correlation between dioxin body burden and incidence or severity of endometriosis. Further evaluation of this health end point awaits reports from these studies.

9.8. DOSE-RESPONSE CONSIDERATIONS

The current efforts to evaluate the risks of dioxin and related compounds have focused on the understanding of the biological basis of response as well as evaluation of the weight of the empirical observations on inferences regarding hazard and risk. Previous sections have discussed the relationship of binding of this class of compounds to a specific receptor and subsequent events. It is generally accepted that all well-studied responses to dioxin appear to be mediated by receptor binding. This situation is not unlike the signal transduction pathways that have been described for hormone action, particularly exemplified by the well-studied family of steroid hormones, although the dioxin receptor does not belong to the steroid receptor family.

The fact that much of the biological activity of this class of compounds follows the rank order of binding affinity of the congeners to the Ah-receptor supports the concept that these earliest steps play a determining role in the probability that later responses will occur. This does not imply that a simple proportional relationship between receptor binding and biological response can explain the diversity of biological responses described for dioxin and related compounds. It is likely that differences in response will be due to tissue and cell-specific factors that modulate the qualitative relationship between receptor binding, or more precisely, occupancy and response. It is expected that there may be markedly different dose-response relationships for different effects of dioxin, depending on the respective roles of modulating activities. Coordinated biological responses, such as TCDD-mediated increases in cell proliferation, likely involve numerous cellular factors and hormone systems. This means that the dose-response for relatively simple sequelae of the early binding events such as cytochrome (CYP1A1) induction may not accurately predict dose-response relationships for more complex responses such as cancer. Much additional knowledge will be required before we can accurately predict these complex dose-response relationships.

Development of biologically based dose-response models for dioxin and related compounds as a part of this reassessment has led to considerable and valuable insights

regarding both mechanisms of dioxin action and dose-response relationships for dioxin effects. These are described in some detail in Chapter 8. These efforts have provided additional perspectives on traditional methods such as the linearized multistage (LMS) procedure for estimating cancer potency or the uncertainty factor approach for estimating levels below which noncancer effects are not likely to occur. These methods have also provided a biologically based rationale for what had been primarily statistical approaches. The development of models like those in Chapter 8 allows for an iterative process of data development, hypothesis testing, and model development. These efforts have resulted in incorporation of more of the available biological data into models to predict human risk at low increments of exposure.

Tables 9-3 through 9-6 summarize estimated body burdens and effect levels for a variety of species, including the lowest observed effect levels (LOELs) for some of the more sensitive indicators of biological response induced by dioxin and related compounds. Important assumptions used in deriving these values are included as part of this table. It is particularly important to note that the estimated body burdens associated with several of these experimental doses are quite low relative to background body burdens in the general human population. The implications of this observation will be discussed later in this chapter.

Dose-response modeling efforts in Chapter 8 for liver cancer in female rats and for lung cancer and all cancers combined in humans have produced results that can be used to estimate risk-specific doses and risk estimates. Estimates from these efforts differ with models based on the human data, providing somewhat higher risk estimates than the animal-based estimates. The risk estimates resulting from these models have uncertainties that cause their ranges to overlap, and all models produce fits that are consistent with the linearized multistage model commonly used for cancer risk estimates. By the definitions of mechanistic modeling given in Chapter 8, both modeling efforts fall short of completely explaining conditions of biology or exposure. However, because the animal modeling establishes a better mechanistic basis for extrapolation to low doses and the animal data have greater certainty in terms of causal association for cancer (especially considering that smoking may

Table 9-3. Estimated Body Burdens of Experimental Animals and Humans Exposed to Dioxins: Responses in Humans Causally Associated With Exposure to Dioxins and Comparable Effects in Experimental Animals

Effect	Species	Experimental Dose	Body Burden	Ref./Note
Chloracne	Humans		45-3,000 ng/kg	Ryan et al., 1990; Beck et al., 1989/a,b
Chloracne	Monkey	1,000 ng/kg	1,000 ng/kg	McNulty, 1985/c
Chloracne	Rabbits	4 ng/kg 5d/wk/4wk	220 ng/kg	Schwetz et al., 1973/d
Chloracne	Mice	4,000 ng/kg 3d/wk/2wk	14,000 ng/kg	Puvel and Sakamoto, 1988/e
Decreased Birth Weight	Humans	Mother's body burden	1,460 ng/kg	Lucier, 1991/f
Decreased Growth	Humans	Mother's body burden	1,460 ng/kg	Guo et al., 1994/f
Decreased Growth	Rats	400 ng/kg maternal dose gd 15	400 ng/kg	Mably et al., 1992a/g
Delayed Developmental Milestones	Humans		1,460 ng/kg	Rogan et al., 1988/f
Object Learning	Monkey	1.26 ng/kg/d	19 ng/kg	Schantz and Bowman, 1989/h
Down Regulation of EGFR in Placenta (Maximal Effect)	Humans		1,460 ng/kg	Lucier, 1991/f

