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 pelvises 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

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

*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

Exposure duration	Child	Adult
acute	5	70
intermediate	0.05	0.7
chronic	0.05	0.7

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

Exposure duration	Child	Adult
acute	1	14
intermediate	5	5
chronic	0.04	0.5

*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., 1992; 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 (Umbreit 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**

Duration of exposure	System	Effect	Body burdens ng/kg body weight	Reference
< 1 year	Dermal	Chloracne in children	2357[a]	Mocarelli et al., 1991
< 1 year	Reproductive	No increased risk of spontaneous abortion	> 24[b]	Wolfe et al., 1995
≥ 15 years	Gastrointestinal	No increased risk of clinical gastrointestinal disease	418[c]	Calvert et al., 1992
≥ 15 years	Hepatic	No increased risk of clinical hepatic disease	418[c]	Calvert et al., 1992
Not specified	Dermal	Chloracne in 5/7 subjects	80.5[d] 18[e]	Schecter et al., 1993
11 years	Dermal	Chloracne	646[f]	Jansing and Korff, 1994
6.5 years	Immunologic	Immunosuppression	156–176[g]	Tonn et al., 1996
≥ 15 years	Neurologic	No increased risk for peripheral neuropathy	418[c]	Sweeney et al., 1993
≥ 15 years	Reproductive	Increased prevalence of high luteinizing hormone and low testosterone levels	31[h]	Egeland et al., 1994
Not specified	Genotoxicity	No chromosome aberrations or sister chromatid exchanges	63-833[i]	Zober et al., 1993
≥ 1 year	Cancer	Increased cancer mortality risk	124–459[j]	Fingerhut et al., 1991
≥ 20 years	Cancer	Increased cancer mortality rate	69–461[k]	Manz et al., 1991

TABLE 4-1. **Health Effects Associated with Exposure to TCDD and Body Burdens in Humans (cont'd)**

[a]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).

[b]Calculated using the reported mean half-life adjusted serum TCDD level of > 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.

[c]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).

[d]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.

[e]Same as footnoted, but using a half-life of 10 years.

[f]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.

[g]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).

[h]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).

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).

[j]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).

[k]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.

TABLE 4-2. **Breast Milk Levels of Total TEQs Associated with Health Effects in Human Infants**

Number of Children	Breast milk levels (mean levels in pg of TEQs per g of milk fat)	Health Effects	References
17	(29.85–92.88)	Late-type hemorrhagic disease of newborns correlated with increased TCDD levels in maternal milk	Koppe et al., 1991
32	29.4 (13.7–62.6)	Decreased vitamin K_1 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	Pluim et al., 1994a
78	> 30.75	Higher CDD and CDF levels in breast milk correlated with higher plasma levels of TSH in infants in 2nd week and 3rd month postnatally	Koopman-Esseboom et al., 1994
104	30.19	Higher CDD and CDF levels were related to reduced neonatal neurologic optimality	Huisman et al., 1995
48	not specified	Higher exposure to CDDs in breast milk was associated with increase in total T cells and lower monocyte and granulocyte counts	Weisglas-Kuperus et al., 1995
35	28.1 (8.7–62.7)	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	Pluim et al., 1994b
19	37.5 (29.2–62.7) high exposure group	Increased thyroxine levels and increased thyroxine/thyroid binding globulin ratios in a group with higher breast milk exposure as compared to lower exposure group	Pluim et al., 1992
19	18.6 (8.7–28.0) low exposure group	Baseline control values	Pluim et al., 1992

AST = aspartate aminotransferase; ALT = alanine aminotransferase; TEQs = toxicity equivalents; TSH = thyroid-stimulating hormone

TABLE 4-3. **Human Body Burdens and Animal Body Burdens Associated with Health Effects**

