Minimal risk levels (MRLs) listed in the profile were for acute, intermediate-duration, and chronic oral exposures (see Table 3-1).

**Acute Oral MRL**

The acute oral MRL of 100 pg/kg/day was based on hepatotoxic effects in guinea pigs that were observed following administration of a single gavage dose of 0.1 μg/kg TCDD (Turner and Collins, 1983).

An uncertainty factor of 10 was used for extrapolation from animals to humans, a factor of 10 for human variability, and a factor of 10 for the use of a lowest-observed-adverse-effect level (LOAEL).

**Intermediate Oral MRL**

The LOAEL of 0.001 μg/kg/day was considered for derivation of the intermediate-duration oral MRL of 1 pg/kg/day. At this exposure level, dilated pelvices and changes in gestational index were observed in rats (Murray et al., 1979) and abortions were reported in monkeys (Allen et al., 1979).

An uncertainty factor of 10 was used for extrapolation from animals to humans, a factor of 10 for human variability, and a factor of 10 for the use of a LOAEL.

**Chronic Oral MRL**

The intermediate-duration oral MRL of 1 pg/kg/day was also adopted as the chronic oral MRL.

PROPOSED MRLs

The *Toxicological Profile for CDDs* was in a draft stage in 1993/1994. The internal MRL workgroup proposed oral MRLs for TCDD (see Table 3-1).

**Acute Oral MRL**

The acute oral MRL of 20 pg/kg/day was based on the LOAEL of 0.01 μg/kg/day TCDD that induced suppressed serum complement activity in B6C3F1 mice exposed to 14 daily doses administered by gavage-in-oil vehicle (White et al., 1986).

An uncertainty factor of 10 was used for extrapolation from animals to humans, a factor of 10 for human variability, and a factor of 10 for the use of a LOAEL. Furthermore, a modifying factor of 0.5 was applied to adjust for the difference in higher bioavailability of TCDD from gavage-in-oil vehicle than from food or soil.
Intermediate Oral MRL
The intermediate-duration oral MRL of 7 pg/kg/day was based on a no-observed-adverse-effect level (NOAEL) of 0.0007 µg/kg/day TCDD for decreased thymus weight in guinea pigs exposed for 90 days in their feed (DeCaprio et al., 1986). The LOAEL in the study was 0.005 µg/kg/day.

An uncertainty factor of 10 was used for interspecies extrapolation and a factor of 10 for human variability. The NOAEL for deriving an intermediate-duration exposure MRL is also supported by the same level NOAEL for liver effects in the DeCaprio et al. study. The liver effects reported at higher levels consisted of hepatocellular inclusions and hypertriglyceridemia.

Chronic Oral MRL
A chronic oral MRL of 0.7 pg/kg/day was based on a LOAEL of 0.0002 µg/kg/day TCDD in the feed of monkeys that resulted in mild learning and behavioral impairment in their offspring (Bowman et al., 1989).

An uncertainty factor of 3 was used for the use of a minimal LOAEL, a factor of 10 was used for interspecies extrapolation, and a factor of 10 for human variability.

Environmental media evaluation guides (EMEGs) are media-specific comparison values that are used to select contaminants of concern at hazardous waste sites.

EMEGs are derived for air, water, and soil environmental media. They are based on inhalation and oral MRLs for air and water/soil exposures, respectively. The methodology and formula for derivation of EMEGs are described in ATSDR’s Public Health Assessment Guidance Manual (ATSDR, 1992).

EMEGs are estimates of external dose. They do not provide data on how much of the dose is actually absorbed. No EMEGs are available for the dermal exposure route.

EMEGs based on these MRLs are presented in Tables 3-2a and 3-2b.
TABLE 3-1. MRLs' for TCDD