Table 9-3. (continued)

Effect	Species	Experimental Dose	Body Burden	Ref./Note
Down Regulation of EGFR in Liver (Maximal Effect)	Rats	125 ng/kg/d 30 weeks	1,600 ng/kg	Sewall et al., 1993/i
Increase in Placental CYP1A1 (Maximal Effect)	Humans		1,460 ng/kg	Lucier, 1991/f
Increase in Liver CYP1A1 (Maximal Effect)	Rats	125 ng/kg/d 30 weeks	1,600 ng/kg	Tritscher et al., 1992/i
Enzyme Induction CYP1A1 (LOEL)	Rats	1 ng/kg single dose sac 24 hr	1 ng/kg	Van den Heuvel et al., 1993/j
Enzyme Induction CYP1A1/1A2 (LOEL)	Mice	1.5 ng/kg/d 5 d/wk 13 wk	23 ng/kg	DeVito et al., 1994/k
Hepatic Sequestration	Human		150 ng/kg	Carrier et al., submitted/l
Hepatic Sequestration	Rats		300 ng/kg	Carrier et al., submitted/l
Background	Human	60 TEQ ppt in serum	9 ng/kg	m
Background	Mouse		4 ng/kg	n

Notes:

a. All human data assume a background level of 60 ppt TEQs in serum (lipid adjusted) in addition to the dioxin levels presented in the referenced papers. Dioxins are assumed to be distributed in the body lipid. Thus the concentration of dioxins in serum expressed as lipid adjusted are assumed to be equivalent to the concentration of dioxins in total body lipids. In addition, the average person is assumed to weigh 70 kg with 15% of the weight from body fat. Hence a person with background levels of 60 ppt TEQs in serum (lipid-adjusted levels) has a body burden of 9 ppt or 9 ng/kg. Although unpublished

Table 9-3. (continued)

studies in our laboratory indicate that untreated 150-day-old mice also have background levels of dioxins and dibenzofurans of approximately 4 ng TEQ/kg, these values were not included in body-burden estimates for the effects seen in experimental animals.

b. The lower value, 45 ng/kg, is from a patient with chloracne who had the lowest reported serum dioxin level for any patient with chloracne (Ryan et al., 1990). In this patient adipose tissue levels at the time of exposure, and the development of chloracne, are estimated by the authors (Ryan et al., 1990) based on the patient's adipose tissue level of dioxins of 237 ppt and assuming a half-life of dioxin of 7.1 years. The higher of the two values is from Ryan et al., 1989 and represents the average body burden of dioxins in persons from Yu-Cheng who developed chloracne (Beck et al., 1989). Estimates of body burdens from the Yu-Cheng patients were determined by Ryan et al. in Beck et al. (1989).

c. Animal administered 1 μg/kg TCDD and it is assumed that essentially no TCDD was eliminated when the animal developed a chloracnegenic response. This is a LOEL dose; no lower doses were tested.

d. Assumes the same rate of elimination as the rat and that the animals weighs 2.5 kg throughout the experiment. This is a LOEL dose and no lower doses were tested.

e. Assumes a half-life of 11 days and an average weight of the animal at 25 grams. This is a LOEL dose, and no lower doses were administered.

f. According to the author (Lucier, 1991), in highly exposed patients from Yu-Cheng, there is a decrease in birth weights of children born from these patients compared to unexposed control populations. In addition, there is an association between placental levels of dioxins and alterations in placental epidermal growth factor receptor (EGFR) and CYP1A1. In addition, the author suggested that the changes in placental EGFR and CYP1A1 in these patients were maximal. Body burdens determined based on levels of 2,3,4,7,8-pentachlorodibenzofuran (TEF=0.1) and 1,2,3,4,7,8-hexachlorodibenzofuran in placenta tissue. Assumes placenta is 1% lipid (Beck et al., 1994) and that women have a fat content of 21% of body weight (Ganong, 1982). Also used these body burdens to estimate body burden of mothers of the children with decreased growth (Guo et al., 1994) and delayed developmental milestones (Rogan et al., 1988). All patients are from the Yu-Cheng rice oil poisoning.

g. Assumes pups exposed to an equal dose of TCDD as are the dams on a weight basis and that the pups do not eliminate any of the TCDD. For decreased body weight in pups

Table 9-3. (continued)

400 ng/kg is the LOEL, a dose of 64 ng/kg to the dam was the NOEL for this response. For decreased sperm count, the LOEL is 64 ng/kg, and no lower doses were tested.

h. Assumes a single first-order elimination rate constant and a half-life for the whole body elimination of 400 days (McNulty, 1985) and a gastrointestinal absorption of 86% (Rose et al., 1976). This is the LOEL from this study; no lower doses tested.