Duration of exposure	System	Effect	Body burdens ng/kg body weight	Reference
Studies in humans				
< 1 year	Dermal	Chloracne in children	2357[a]	Mocarelli et al., 1991
Not specified	Dermal	Chloracne in 5/7 subjects	80.5[b] 18[c]	Schecter et al., 1993
11 years	Dermal	Chloracne	646[d]	Jansing and Korff, 1994
6.5 years	Immunologic	Immunosuppression	156-176[e]	Tonn et al., 1996
≥ 15 years	Reproductive	Increased prevalence of high luteinizing hormone and low testosterone levels	31[f]	Egeland et al., 1994
≥ 1 year	Cancer	Increased cancer mortality risk	124-459[g]	Fingerhut et al., 1991
> 20 years	Cancer	Increased cancer mortality rate	69–461[h]	Manz et al., 1991
Studies in animals				
14 days	Immunologic	Suppressed serum complement in mice	74[i]	White et al., 1986
90 days	Reproductive	Decreased litter size in rats	26[j]	Murray et al., 1979
90 days	Immunologic	Decreased thymus weight in guinea pigs	164[k]	DeCaprio et al., 1986
16 months	Developmental	Behavioral alterations in offspring in monkeys	32[l]	Schantz et al., 1992
2 years	Cancer	Liver, lung carcinoma in rats	2976[m]	Kociba et al., 1978
2 years	Cancer	Liver carcinoma in mice	944[n]	NTP, 1972

TABLE 4-3. **Human Body Burdens and Animal Body Burdens Associated with Health Effects (cont'd)**

*Studies which serve as the basis for ATSDR's health guidance values

[a]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).

[b]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.

[c]Same as footnote d but using a half-life of 10 years.

[d]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.

[e]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).

[f]Calculated using the reported half-life adjusted serum TCDD level of > 140 pg/g blood lipid and assuming the average worker weighed 70 kg with 22% body fat (DeVito et al., 1995). The authors calculated the adjusted serum dioxin level using a dioxin half-life of 7.1 years and background dioxin level of 6.08 pg/g blood lipid.

[g]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).

[h]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).

[i] Acute exposure study in mice (White et al., 1986). Assumed parameter values a: = 0.8 (Curtis et al., 1990), $t_{1/2}$ = 11 days (Birnbaum, 1986).

[j] Intermediate-duration exposure study in rats (Murray et al., 1979) Assumed parameter values a: = 0.8 (Curtis et al., 1990), $t_{1/2}$ = 24 days (Van den Berg et al., 1994).

[k] Assumed parameter values for guinea pigs in DeCaprio et al. (1986) study: a = 0.5 (Van den Berg et al., 1994), $t_{1/2}$ = 94 days (Olson, 1986).

[l]The lowest effect level in the current database for chronic-duration exposure. Assumed parameter values for monkeys in Schantz et al. (1992) study: a = 0.8 (value for rats from Van den Berg et al., 1994), $t_{1/2}$ = 391 days (Bowman et al., 1989).

[m]A cancer study in rats. Body burdens calculated in De Vito et al., 1995.

[n]A cancer study in mice. Body burdens calculated in De Vito et al., 1995.

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, q_1^*, of 1.56×10^5 $(mg/kg/day)^{-1}$ 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 (CCEHRP) 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 CCEHRP statement, ATSDR's practice incorporates the TEQ approach.

1993

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.

1995

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.

APPENDIX 6 - REFERENCES

AHLBORG, U.G., BECKING, G.C., BIRNBAUM, L.S., et al. (1994). "Toxic equivalency factors for dioxin-like PCBs." Chemosphere 28(6):1049–67.

ALLEN, J.R., BARSOTTI, D.A., LAMBRECHT, L.K., et al. (1979). "Reproductive effects of halogenated aromatic hydrocarbons on nonhuman primates." Ann. N.Y. Acad. Sci. 320:419–425.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1989). Toxicological Profile for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Atlanta, GA.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1992). Public Health Assessment Guidance Manual. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. NTIS PB92-147164. Atlanta, GA.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1993). Dioxin issue paper. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Atlanta, GA.

AYLWARD, L.L., HAYS, S.M., KARCH, N.J., and PAUSTENBACH, D.J. (1996). "Relative susceptibility of animals and humans to the cancer hazard posed by 2,3,7,8-tetrachlorodibenzo-p-dioxin using internal measures of dose." Environ. Sci. Technol. 30:3534–3543.