<table>
<thead>
<tr>
<th>Year</th>
<th>Exposure duration</th>
<th>MRL* in pg/kg/day</th>
<th>UF LOAEL/NOAEL</th>
<th>UF interspecies sensitivity</th>
<th>UF</th>
<th>MF*</th>
<th>End point</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>acute</td>
<td>100</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
<td>LOAEL for hepatotoxicity guinea pigs</td>
<td>Turner and Collins, 1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LOAEL for abortions and other reproductive, developmental effects rats, monkeys</td>
<td>Murray et al., 1979</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LOAEL for abortions and other reproductive, developmental effects rats, monkeys</td>
<td>Allen et al., 1979</td>
</tr>
<tr>
<td></td>
<td>intermediate</td>
<td>1</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
<td>LOAEL for suppressed serum complement activity mice</td>
<td>Murray et al., 1979</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NOAEL for decreased thymus weight: liver toxicity guinea pigs</td>
<td>Allen et al., 1979</td>
</tr>
<tr>
<td>1994</td>
<td>acute</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>0.5</td>
<td></td>
<td>LOAEL for mild learning and behavioral impairment monkey offspring</td>
<td>White et al., 1986</td>
</tr>
<tr>
<td></td>
<td>intermediate</td>
<td>7</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td>NOAEL for decreased thymus weight: liver toxicity guinea pigs</td>
<td>DeCaprio et al., 1986</td>
</tr>
<tr>
<td>1994</td>
<td>chronic</td>
<td>0.7</td>
<td>3</td>
<td>10</td>
<td>10</td>
<td></td>
<td>LOAEL for suppressed serum complement activity mice</td>
<td>Bowman et al., 1989</td>
</tr>
</tbody>
</table>

The MRL is calculated as MRL = (NOAEL or LOAEL)/(UF x MF), where MRL = minimal risk level (mg/kg/day), NOAEL = no-observed-adverse-effect level (mg/kg/day), LOAEL = lowest-observed-adverse-effect level (mg/kg/day), UF = uncertainty factor (unitless), MF = modifying factor (unitless) **MF for bioavailability was used in the derivation of an acute MRL (1994)

TABLE 3-2a. EMEGs (in ppb) Based on 1989 TCDD MRLs

<table>
<thead>
<tr>
<th>Exposure duration</th>
<th>Child</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute</td>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td>intermediate</td>
<td>0.05</td>
<td>0.7</td>
</tr>
<tr>
<td>chronic</td>
<td>0.05</td>
<td>0.7</td>
</tr>
</tbody>
</table>

TABLE 3-2b. EMEGs (in ppb) Based on 1994 TCDD MRLs

<table>
<thead>
<tr>
<th>Exposure duration</th>
<th>Child</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>intermediate</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>chronic</td>
<td>0.04</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The EMEG is calculated as EMEG = (MRL)(BW)/IR, where EMEG = environmental media evaluation guide (mg/kg), BW = body weight in kg (adult = 70 kg: child = 10 kg), IR = soil ingestion rate (mg/day) (adult = 100 mg/day: child = 200 mg/day)
APPENDIX 4 - RECENT HEALTH EFFECTS STUDIES

Introduction
A significant number of toxicological studies have been conducted since the development of the 1 ppb action level for dioxin and dioxin-like compounds in residential soil. Many of these studies have examined human health effects after known or suspected exposure. In addition, in these intervening years, analytical techniques have been perfected to permit determination of very low levels of dioxin and dioxin-like compounds in environmental and biologic media. Significant advances have also been made in assessing possible health effects associated with exposure. This appendix is a synopsis of this more recent information.

Mechanism of Action
Recent studies have indicated that dioxin and dioxin-like compounds act through the same mechanism of action mediated by the Ah receptor, and that responses to their toxicity have been shown to be similar in several species (Birnbaum, 1994; DeVito et al., 1995).

Human Studies
Direct exposure information is generally not available in human studies, and so body burden is used as a surrogate. In this approach, the exposure is estimated from measured body burden, the elimination rate for humans, and the time since the exposure incident. Positive correlations have been observed between dioxin exposure and cancer (Fingerhut et al., 1991; Zober et al., 1990; Manz et al., 1991). More recent studies on cohorts investigated previously confirmed the association between dioxin exposure and higher cancer mortality (Flesch-Janys et al., 1995; Becher et al., 1996; Ott and Zober, 1996). The correlation was dose-dependent and increased with the latency period. IARC (1997) classified TCDD as a Group 1 carcinogen (carcinogenic to humans).

For health end points other than cancer, epidemiologic studies suggest a positive correlation between exposure to TCDD and development of chloracne (Mocarelli et al., 1986; Pazderova-Vejlupkova et al., 1981; Reggiani, 1980; Zober et al., 1990), dermal hyperpigmentation and hirsutism (Poland et al., 1971; Jirasek et al., 1974), elevated hepatic enzyme levels, mainly γ-glutamyl transferase (Mocarelli et al., 1986; May, 1982), and increased risk of diabetes (Sweeney et al., 1997; Table 4-1).