i. From Tritscher et al. (1992) and Maronpot et al. (1993). Liver levels measured in study at approximately 30 ppb. Liver and body weights were reported in 40. Assumes animal is 20% body fat by weight and that at this dose, the liver has four times the concentration of TCDD than adipose tissue. The body-burden calculation assumes that liver and fat account for 90% of the body burden in these animals. For tumor promotion, this is the LOEL in these animals. A NOEL for tumor promotion was observed at a dose of 35 ng/kg/d. For induction of CYP1A1 and downregulation of EGF-R, this body burden produces a maximal response.

j. Animals received a single dose and were sacrificed 24 hours later. Assumes no TCDD eliminated at this time. CYP1A1 induction determined by RT-PCR. This is the LOEL for this response; a NOEL from this study is 0.1 ng/kg.

k. Animals received 1.5 ng/kg/d, 5 d/wk for 13 wk. Animals sacrificed 3 days after last dose. Hepatic, dermal, and pulmonary EROD activity induced at this dose. Tissue levels measured in liver, skin, and fat. Assumes 100% of the body burden is in liver, skin, and fat. This is the LOEL from this study; no lower doses were tested.

l. Body burdens are estimated by Zinkl et al. (1973) for the increased accumulation of PCDD/PCDF in liver compared to adipose tissue.

m. Assumes a background TEQ of 60 ppt for dioxins, dibenzofurans, and PCBs. Also assumes a body weight of 70 kg with 15% body fat.

n. Data from DeVito and Birnbaum. TEQ for TCDD 1,2,3,7,8-PCDD; 2,3,7,8-TCDF; 1,2,3,7,8-PCDF; 2,3,4,7,8-PCDF; and OCDF in 150 day old female B6C3F1 mice. Chemicals were determined in liver, fat and skin of these animals. Assumes that 100% of the body burden is in liver, fat, and skin.

Table 9-4. Estimated Body Burdens of Experimental Animals and Humans Exposed to Dioxins: Responses in Humans Associated With Dioxin Exposure and Comparable Effects in Experimental Animals

Effect	Species	Experimental Dose	Body Burden	Ref./Note
Cancer	Humans		109-7,000 ng/kg	Fingerhut et al., 1991; Bertazzi et al., 1993/a
Cancer	Hamsters	100 μg/kg 6 doses (600 μg/kg total dose)	500 ng/kg	Rao et al., 1988/b
Cancer	Rats	100 ng/kg/d for 2 years	1,400 ng/kg	Kociba et al., 1978/c
Cancer	Mice	400 ng/kg/d for 2 years	1,000 ng/kg	NTP, 1982/d
Liver Tumor Promotion	Rats	125 ng/kg/d 30 weeks	1,600 ng/kg	Maronpot et al., 1993/e
Skin Tumor Promotion	Mice	7.5 ng/kg/wk for 20 wks dermal exposure	1,100 ng/kg	Poland et al., 1982/f
Decreased Testosterone	Humans		83 ng/kg	Egeland et al., 1994/g
Decreased Testosterone	Rats	12,500 ng/kg sac day 7	10,200 ng/kg	Moore et al., 1985/h
Decreased Testis Size	Humans		14 ng/kg	Air Force Study, 1991/i
Altered Glucose Tolerance	Humans		110 ng/kg	Sweeney et al., 1992/j
Altered Glucose Tolerance	Humans		14 ng/kg	Wolfe et al., 1992/i

Table 9-4. (continued)

Effect	Species	Experimental Dose	Body Burden	Ref./Note
Decreased Glucose Uptake Adipocytes	Guinea Pigs	30 ng/kg sac day 1	30 ng/kg	Enan et al., 1992/k
Decreased Serum Glucose	Rats	100 ng/kg/d 30 days	1,900 ng/kg	Zinkl et al., 1973/l
Background	Human	60 TEQ ppt in serum	9 ng/kg	m
Background	Mouse		4 ng/kg	n

Notes:

a. Estimated highest body burden at time of last exposure. Calculations based on measured TCDD levels in serum (lipid adjusted) and assuming a first-order elimination kinetics and a half-life for elimination of 7.1 years. Also assumes a body weight of 70 kg and 22% body fat. Calculations for estimated serum concentrations at last time of exposure performed by authors (Fingerhut et al., 1991; Bertazzi et al., 1993).

b. Animals administered 100 μg/kg six times over a 4-week period. Assumes a half-life of 23.4 days and that animals are sacrificed at 10 months after the first dose. This is the LOEL; however, no other doses tested in this study.

c. Assumes a single first-order elimination rate constant and a half-life for the whole body elimination of 23.7 days (Rose et al., 1976) and a gastrointestinal tract absorption of 86% (Rose et al., 1976). This is the LOEL of the study; a dose of 10 ng/kg/d was also tested with no significant increase in tumors.