BECHER, H., FLESCH-JANYS, D., KAUPPINEN, T., KOGEVINAS, M., STEINFORF, K., MANZ, A., and WAHRENDORF, J. (1996). "Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins." Canc. Causes Control 7:312–321.

BINDER, S., SOKAL, D., and MAUGHN, D. (1986). "The use of tracer elements in estimating the amount of soil ingested by young children." Arch. Environ. Health 41:341–345.

BIRNBAUM, L.S. (1986). "Distribution and excretion of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in cogenic strains of mice which differ at the Ah locus." Drug Metab Dispos. 14:34–40.

BIRNBAUM, L.S. (1994). "The mechanism of dioxin toxicity: relationship to risk assessment." Environ Health Perspect 102 (suppl. 9):157–167.

BJERKE, D.L. and PETERSON, R.E. (1994). "Reproductive toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in male rats: different effects of *in utero* versus lactational exposure." Toxicol. Appl. Pharmacol. 127:241–249.

BJERKE, D.L., SOMMER, R.J., MOORE, R.W., and PETERSON, R.E. (1994). "Effects of *in utero* and lactational 2,3,7,8-tetrachlorodibenzo-*p*-dioxin exposure on responsiveness of the male rat reproductive system to testosterone stimulation in adulthood." Toxicol. Appl. Pharmacol 127:250–257.

BOWMAN, R.E., SCHANTZ, S.L., GROSS, M.L., et al. (1989). "Behavioral effects in monkeys exposed to 2,3,7,8-TCDD transmitted maternally during gestation and for four months of nursing." Chemosphere 18:235–242.

CALVERT, G.M., HONUNG, R.W., SWEENEY, M.H., et al. (1992). "Hepatic and gastrointestinal effects in an occupational cohort exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin." JAMA 267:2209–2214.

COMMITTEE TO COORDINATE ENVIRONMENTAL HEALTH AND RELATED PROGRAMS (CCEHRP). 1992. Internal Memorandum. U.S. Public Health Service. Washington, DC.

COUNCIL ON ENVIRONMENTAL QUALITY (CEQ) (1989). Risk Analysis: A Guide to Principles and Methods for Analyzing Health and Environmental Risks. NTIS: PB89-137772. Council on Environmental Quality. Washington, DC.

CLAUSING, P., BRUNEKREFF, B., and VAN WIJEN, J.H. (1987). "A method for estimating soil ingestion by children." Int. Arch. Occup. Environ. Health 59:73–82.

CURTIS, L.R., KERKVLIET, N.I., BAECHER-STEPPAN, L., et al. (1990). "2,3,7,8-Tetrachlorodibenzo-*p*-dioxin pretreatment of female mice altered tissue distribution but not hepatic metabolism of a subsequent dose." Fundam. Appl. Toxicol. 14:523–531.

DECAPRIO, A.P., MCMARTIN, D.M., O'KEEFE, P.W., et al. (1986). "Subchronic oral toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the guinea pig: comparisons with a PCB-containing transformer fluid pyrolysate." Fundam. Appl. Toxicol. 6:454–463.

DEVITO, M.J., BIRNBAUM, L.S., FARLAND, W.H., and GASIEWICZ, T.A. (1995). "Comparisons of estimated human body burdens of dioxin-like chemicals and TCDD body burdens in experimentally exposed animals." Environ. Health Perspect. 103(9):820–829.

DiBARTOLOMEIS, M.J., MOORE, R.W., PETERSON, R.E., et al. (1987). "Altered regulation of adrenal steroidogenesis in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-treated rats." Biochem. Pharmacol. 36:59–67.

EGELAND, G., SWEENEY, M., FINGERHUT, M.A., et al. (1992). "Serum dioxin (2,3,7,8-TCDD) and total serum testosterone, and gonadotropins in occupationally exposed men." Am. J. Epidemiol. 136:1014.

EGELAND, G.M., SWEENEY, M.G., FINGERHUT, M.A., et al. (1994). "Total serum testosterone and gonadotropins in workers exposed to dioxins." Am. J. Epidemiol. 139:272–281.