Other studies showed an association between development of subtle health effects (e.g., lower vitamin K levels, mild changes in liver enzymes, decreased neurologic optimality, and subtle changes in hormonal levels) in infants and their exposure to dioxin and dioxin-like chemicals from maternal milk (Pluim et al., 1992, 1994a, 1994b; Huisman et al., 1995; Koopman-Esseboom et al., 1994; Table 4-2). It is important to note that in reviewing the issues surrounding breastfeeding, the World Health Organization has concluded that the risks to infants do not outweigh the positive biologic and psychologic aspects of breastfeeding (Johnson, 1992a).
It has been suggested that dioxin and dioxin-like chemicals have the ability to disrupt endocrine function at low levels of exposure. A recent study of the cohort of people exposed during the Seveso accident indicated an alteration of the human sex ratio in their offspring (Mocarelli et al., 1996). In the 7-year period following the exposure, 26 males versus 48 females were born, but the study was limited by not providing information on sex-related spontaneous abortions in the cohort. A study of occupationally exposed workers reported altered reproductive hormone levels (Egeland et al., 1992). Other studies indicate low-exposure contamination of maternal milk with dioxin and dioxin-like compounds may have an impact on the hypothalamic-pituitary-thyroid regulatory system in newborns (Pluim et al., 1992; Koopman-Esseboom et al., 1994).

Animal Studies

Studies in animals demonstrated a wide range of effects associated with CDDs exposure including mortality, cancer, wasting, and hepatic, immunologic, neurologic, reproductive, and developmental effects (ATSDR, 1989). In support of the findings that showed endocrine system disruption in humans, studies in animals reported that TCDD affects the adrenal (DiBartolomeis et al., 1987; Gorski et al., 1988a, 1988b) and thyroid glands (Hermansky et al., 1988; Hong et al., 1987; Lu et al., 1986; Henry and Gasiewicz, 1987; Rozman et al., 1985) and also alters estradiol (Umbrecht et al., 1987), testosterone, and dihydrotestosterone levels (Mebus et al., 1987; Moore et al., 1985). TCDD decreased responsiveness of the ventral prostate to testosterone in male offspring of exposed female rats and inhibited sexual differentiation in the central nervous system without altering sexual dimorphism in estrogen-receptor concentrations (Bjerke et al., 1994; Bjerke and Peterson, 1994). In animal studies, effects have been seen with the lowest doses evaluated, with the most sensitive end point being neurobehavioral changes in the offspring of dioxin-exposed monkeys (Schantz et al., 1992). A summary of critical study results and observed effect levels is presented in Table 4-3.

Body Burdens and Associated Health Effects

Health effects reported from human studies and associated body burdens of TCDD are listed in Table 4-1; these body burdens range from concentrations of 18 to 2,357 ng/kg. As can be seen from a comparison of animal and human studies shown in Table 4-3, body burden concentrations calculated for effect dosage rates in animal studies are in the same range as body burden concentrations associated with health effects in human studies. These results underscore the need for research to elucidate the toxicity of dioxin at low doses to human populations (CCEHRP, 1992) and to evaluate exposures in at-risk populations in view of total body burdens of dioxin and dioxin-like compounds.

Based on this review of more recent data, ATSDR has determined that its MRL of 1 pg/kg/day for TCDD is approximately two orders of magnitude below the health effect levels observed in recent studies. This is also true of cancer effect levels (Kociba et al., 1978). Independently, the Health Council of the Netherlands (1996) reassessed the risk associated with dioxin and dioxin-like compounds based on recent studies and recommended a health-based exposure limit equal to 1 pg/kg/day total TEQs.
ATSDR concludes that the chronic oral MRL of 1 pg/kg/day TCDD is protective of public health based on the fact that the MRL is approximately two orders of magnitude below the effect levels demonstrated experimentally and in epidemiologic studies.