d. Body burden estimated from animals treated with 450 ng/kg/d for 90 days (DeVito and Birnbaum, unpublished results).

e. From Tritscher et al. (1992) and Maronpot et al. (1993). Liver levels measured in study at approximately 30 ppb. Liver and body weights were reported in White and Gasiewicz (1993). Assumes animal is 20% body fat by weight and that at this dose, the liver has four times the concentration of TCDD than adipose tissue. The body-burden calculation assumes that liver and fat account for 90% of the body burden in these animals. For tumor promotion, this is the LOEL in these animals. A NOEL for tumor promotion was

Table 9-4. (continued)

observed at a dose of 35 ng/kg/d. For induction of CYP1A1 and downregulation of EGF-R, this body burden produces a maximal response.

f. Assumes an elimination rate of 11 days and a body weight of 20 grams.

g. From Egeland et al. (1994) in which workers with half-life extrapolated levels of TCDD of 496-1,860 ppt have a greater percentage of workers with low testosterone levels. Extrapolation performed by Egeland et al. (1994) assuming a half-life of 7.1 years. Also assumed that the background TEQ was 60 ppt so that the total serum TEQ was 496 ppt + 60 ppt = 556 ppt (lipid adjusted). Average worker was male weighing 70 kg with 15% body fat.

h. Animals received single exposure of 12.5 μg/kg (LOAEL) and sacrificed 7 days after dosing. Assumes a half-life of 23.4 days and body burden corrected for elimination. A dose of 6.25 μg/kg was tested and is the NOEL for this study.

i. From Ranch Hand study (Sweeney et al., 1992), assumes that high exposed group (>33 ppt) had a background of 60 TEQ ppt. Thus, this group had at least 93 TEQ ppt. Assumes average Ranch Hand patient was male weighing 70 kg with 15% body fat.

j. Same assumptions in note g except average serum level in affected workers is 640 ppt.

k. Guinea pigs received 0.03 μg TCDD/kg i.p. and sacrificed 24 hours after dose. Assumes that no TCDD was eliminated at this time. This is a LOEL; no other doses tested.

l. Animals were treated with 0.1 μg/kg/day for 30 days and assumes half-life of TCDD in the rat is 23.4 days.

m. Assumes a background TEQ of 60 ppt for dioxins, dibenzofurans, and PCBs. Also assumes a body weight of 70 kg with 15% body fat.

n. Data from DeVito and Birnbaum (1994). TEQ for TCDD, 1,2,3,7,8-PCDD; 2,3,7,8-TCDF; 1,2,3,7,8-PCDF; 2,3,4,7,8-PCDF; and OCDF in 150-day-old female B6C3F1 mice. Chemicals were determined in liver, fat, and skin of these animals. Assumes that 100% of the body burden is in liver, fat, and skin.

Table 9-5. Estimated Body Burdens of Experimental Animals and Humans Exposed to Dioxins: Low-Dose Effects in Animals Exposed to Dioxins and Their Relationship to Background Human Exposure

Effect	Species	Experimental Dose	Body Burden	Ref./Note
Decreased Offspring Viability	Rhesus Monkeys	25 ppt in diet for 4 years	270 ng/kg	Hong et al., 1989/a
Altered Lymphocyte Subsets	Rhesus Monkeys	25 ppt in diet for 4 years	270 ng/kg	Hong et al., 1989/a
Altered Lymphocyte Subsets	Marmosets	0.3 ng/kg/wk for 24 weeks 1.5 ng/kg/wk for 12 weeks	6-8 ng/kg	Neubert et al., 1992/b
Enhanced Viral Susceptibility	Mice	10 ng/kg sac day 7	7 ng/kg	Burelson et al., 1994/c
Endometriosis	Monkeys	5 ppt in diet 4 years	54 ng/kg	Reier et al., 1993/a
Decreased Sperm Count	Rats	64 ng/kg maternal dose gd 15	64 ng/kg	Mably et al., 1992b/d
Background	Human	60 TEQ ppt in serum	9 ng/kg	e
Background	Mouse		4 ng/kg	f

Notes:

a. Assumes a single first-order elimination rate constant and a half-life for the whole body elimination of 400 days (McNulty, 1985) and a gastrointestinal absorption of 86% (Rose et al., 1976). This is the LOEL from this study; no lower doses tested.

b. Assuming a single first-order elimination rate constant and a half-life of 6-8 wks. Body burdens calculated by authors (Neubert et al., 1992).