EMMETT, H. and JORDAN-IZAGUIRRe, D. (1994). Dioxin Issue Paper. Office of Regional Operations and Division of Health Assessment and Consultation, Agency for Toxic Substances and Disease Registry, Atlanta, GA (internal document).

FINGERHUT, M.A., HALPERIN, W.E., MARLOW, D.A., et al. (1991). "Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin." N. Engl. J. Med. 324:212–218.

FLESCH-JANYS, D., BECHER, H., GURN, P., JUNG, D., et al. (1996). "Elimination of polychlorinated dibenzo-p- dioxins and dibenzofurans in occupationally exposed persons." J. Toxicol. Environ. Health 47:363–378.

FLESCH-JANYS, D., BERGER, J., GURN, P., MANZ, A., NAGEL, S., WALTSGOTT, H., and DWYER, J.H. (1995). "Exposure to polychlorinated dioxins and furans and mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany." Am. J. Epidemiol. 142:1165–1175.

FRIES, G.F. and MARROW, G.S. (1975). "Retention and excretion of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin by rats." J. Agric. Food Chem. 23:265–269.

GORSKI, J.R., MUZI, G., WEBER, L.W., et al. (1988a). "Elevated plasma corticosterone levels and histopathology of the adrenals and thymuses in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-treated rats." Toxicol. 53:19–32.

GORSKI, J.R., MUZI, G., WEBER, L.W., et al. (1988b). "Some endocrine and morphological aspects of the acute toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)." Toxicol. Pathol. 16:313–320.

GOUGH, M. (1991). "Human exposures from dioxin in soil—a meeting report." J. Toxicol. Environ. Health 32:205–245.

HEALTH COUNCIL OF THE NETHERLANDS (1996). Report on Dioxins. Report available from the Health Council Secretariat.

HENRY, E.C. and GASIEWICZ, T.A. (1987). "Changes in thyroid hormones and thyroxine glucuronidation in hamsters compared with rats following treatment with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin." Toxicol. Appl. Pharmacol. 89:165–174.

HERMANSKY, S.J., HOLCZLAW, T.L., MURRAY, W.J., et al. (1988). "Biochemical and functional effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in the heart of female rats." Toxicol. Appl. Pharmacol. 95:175–184.

HODGSON, E., MAILMAN, R.B., and CHAMBERS, J.E. (1988). Dictionary of Toxicology. Van Nostrand Reinhold, New York, NY. p. 62.

HONG, L.H., McKINNEY, J.D., and LUSTER, M.I. (1987). "Modulation of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)-mediated myelotoxicity by thyroid hormones." Biochem. Pharmacol. 36:1361–1365.

HUISMAN, M., KOOPMAN-ESSEBOOM, C., FIDLER, V., HADDERS-ALGRA, M., VAN DER PAAUW, C.G., TUINSTRA, L.G.M., et al. 1995. "Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development." Early Hum. Dev. 41:111–127.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC) (1997). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 69 (in press). World Health Organization. Lyons, France.

INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION (ICRP) (1981). Report of the Task Group on Reference Manual ICRP Publication No. 23. Pergamon Press.

JANSING, P.J. and KORFF, R. (1994). "Blood levels of 2,3,7,8-tetrachlorodibenzodioxin and globulins in a follow-up investigation of employees with chloracne." J. Dermatol. Sci. 8:91–95.

JIRASEK, L., KALENSKY, K., KUBEC, K., et al. (1974). "Chronic poisoning by 2.3,7.8-TCDD." Cesk. Derm. 48:306–317.

JOHNSON, B.L. (1992a). Testimony before the Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Operations. Washington, DC.

JOHNSON, B.L. (1992b). Memo to ATSDR Senior Management. Agency for Toxic Substances and Disease Registry, Atlanta, GA (internal document).

KIMBROUGH, R.D., FALK, H., STEHR, P., et al. (1984). "Health implications of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) contamination of residential soil." J. Toxicol. Environ. Health 14:47–93.