**TABLE 4-1. Health Effects Associated with Exposure to TCDD and Body Burdens in Humans**

<table>
<thead>
<tr>
<th>Duration of exposure</th>
<th>System</th>
<th>Effect</th>
<th>Body burdens ng/kg body weight</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>Dermal</td>
<td>Chloracne in children</td>
<td>2357&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mocarelli et al., 1991</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>Reproductive</td>
<td>No increased risk of spontaneous abortion</td>
<td>&gt; 24&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Wolfe et al., 1995</td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>Gastrointestinal</td>
<td>No increased risk of clinical gastrointestinal disease</td>
<td>418&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Calvert et al., 1992</td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>Hepatic</td>
<td>No increased risk of clinical hepatic disease</td>
<td>418&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Calvert et al., 1992</td>
</tr>
<tr>
<td>Not specified</td>
<td>Dermal</td>
<td>Chloracne in 577 subjects</td>
<td>80.5&lt;sup&gt;d&lt;/sup&gt; 18&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Schecter et al., 1993</td>
</tr>
<tr>
<td>11 years</td>
<td>Dermal</td>
<td>Chloracne</td>
<td>646&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Jansing and Korff, 1994</td>
</tr>
<tr>
<td>6.5 years</td>
<td>Immunologic</td>
<td>Immunosuppression</td>
<td>156–176&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Tonn et al., 1996</td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>Neurologic</td>
<td>No increased risk for peripheral neuropathy</td>
<td>418&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Sweeney et al., 1993</td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>Reproductive</td>
<td>Increased prevalence of high luteinizing hormone and low testosterone levels</td>
<td>31&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Egeland et al., 1994</td>
</tr>
<tr>
<td>Not specified</td>
<td>Genotoxicity</td>
<td>No chromosome aberrations or sister chromatid exchanges</td>
<td>63–833&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Zober et al., 1993</td>
</tr>
<tr>
<td>≥ 1 year</td>
<td>Cancer</td>
<td>Increased cancer mortality risk</td>
<td>124–459&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Fingerhut et al., 1991</td>
</tr>
<tr>
<td>≥ 20 years</td>
<td>Cancer</td>
<td>Increased cancer mortality rate</td>
<td>69–461&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Manz et al., 1991</td>
</tr>
<tr>
<td>TABLE 4-1. Health Effects Associated with Exposure to TCDD and Body Burdens in Humans (cont’d)</td>
<td></td>
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<tr>
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</tr>
<tr>
<td>^c^Calculated using serum TCDD levels measured shortly after exposure. Body burdens were calculated using body weights of 13 kg for 1–3 year olds, 20 kg for 4–6 year olds, 28 kg for 7–10 year olds, 45 kg for 11-year-old males, and 55 kg for 16-year-old females and body fat percentages of 15% for 0–10 year olds, 15% for 11-year-old males, and 20% for 16-year-old females (ICRP, 1981).</td>
<td></td>
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</tr>
<tr>
<td>^d^Calculated using the reported mean half-life adjusted serum TCDD level of &gt;110 ppt and assuming the average worker weighed 70 kg with 22% body fat (DeVito et al., 1995). The authors calculated the half-life adjusted serum TCDD level using a half-life of 7.1 years.</td>
<td></td>
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</tr>
<tr>
<td>^e^Calculated using the reported mean half-life adjusted serum TCDD level of 1900 pg/g lipid and assuming the average worker weighed 70 kg with 22% body fat (DeVito et al., 1995).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>^f^Calculated by averaging the reported individual body burdens divided by the reference body weight of 75 kg for males and 65 kg for females. The authors calculated half-life adjusted serum TCDD levels using the assumption of 75 kg and 65 kg body weights for male and female workers, respectively, and a half-life of 5 years.</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>^g^Same as footnoted, but using a half-life of 10 years.</td>
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<tr>
<td>^h^Calculated using the reported mean half-life adjusted serum TCDD level of 2935 pg/g blood fat and assuming the average worker weighed 70 kg with 22% body fat (DeVito et al., 1995). The authors calculated the half-life adjusted serum TCDD level using a half-life of 7 years.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>^i^Calculated using the reported mean current serum TCDD level of 329.5 pg/g blood lipid. Half-life adjusted serum TCDD level was calculated using a half-life of 11.6 years (Wolfe et al., 1994), background TCDD concentration of 5 ng/kg lipid, and 13–15 years elapsed time. Body burdens were calculated assuming the average worker weighed 70 kg with 22% body fat (DeVito et al., 1995).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>^j^Calculated using the reported mean current serum TCDD level of 15 ppt. Half-life adjusted serum TCDD levels were calculated using a half-life of 11.6 years (Wolfe et al., 1994), background TCDD concentration of 5 ng/kg lipid, and 34 years of elapsed time. Body burdens were calculated assuming the average worker weighed 70 kg with 22% body fat (DeVito et al., 1995).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculated using the reported mean of current serum TCDD levels of 340–472 ppt (based on lipid content of blood). Half-life adjusted serum TCDD levels were calculated using a half-life of 11.6 years (Wolfe et al., 1994), background TCDD concentration of 5 ng/kg lipid, and 35 years of elapsed time. Body burdens were calculated assuming the average worker weighed 70 kg with 22% body fat (DeVito et al., 1995).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>^k^Calculated using the reported mean current serum TCDD level of 233 pg/g lipid. Half-life adjusted serum TCDD levels were calculated using a half-life of 11.6 years (Wolfe et al., 1994), background TCDD concentration of 5 ng/kg lipid, and 35 years of elapsed time. Body burdens were calculated assuming the average worker weighed 70 kg with 22% body fat (DeVito et al., 1995).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>^l^Calculated using the reported mean current adipose tissue TCDD level of 296 ng/kg. Half-life adjusted adipose TCDD levels were calculated using a half-life of 11.6 years (Wolfe et al., 1994), background TCDD concentration of 5 ng/kg lipid, and 1–33 years of elapsed time.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Children</td>
<td>Breast milk levels (mean levels in pg of TEQs per g of milk fat)</td>
<td>Health Effects</td>
<td>References</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------------------------------------</td>
<td>----------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>(29.85–92.88)</td>
<td>Late-type hemorrhagic disease of newborns correlated with increased TCDD levels in maternal milk</td>
<td>Koppe et al., 1991</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>29.4 (13.7–62.6)</td>
<td>Decreased vitamin K$_i$ and decarboxylated prothrombin levels in infants correlated with increased 2,3,7,8-tetraCDF and 1,2,3,6,7,8-hexaCDF levels, respectively, in breast milk at 11 weeks of age</td>
<td>Pluim et al., 1994a</td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>&gt; 30.75</td>
<td>Higher CDD and CDF levels in breast milk correlated with higher plasma levels of TSH in infants in 2nd week and 3rd month postnatally</td>
<td>Koopman-Esseboom et al., 1994</td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>30.19</td>
<td>Higher CDD and CDF levels were related to reduced neonatal neurologic optimality</td>
<td>Huisman et al., 1995</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>not specified</td>
<td>Higher exposure to CDDs in breast milk was associated with increase in total T cells and lower monocyte and granulocyte counts</td>
<td>Weisglas-Kuperus et al., 1995</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>28.1 (8.7–62.7)</td>
<td>Cumulative intake correlated with ALT and AST plasma activities; inverse correlation was found between cumulative intake and number of platelets at 11 weeks of age</td>
<td>Pluim et al., 1994b</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>37.5 (29.2–62.7) high exposure group</td>
<td>Increased thyroxine levels and increased thyroxine/thyroid binding globulin ratios in a group with higher breast milk exposure as compared to lower exposure group</td>
<td>Pluim et al., 1992</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>18.6 (8.7–28.0) low exposure group</td>
<td>Baseline control values</td>
<td>Pluim et al., 1992</td>
<td></td>
</tr>
</tbody>
</table>