Table 9-5. (continued)

c. Body burden determined in these animals (Diliberto et al., submitted). Approximately 70% of the body burden remains at 7 days after dosing. This is the LOEL from this study. A dose of 5 ng/kg was also tested in this study with no effect (NOEL).

d. Assumes pups exposed to an equal dose of TCDD as are the dams on a weight basis and that the pups do not eliminate any of the TCDD. For decreased body weight in pups 400 ng/kg is the LOEL, a dose of 64 ng/kg to the dam was the NOEL for this response. For decreased sperm count, the LOEL is 64 ng/kg, and no lower doses were tested.

e. Assumes a background TEQ of 60 ppt for dioxins, dibenzofurans, and PCBs. Also assumes a body weight of 70 kg with 15% body fat.

f. Data from DeVito and Birnbaum (1994). TEQ for TCDD, 1,2,3,7,8-PCDD; 2,3,7,8-TCDF; 1,2,3,7,8-PCDF; 2,3,4,7,8-PCDF; and OCDF in 150-day-old female B6C3F1 mice. Chemicals were determined in liver, fat, and skin of these animals. Assumes that 100% of the body burden is in liver, fat, and skin.

Table 9-6. Comparison of the Effects of TCDD Exposure on Human and Animal Tissue In Vitro

Effect	Cell Line/Species	Concentration	Ref./Note
Binding to CYP1A1 DRE	Hepa-1c1c7/mouse	2 nM	Probst et al., 1993/a
Binding to CYP1A1 DRE	LS180/human	10 nM	Probst et al., 1993/a
Binding to ER DRE	Hepa 1c1c7/mouse	15.5 nM	White and Gasiewicz, 1993/b
Binding to ER DRE	MCF-7/human	5.6 nM	White and Gasiewicz, 1993/b
Induction CYP1A1	Lymphocytes mouse	1.3 nM	Clark et al., 1992/c
Induction CYP1A1	Lymphocytes human	1.8 nM	Clark et al., 1992/c
Cytotoxicity	Embryonic palate mouse	0.1 nM	Abbott and Birnbaum, 1991/d
Cytotoxicity	Embryonic palate rat	100 nM	Abbott and Birnbaum, 1991/d
Cytotoxicity	Embryonic palate human	100 nM	Abbott and Birnbaum, 1991/d
Altered Lymphocyte Subsets	Peripheral lymphocytes marmoset	0.0001 nM	Neubert et al., 1991/e
Altered Lymphocyte Subsets	Peripheral lymphocytes human	0.0001 nM	Neubert et al., 1991/e
Inhibition of Proliferation	Thymocytes mouse	0.1 nM	Greenlee et al., 1985/f
Inhibition of Proliferation	Thymocytes human	0.1 nM	Cook et al., 1987/f
Inhibition of Proliferation	Tonsilar lymphocytes human	0.3 nM	Wood et al., 1993/g
Inhibition of Proliferation	Splenic lymphocytes murine	3.0 nM	Wood et al., 1993/g

Table 9-6. (continued)

Effect	Cell Line/Species	Concentration	Ref./Note
Inhibition of IgM Secretion	Splenic lymphocytes murine	3.0 nM	Wood et al., 1993/g
Inhibition of IgM Secretion	Tonsilar lymphocytes human	0.3 nM	Wood et al., 1993/g

Notes:

a. Using gel retardation assay, Probst et al. (1993) compared the ability of the Ah receptor isolated from either murine or human cell lines to bind to a dioxin response element (DRE). The authors used only one concentration of TCDD for either cell type, 2 nM for murine cells and 10 nM for human cells.

b. White and Gasiewicz (1993) compared the ability of Ah receptors isolated from either murine or human cell lines to bind to a DRE found in the human estrogen receptor (ER) structural gene. Concentration values are binding affinities to this DRE.

c. Splenic lymphocytes from C57Bl/6 mice and peripheral blood lymphocytes were isolated, cultured, and exposed to TCDD. EROD activity, a marker for CYP1A1, was determined following TCDD exposure. Data presented are EC_{50}.

d. Abbott and Birnbaum (1991) compared the cytotoxic effects of TCDD on organ culture of human, mouse, and rat embryonic palatal shelves. Embryonic palates from human mouse and rat were grown in the same organ culture system and exposed to TCDD. Cytotoxicity was detected using transmission electron microscopy. Concentrations are the lowest observable effect level.

e. Neubert et al. (1991) isolated lymphocytes from human and primates and determined lymphocyte subsets following antigen stimulation in cells treated with TCDD. The concentration is the level at which the authors describe a consistent effect on lymphocyte subsets in this system.

f. Thymocytes were isolated from either human or murine sources and cocultured with a human thymic epithelium culture (human thymocytes) or with murine thymic epithelium (murine thymocytes). The incorporation of tritiated thymidine was determined in cells treated with TCDD following antigen stimulation. Data presented are LOEL for both cell lines.

Table 9-6. (continued)

g. Human tonsilar lymphocytes and murine splenic lymphocytes were used to isolate B cells. Human and murine B cells were grown under identical conditions and exposed to TCDD. Proliferation and IgM secretion were determined in response to different concentrations of TCDD ranging from 0.3 to 30 nM. Values presented are LOELs from Wood et al. (1993).

have a potentiating effect with dioxin for lung cancer in the human studies), the animal model will be the focus of estimates of cancer risk.