KOCIBA, R.J., KEYES, D.G., BEYER, J.E., et al. (1978). "Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-TCDD in rats." Toxicol. Appl. Pharmacol. 46:281–287.

KOOPMAN-ESSEBOOM, C., MORSE, D.C., WEISGLAS-KUPERUS, N., LUTKESCHIPHOLT, I.J., et al. (1994). "Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants." Pediatr. Res. 36(4):468–473.

KOPPE, J.G., PLUIM, H.J., OLIE, K., and VAN WIJNEN, J. (1991). "Breast milk, dioxins, and the possible effects on the health of newborn infants." Sci. Total Environ. 106:33–41.

LU, C.H., BAGGS, R.B., REDMOND, D., et al. (1986). "Toxicity and evidence for metabolic alterations in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-treated guinea pigs fed by total parenteral nutrition." Toxicol. Appl. Pharmacol. 84:439–453.

LUCIER, G.W., RUMBAUGH, R.C., McCOY, Z., et al. (1986). "Ingestion of soil contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) alters hepatic enzyme activities in rats." Fundam. Appl. Toxicol. 6:364–371.

MANZ, A., BERGER, J., DWYER, J.H., et al. (1991). "Cancer mortality among workers in chemical plant contaminated with dioxin." Lancet 338:959–964.

MAY, G. (1982). "Tetrachlorodibenzodioxin: survey of subjects ten years after exposure." Br. J. Ind. Med. 30:276–283.

McCONNELL, E.E., LUCIER, G.W., RUMBAUGH, R.C., et al. (1984). "Dioxin in soil: bioavailability after ingestion by rats and guinea pigs." Sci. 223:1077–1079.

MEBUS, C.A., REDDY, V.R., and PIPER, W.N. (1987). "Depression of rat testicular 17-hydroxylase and 17,20-hydroxlyase after administration of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)." Biochem. Pharmacol. 36:727–731.

MOCARELLI, P., MAROCCHI, A., BRAMBILLA, P., et al. (1986). "Clinical laboratory manifestations of exposure to dioxin in children." JAMA 256:2687–2695.

MOCARELLI, P., NEEDHAM, L.L., MAROCCHI, A., et al. (1991). "Serum concentrations of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and test results from selected residents of Seveso, Italy." J. Toxicol. Environ. Health 32:357–366.

MOCARELLI, P., BRAMBILL, P., GARTHOUX, P.M., et al. (1996). "Change in sex ratio with exposure to dioxin." Lancet 348:409.

MOORE, R.W., POTTER, C.L., THEOBALD, H.M., et al. (1985). "Androgenic deficiency in male rats treated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin." Toxicol. Appl. Pharmacol. 79:99–111.

MURRAY, F.J., SMITH, F.A., NITSCHKE, K.D., HUMISTON, C.G., KOCIBA, R.J., and SCHWETZ, B.A. (1979). "Three-generation reproduction study of rats given 2,3,7,8-tetrachlorodibenzo-*p*-dioxin isomers using a polymeric liquid crystal capillary column." J. Chromatogr. 369(1):203–207.

NESTRICK, T.J., LAMPARSKI, L.L., FRAWLEY, N.N., et al. (1986). "Perspectives of a large scale environmental survey for chlorinated dioxins: overview and soil data." Chemosphere 15:1453–1460.

NATIONAL RESEARCH COUNCIL (NRC) (1994). Science and judgment in risk assessment. National Academy Press. Washington, DC.

NATIONAL TOXICOLOGY PROGRAM (NTP) (1972). "Bioassay of 2,3,7,8-TCDD for possible carcinogenicity (gavage study)." Technical report series no. 102. National Toxicology Program. Research Triangle Park, NC.

OLSON, J.R. (1986). "Metabolism and disposition of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in guinea pigs." Toxicol. Appl. Pharmacol. 85:263–273.

OTT, M.G. and ZOBER, A. (1996). "Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after 1953 reactor accident." Occup. Environ. Med. 53:606–612.