AST = aspartate aminotransferase; ALT = alanine aminotransferase; TEQs = toxicity equivalents; TSH = thyroid-stimulating hormone
<table>
<thead>
<tr>
<th>Duration of exposure</th>
<th>System</th>
<th>Effect</th>
<th>Body burdens ng/kg body weight</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies in humans</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>Dermal</td>
<td>Chloracene in children</td>
<td>2357&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mocarelli et al., 1991</td>
</tr>
<tr>
<td></td>
<td>Dermal</td>
<td>Chloracene in 5/7 subjects</td>
<td>80.5&lt;sup&gt;e&lt;/sup&gt; 18&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Schecter et al., 1993</td>
</tr>
<tr>
<td>11 years</td>
<td>Dermal</td>
<td>Chloracene</td>
<td>646&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Jansing and Korff, 1994</td>
</tr>
<tr>
<td>6.5 years</td>
<td>Immunologic</td>
<td>Immunosuppression</td>
<td>156-176&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Tonn et al., 1996</td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>Reproductive</td>
<td>Increased prevalence of high luteinizing hormone and low testosterone levels</td>
<td>31&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Egeland et al., 1994</td>
</tr>
<tr>
<td>≥ 1 year</td>
<td>Cancer</td>
<td>Increased cancer mortality risk</td>
<td>124-459&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Fingerhut et al., 1991</td>
</tr>
<tr>
<td>&gt; 20 years</td>
<td>Cancer</td>
<td>Increased cancer mortality rate</td>
<td>69-461&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Manz et al., 1991</td>
</tr>
<tr>
<td>Studies in animals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 days</td>
<td>Immunologic</td>
<td>Suppressed serum complement in mice</td>
<td>74&lt;sup&gt;e&lt;/sup&gt;</td>
<td>'White et al., 1986</td>
</tr>
<tr>
<td>90 days</td>
<td>Reproductive</td>
<td>Decreased litter size in rats</td>
<td>26&lt;sup&gt;e&lt;/sup&gt;</td>
<td>'Murray et al., 1979</td>
</tr>
<tr>
<td>90 days</td>
<td>Immunologic</td>
<td>Decreased thymus weight in guinea pigs</td>
<td>164&lt;sup&gt;e&lt;/sup&gt;</td>
<td>'DeCaprio et al., 1986</td>
</tr>
<tr>
<td>16 months</td>
<td>Developmental</td>
<td>Behavioral alterations in offspring in monkeys</td>
<td>32&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Schantz et al., 1992</td>
</tr>
<tr>
<td>2 years</td>
<td>Cancer</td>
<td>Liver, lung carcinoma in rats</td>
<td>2976&lt;sup&gt;±&lt;/sup&gt;</td>
<td>Kociba et al., 1978</td>
</tr>
<tr>
<td>2 years</td>
<td>Cancer</td>
<td>Liver carcinoma in mice</td>
<td>944&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NTP, 1972</td>
</tr>
</tbody>
</table>
TABLE 4-3. Human Body Burdens and Animal Body Burdens Associated with Health Effects (cont’d)