Many scientists agree that the cancer modeling efforts should continue to focus on the animal studies in the absence of better quantitative human data. Others suggest that there is no compelling reason to conclude that estimates derived from the human data are any more uncertain than the estimates based on the rodent bioassay. In both cases, modeling efforts have indicated the sensitivity of certain model parameters to choice of data sets and/or assumptions. Analyses in Chapter 8 illustrate that the slope of the dose-response curve for surrogate markers of low-dose response such as enzyme induction or indirect mutagenic activity on estimates of cancer risk using animal data are highly dependent on the assumptions that go into the modeling. Dependent on assumptions, use of the obvious dose surrogates could predict very different low-dose risks, differing by orders of magnitude from the estimates described above. For gene expression of biological markers, the major factor controlling this broad range of low-dose risk estimates is the mechanism by which dioxin modifies constitutive expression. However, as expressed in Appendix D of Chapter 8, reasonable assumptions concerning constitutive expression of the biochemical markers will result in low-dose linearity and risk estimates consistent with that obtained using the linearized multistage approach.

The two-stage modeling of the Kociba et al. (1978) female rat liver tumor data in Chapter 8 incorporates data from earlier events in the carcinogenic process into the estimation of model parameters. In fact, the results using the two-stage model incorporating dioxin-altered hepatic foci data to estimate mutation and growth parameters provide nearly the same low-dose estimates as the linearized multistage model using only the tumor data. When using the default species extrapolation from animals to humans (body weight ratio to the 3/4 power), both models yield oral intake risk-specific doses of slightly less than 0.01 pg TCDD/kg/day, corresponding to unit risk estimates of 1×10^{-4} per pg TCDD/kg/day. Chapter 8 discusses other potential models that might fit these data as well as the best-fitting model (Appendix C, Chapter 8). These analyses indicate that, unless a protective effect of TCDD on mutation rates occurs at low doses, low-dose risk will remain proportionate to exposure and consistent with the linearized multistage model. If protective effects are

allowed in the model, the low-dose risks may be substantially reduced. The focal lesion data and the biochemical markers generally agree and do not suggest the protective effect discussed above. These models assume that the PGST foci are precursors to cancer. Other hepatic focal lesion markers could be used in this context and may lead to different dose-response curves for tumor response (see discussion in Chapter 8).

Uncertainty in estimates of human half-life for dioxin and related compounds represents an important factor in comparing human-based risk estimates versus animal-based risk estimates. For instance, if the dose-dependent pharmacokinetic model of Carrier (1991) is correct, exposures in the occupational studies must have been greater than the fixed half-life model would suggest, so that the estimated risk per unit of exposure may well have been lower. However, this reduction will be relatively small and is unlikely to move the risks outside the range of risk estimated by the linearized multistage model.

An additional consideration regarding the evaluation of dose response for dioxin and related compounds involves the ubiquity of background exposure to these compounds. Body burdens of these compounds have been discussed previously in several parts of this assessment. In all studies, both in laboratory animals and in humans, incremental exposures are being added onto an existing body burden that is present at birth and appears to increase with age. This background is often insignificant from the standpoint of added dose in experimental studies or for highly exposed human cohorts. On the other hand, it has real implications relative to the detectability of response at low incremental exposures and may have implications for the use of models that assume additivity to ongoing processes that may have been stimulated by background levels. Modeling estimates suggest that, if dioxin and related compounds are adding to human cancer burden, current background exposures may result in upper bound population cancer risk estimates attributable to exposure to dioxin and related compounds in the range of 1 in 10,000 (10^{-4}) for the average population exposures to 1 in 1,000 (10^{-3}) for more highly exposed members of the population (e.g., individuals consuming high levels of dioxin-containing foods). Actual risk for individuals exposed to background levels in the population is likely to be less than these upper bound estimates and, for some, may even be zero. More highly exposed populations with exposures to specific

sources of dioxin and related compounds such as those exposed under occupational or accident conditions may, on average, experience proportionately higher risk.

Background levels also complicate the evaluation of no observed or low observed adverse effect levels (NOAELs or LOAELs). Incremental exposures must be considered in light of existing body burdens in determining whether increased probability of effects having biological thresholds is likely. The concept that an incremental exposure is below an experimental threshold is moot unless the combined background and incremental exposure are below the threshold level. This has important consequences for the assessment of compounds like dioxin where certain biochemical alterations can be detected at or near equivalent human background body burden levels.