PAUSTENBACH, D.J., SHU, H.P., and MURRAY, F.J. (1986). "A critical examination of assumptions used in risk assessments of dioxin contaminated soil." Regul. Toxicol. Pharmacol. 6:284–307.

PAUSTENBACH, D.J., WENNING, R.J., LAU, V., HARRINGTON, N.W., RENNIX, D.K., and PARSONS, A.H. (1992). "Recent development on the hazards posed by 2,3,7,8-TCDD in soil; implications for setting risk-based cleanup levels at residential and industrial sites." J. Toxicol. Environ. Health 36:103–149.

PAZDEROVA-VEJLUPKOVA, J., NEMCOVA, M., PICKOVA, J., et al. (1981). "The development and prognosis of chronic intoxication by tetrachlorodibenzo-*p*-dioxin in men." Arch. Environ. Health 36:5–11.

PLUIM, H.J., KOPPE, J.G., OLIE, K., et al. (1992). "Effects of dioxins on thyroid function in newborn babies." Lancet 339:1303.

PLUIM, H.J., VAN DER SLIKKE, J.W., OLIE, K., et al. (1994a). "Dioxins and vitamin K status of the newborn." J. Environ. Sci. Health A29(4):793–802.

PLUIM, H.J., KOPPE, J.G., OLIE, K., VAN DER SLIKKE, J.W., et al. (1994b). "Clinical laboratory manifestation of exposure to background levels of dioxins in the perinatal period." Acta. Paediatr. 83:583–587.

POHL, H., DE ROSA, C., and HOLLER, J. (1995). "Public health assessment for dioxins exposure from soil." Chemosphere 31(1):2437–2454.

POIGER, H. and SCHLATTER, C. (1986). "Pharmacokinetics of 2,3,7,8-TCDD in man." Chemosphere 15:1489–1494.

POLAND, A.P., SMITH, D., METTER, G., et al. (1971). "A health survey of workers in a 2,4-D and 2,4,5-T plant with special attention to chloracne, porphyria cutanea tarda, and psychologic parameters." Arch. Environ. Health 22:316–327.

REGGIANI, G. (1980). "Acute human exposure to TCDD in Seveso, Italy." J. Toxicol. Environ. Health 6:27–43.

ROZMAN, K., ROZMAN, T., SCHEUFLER, E., et al. (1985). "Thyroid hormones modulate the toxicity of 2,3,7,8-TCDD." J. Toxicol. Environ. Health 16:481–491.

SCHANTZ, S.L., FERGUSON, S.A., and BOWMAN, R.E. (1992). "Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on behavior of monkey in peer groups." Neurotoxicol. Teratol. 14:433–446.

SCHECTER, A., RYAN, J.J., PAPKE, O., et al. (1993). "Elevated dioxin levels in the blood of male and female Russian workers with and without chloracne 25 years after phenoxyherbicide exposure: the UFA 'Khimprom' incident." Chemosphere 27:253–258.

SCHIEROW, L.J. (1995). Dioxin: Reassessing the Risk. CRS Report to Congress. Environment and Natural Resources Policy Division.

SWEENEY, M.H., FINGERHUT, M.A., AREZZO, J., et al. (1993). "Peripheral neuropathy after occupational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)." Am. J. Ind. Med. 23:845–858.

SWEENEY, M.H., HORNUNG, R.W., WALL, D.K., et al. (1992). "Prevalence of diabetes and increased fasting serum glucose in workers with long-term exposure to 2,3,7,8-TCDD." 12th International Symposium on Dioxins and Related Compounds. August 23–28, Tampere, Finland.

TONN, T., ESSER, C., SCHNEIDER, E.M., et al. (1996). "Persistence of decreased T-helper cell function in industrial workers 20 years after exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin." Environ. Health Perspect. 104:422–426.

TURNER, J.N. and COLLINS, D.N. (1983). "Liver morphology in guinea pigs administered either pyrolysis products of a polychlorinated biphenyl transformer fluid or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin." Toxicol. Appl. Pharmacol. 67:417–429.