<table>
<thead>
<tr>
<th>Study Description</th>
<th>TCDD Levels</th>
<th>Body Fat</th>
<th>Time</th>
<th>Background TCDD</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Studies which serve as the basis for ATSDR’s health guidance values</td>
<td>Calculated using serum TCDD levels measured shortly after exposure. Body burdens were calculated using body weights of 13 kg for 1–3 year olds, 20 kg for 4–6 year olds, 28 kg for 7–10 year olds, 45 kg for 11-year-old males, and 55 kg for 16-year-old females and body fat percentages of 15% for 0–10 year olds, 15% for 11-year-old males, and 20% for 16-year-old females (ICRP, 1981).</td>
<td>Calculated by averaging the reported individual body burdens divided by the reference body weight of 75 kg for males and 65 kg for females. The authors calculated half-life adjusted serum TCDD levels using the assumption of 75 kg and 65 kg body weights for male and female workers, respectively, and a half-life of 5 years.</td>
<td>Same as footnote d but using a half-life of 10 years.</td>
<td>Calculated using the mean half-life adjusted serum TCDD level of 2935 pg/g blood fat and assuming the average worker weighed 70 kg with 22% body fat (DeVito et al., 1995). The authors calculated the half-life adjusted serum TCDD level using a half-life of 7 years.</td>
<td>Calculated using the mean current serum TCDD level of 329.5 pg/g blood lipid. Half-life adjusted serum TCDD level was calculated using a half-life of 11.6 years (Wolfe et al., 1994), background TCDD concentration of 5 ng/kg lipid, and 13–15 years elapsed time. Body burdens were calculated assuming the average worker weighed 70 kg with 22% body fat (DeVito et al., 1995).</td>
</tr>
<tr>
<td>Calculated using the reported mean current serum TCDD level of 233 pg/g lipid. Half-life adjusted serum TCDD levels were calculated using a half-life of 11.6 years (Wolfe et al., 1994), background TCDD concentration of 5 ng/kg lipid, and 35 years of elapsed time. Body burdens were calculated assuming the average worker weighed 70 kg with 22% body fat (DeVito et al., 1995).</td>
<td>Calculated using the reported mean current adipose tissue TCDD level of 296 ng/kg. Half-life adjusted adipose TCDD levels were calculated using a half-life of 11.6 years (Wolfe et al., 1994), background TCDD concentration of 5 ng/kg lipid, and 1–33 years of elapsed time. Body burdens were calculated assuming the average worker weighed 70 kg with 22% body fat (DeVito et al., 1995).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX 5 - CHRONOLOGY FOR DIOXIN AND DIOXIN-LIKE COMPOUNDS:
HEALTH GUIDANCE VALUES AND POLICY STATEMENTS