9.9. USE OF TOXICITY EQUIVALENCE

The concept of toxicity equivalence in evaluating mixtures of dioxin-like compounds is fundamental to many of the conclusions reached in this characterization. This is based on the fact that most data described in this and preceding chapters were obtained using 2,3,7,8-TCDD as the experimental compound. More limited data exist as individual congeners are evaluated. Nonetheless, estimates of body burden as derived in this reassessment suggest that greater than 90% of the total dioxin equivalence is due to dioxin-like compounds other than 2,3,7,8-TCDD. While there are empirical bases for the toxicity equivalence factors assigned to dioxin-like compounds relative to 2,3,7,8-TCDD, they generally represent order of magnitude estimates of relative toxicity and are not meant to be used precisely. The potency for most, if not all, of the toxic end points is determined by the number and position of the halogen (chlorine or bromine) atoms on the dioxin-like molecule. This appears, based on a substantial body of evidence, to be a function of relative ability to bind to a specific cellular receptor that mediates most, if not all, of the toxic end points of this class of compounds. This inference is based on experimental evidence, primarily in rodents but involving some other species, that for some toxic effects, the potency of the effect itself is proportional to receptor binding as measured by either binding studies or a sensitive measure of receptor binding, AHH induction. When ED_{50s} for effects versus binding are plotted logarithmically, good linear correlations are obtained (Safe, 1990). This approach constitutes

a "relative ranking" scheme based on 2,3,7,8-TCDD. Because the data base for effects for individual congeners is incomplete and because the concept is based on responsiveness of humans to these compounds in a manner similar to that of animals and high to low dose extrapolation, the TEQ approach is considered a useful but uncertain procedure.

In addition to the idea of "relative ranking," there is a second aspect to the TEQ approach. This is the concept of additivity. The hypothesis is that one can estimate the toxicity of a mixture of dioxin-like compounds by adding together the products of the concentrations of the individual congeners and their TEFs. This hypothesis has not been extensively tested although data addressing this issue are generally supportive of additivity. Some data collected using high levels of different congeners have suggested the potential for interactions (mostly, antagonism) between congeners. There is currently general acceptance of the concept of additivity with the recognition that issues such as congener interactions, presence of "spare" receptors, and the unavoidable presence of other dietary constituents that react with the dioxin receptor must be considered to add uncertainty to the concept.

The points discussed above describe the basis of the TEQ concept and indicate some of the assumptions on which they are based. A more detailed description of these issues is contained in U.S. EPA (1989). In addition to scientific grounds, the use of TEQs can be justified on a practical basis, not the least of which is the sheer enormity of the task of attempting to conduct appropriate studies on all toxic end points for all of the congeners. They continue to be described by the EPA and others as an "interim" approach, and the extent of their current use should not detract from the expressed need for more data to further validate their use.

9.10. KEY ASSUMPTIONS AND INFERENCES

One of the primary functions of the risk characterization is to present key assumptions and inferences that are used to reach conclusions in the absence of definitive information. Not all scientists may agree with the use of these specific assumptions and inferences. The degree to which there is disagreement will have profound effects on the acceptance of this analysis. While many of these assumptions and inferences are discussed in previous sections,

it is important that they be recognized in order to put our overall conclusions in a proper perspective. Key assumptions and inferences are listed below.

The limited information on sources, fate, and transport in the environment provides a reasonable basis for predicting human exposure. While data are limited and, therefore, uncertain, information from a variety of studies in industrialized countries coupled with our detailed knowledge of physicochemical properties for this class of compounds allows reasonable assumptions to be made regarding relative ranking of sources with regard to their contribution to environmental loading, the persistence of this class of compounds under specific environmental conditions, and the likelihood that the chemical will be transferred from the environment to biological systems. Nonetheless, these are assumptions that are arguable and that will be refined as more data become available. Additional data will be required to validate the numerous hypotheses that go into assembling models for environmental release, fate, and transport for this complex mixture of individual chemical congeners.

The air to food hypothesis is plausible and is supported by enough data to warrant its use in the absence of more complete information. The air-to-food hypothesis is founded on data evaluating deposition, environmental transport, bioaccumulation, and consumption patterns. It is supported by studies from Europe and Canada. While individual measurement data are still quite limited, the consistency of the evidence supporting the validity of the hypothesis is compelling. The hypothesis has been accepted by a large segment of the knowledgeable scientific community. Because airborne dioxin may come from direct releases to air or from recycling of dioxin-like compounds released into various environmental media from a number of sources, this hypothesis provides a perspective on how dioxin-like compounds move through the environment to humans but does not allow attribution of exposure to particular sources.