UMBREIT, T.H., HESSE, E.J., and GALLO, M.A. (1986a). "Bioavailability of dioxin in soil from a 2,4,5-T manufacturing site." Sci. 232:497–499.

UMBREIT, T.H., HESSE, E.J., and GALLO, M.A. (1986b). "Comparative toxicity of TCDD contaminated soil from Times Beach, Missouri, and Newark, New Jersey." Chemosphere 15:2121–2124.

UMBREIT, T.H., HESSE, E.J., and GALLO, M.A. (1987). "Reproductive toxicity in female mice of dioxin-contaminated soils from a 2,4,5-trichlorophenoxyacetic acid manufacturing site." Arch. Environ. Contam. Toxicol. 16:461–466.

U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA) (1985). Drinking Water Criteria Document for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. EPA Report No. 600/8-194-I. Cincinnati, OH.

U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA) (1987). The Risk Assessment guidelines of 1986. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. EPA/600/8-87/045. Washington, DC.

U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA) (1989a). Interim Procedures for Estimating Risks Associated with Exposure to Mixtures of Chlorinated Dibenzo-*p*-dioxins and Dibenzofurans (CDDs and CDFs) and 1989 Update. Risk Assessment Forum. U.S. Environmental Protection Agency. EPA 625/3-89/016. NTIS PB90-145756. Washington, DC.

U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA) (1989b). Exposure Factors Handbook. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA/600/8-89/043. July 1989. Washington, DC.

U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA) (1994). METHOD 8290: Polychlorinated Dibenzodioxins (PCDDs) and Polychlorinated Dibenzofurans (PCDFs) by High-Resolution Gas Chromatography/High-Resolution Mass Spectrometry (HRGC/HRMS).

U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA) (1995). METHOD 8280A: The Analysis of Polychlorinated Dibenzo-p-dioxins and Polychlorinated Dibenzofurans by High-Resolution Gas Chromatography/Low-Resolution Mass Spectrometry (HRGS/LRMS).

U.S. FOOD AND DRUG ADMINISTRATION (FDA) (1990). Carcinogenic Risk Assessment for Dioxins and Furans in Fish Contaminated by Bleached-paper Mills. Report of the Quantitative Risk Assessment Committee. Food and Drug Administration. Washington, DC.

VAN DEN BERG, M., DEJONGH, J., POIGER, H., and OLSEN, J.R. (1994). "The toxicokinetics and metabolism of polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) and their relevance to toxicity." Crit. Rev. Toxicol. 24:1–74.

WEISGLAS-KUPERUS, N., SAS, T.C.J., KOOPMAN-ESSEBOOM, C., et al. (1995). "Immunologic effects of background prenatal and postnatal exposure to dioxins and polychlorinated biphenyls in Dutch infants." Pediatr. Res. 38(3):404–410.

WHITE, K.L., JR., LYSY, H.H., McCAY, J.A., et al. (1986). "Modulation of serum complement levels following exposure to polychlorinated dibenzo-*p*-dioxins." Toxicol. Appl. Pharmacol. 84:209–219.

WOLFE, W.H., MICHALEK, J.E., MINER, J.C., et al. (1994). "Determinations of TCDD half-life in veterans of Operation Ranch Hand." J. Toxicol. Environ. Health 41:481–488.

WOLFE, W.H., MICHALEK, J.E., MINER, J.C., et al. (1995). "Paternal serum dioxin and reproductive outcomes among veterans of Operation Ranch Hand." Epidemiology 6:17–22.

WORLD HEALTH ORGANIZATION (WHO) (1991). "Consultation on tolerable daily intake from food of PCDDs and PCDFs." Summary report. World Health Organization. Bilthoven, the Netherlands.

ZOBER, A., MESSERER, P., and HUBER, P. (1990). "Thirty-four year mortality followup of BASF employees to TCDD after the 1953 accident." Int. Arch. Occup. Environ. Health 62:139–157.

ZOBER, A., OTT, M., FLEIG, I., et al. (1993). "Cytogenic studies in lymphocytes of workers exposed to 2,3,7,8-TCDD." Int. Arch. Occup. Environ. Health 65:157–161.