1984  
R. Kimbrough, H. Falk, and P. Stehr (1984) recommended 1 ppb of TCDD in soil as a level of concern for human health. They also concluded that “One ppb of 2,3,7,8-TCDD in soil is a reasonable level at which to begin consideration of action to limit human exposure for contaminated soil” (emphasis added) (p. 47). However, the authors cautioned not to use this level for every site, but rather to estimate the risk associated with each site according to specific circumstances at the site.

The estimated risk dose was 1.4 pg/kg/day TCDD (a 95% upper bound for a one-in-a-million risk estimate for cancer). The calculations were based on cancer studies in laboratory animals.

1985  
EPA derived oral slope factor, q1, of 1.56 x 10^3 (mg/kg/day)^-1 for TCDD (EPA, 1985) that represents the mean 95% upper-limit carcinogenic potency factor for humans. Based on this factor, a risk-specific dose of 0.006 pg/kg/day TCDD was calculated.

1989  
ATSDR published the Toxicological Profile for TCDD. The profile describes the use of toxicity equivalents (TEQs) for assessing exposure to dioxin and dioxin-like compounds. MRLs for TCDD listed in the profile for the acute, intermediate-duration, and chronic exposures were 100 pg/kg/day, 1 pg/kg/day, and 1 pg/kg/day, respectively. Developmental and reproductive end points were the bases for intermediate and chronic duration MRLs. Based on the chronic MRL, the EMEG of 50 ppt is typically used in public health assessments for dioxin contaminated soil.

1990  
The Food and Drug Administration (1990) introduced a risk-specific dose of 0.057 pg/kg/day TCDD (a 95% upper bound for a one-in-a-million risk estimate for cancer). The number was based on a linear low-dose extrapolation from the Kociba et al. (1978) cancer study in rats. The value applied to consumption of contaminated food, specifically fish.

1992  
The Public Health Service Committee to Coordinate Environmental Health and Related Programs (CCEHPR) recommended, in the Interim Statement on Dioxins, to adopt the FDA risk-specific dose (0.057 pg/kg/day) as the risk-specific level for TCDD equivalents (TEQs).

1992  
In a memo to ATSDR senior management, B. Johnson stated that “The Interim Statement, while mentioning FDA’s tolerable daily intake of dioxin as 0.057 pg/kg/day, should not be understood to supplant ATSDR’s position of 1 ppb of dioxin in residential soil as a soil action level.” Consistent with the CCEHPR statement, ATSDR’s practice incorporates the TEQ approach.
The Toxicological Profile for CDDs was in a draft stage. The internal MRL workgroup met with representatives of other ATSDR divisions and proposed MRLs for TCDD for the acute, intermediate-duration, and chronic exposures as 20 pg/kg/day, 7 pg/kg/day, and 0.7 pg/kg/day, respectively. Developmental effects were the bases for derivation of the chronic MRL.

Pohl et al. (1995) published the “Public health assessment for dioxins exposure from soil” paper.

This paper reviewed more recent findings on the potential health effects of dioxin. Based upon this review, Pohl et al. presented a proposed chronic MRL for TCDD of 0.7 pg/kg/day and a corresponding EMEG of 40 ppt for children.

From a health risk assessment perspective, the EMEG of 40 ppt is not substantially different from the current EMEG of 50 ppt based on the 1 pg/kg/day MRL (ATSDR, 1989). The MRL of 1 pg/kg/day is approximately two orders of magnitude below effect levels demonstrated experimentally or in epidemiologic studies.
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