Toxicity equivalence is a valid, interim method for assessing exposure to a complex mixture of dioxin and related compounds and predicting likely health outcomes. The EPA and the international scientific community have agreed that the use of toxicity factors to predict relative toxicities of mixtures of this class of compounds has an empirical basis, is theoretically sound, and, in the absence of more complete data sets on the toxicity of

individual members of this class, is a useful procedure. This is not to say that the use of TEFs is a certain procedure. Since 1986 when the first Agency-wide consensus on the use of TEFs was published, additional refinements to the data bases and to the use of TEFs have occurred. Published revisions in accord with international agreement appeared in 1989. In the course of this reassessment, critical data were collected, and agreement was reached regarding the contribution of dioxin-like PCBs to overall TEQs. Additional validation of the TEQ concept in predicting effects of this class of compounds on wildlife species lends further support to the use of this approach. It must be recognized that this relatively simple, additive approach does not take into account interactions between dioxin-like compounds and other chemical exposures. These interactions may result in either an overestimate or an underestimate of likely effects of the complex mixture. While generally accepted as useful for evaluating intakes of various dioxin-like compounds, the application of this approach to the evaluation of measured body burdens remains even more uncertain.

Use of one-half the nondetect level for estimating low levels of exposure is a reasonable but conservative approach to evaluating limited blood and tissue level data. For some data sets, use of zero values for nondetects could result in significantly lower estimates and, therefore, use of the current procedure may be overestimating blood or tissue levels. However, it is widely held that use of zero values for nondetects would most likely underestimate true levels of exposure, particularly where nondetects do not dominate measured values. Similar estimates of TEQs derived from different data sets, developed by different investigators in several countries, strengthen the probability that this inference represents the exposure of the general population in industrialized countries to dioxin and related compounds.

The limited data available from studies of levels of dioxin and related compounds in humans provide an adequate basis to infer general population body burdens. Although there are still limited measurements of general population body burdens, the data provide a consistent picture of background body burdens for industrialized countries. While additional data will help refine the range of general population body burdens as a function of location, human activity, age, and the like, there are adequate data to estimate current body burdens in the general population for the purposes of this assessment. It is highly unlikely that these

estimates would represent a sensitive parameter in estimating margins of exposure within an order of magnitude.

Laboratory animal studies provide useful information in evaluating potential human responses to dioxin and related compounds. Based on our knowledge of the biochemical and biological similarities between laboratory animals and humans, our understanding of some of the fundamental impacts of this class of compounds on biological systems, and comparable responses from animal and human studies both in vitro and in vivo, our decision to use laboratory animal data to contribute to weight-of-the-evidence conclusions on human hazard and risk is reasonable. Humans do not appear to be an unusual responder for dioxin effects, that is, we do not, on average, appear to be either refractory to or exquisitely sensitive to the effects of dioxin-like compounds. While positive human data are preferable for ascribing hazard or risk, the lack of adequate human data to demonstrate causality for many suspected dioxin effects is assumed not to negate the findings from laboratory animal and in vitro studies. Although some scientists may disagree, in our estimation, the data base on dioxin and related compounds is one of the most comprehensive among all environmental chemicals. The fundamental understanding of mechanisms of dioxin action provides a unifying theory for the mechanisms for observed effects in laboratory animals and humans and for using a weight-of-the-evidence approach considering all relevant data to infer the human health impacts of dioxin and related compounds.

Observations of effects from exposure to dioxin and related compounds in humans and other animals suggest that fundamental changes in cellular biochemistry and biology may be related to frankly adverse effects, which can be more readily observed at higher levels of exposure. Observations described in this assessment suggest a continuum of response to exposure to dioxin-like chemicals. By a continuum of response we suggest that as dose increases, the probability of occurrence of individual effects increases and the severity of collective effects increases. This continuum provides a basis for inferring a relationship between some early events that are not necessarily considered to be adverse effects with later events that are adverse effects. Considerable uncertainty remains in inferring how these events are related, although we know more about how dioxin-like compounds may elicit effects than we know about the mechanisms of action for most chemicals. This inference

may be the most contentious of all, and it is likely that a wide range of opinion will be provided by the scientific community regarding the relationship of these mechanistic observations and prediction of potential for adverse effects in exposed humans. This range of opinion must be carefully weighed to assure that the proper perspective concerning the relative likelihood of adverse effects in humans exposed to environmental levels is maintained.

9.11. OVERALL CONCLUSIONS REGARDING THE IMPACT OF DIOXIN AND RELATED COMPOUNDS ON HUMAN HEALTH

An extensive data base provides information pertinent to the evaluation of exposure of humans to dioxin and related compounds. An even larger data base of equal quality suggests that exposure to dioxin results in a broad spectrum of biochemical and biological effects in animals and, based on limited data, some of these effects occur in humans. Relatively speaking, these exposures and effects are observable at very low levels in the laboratory and in the environment when compared with other environmental toxicants. Despite the large amount of information available on exposure and effects of dioxin and related compounds, this risk characterization serves to highlight significant data gaps and identifies information needed to reduce uncertainty in its conclusions.

An extensive data base detailing dioxin emissions and dioxin levels in environmental media and in human serum and tissue indicates widespread, low-level human exposure. Much of the public concern for this potential exposure revolves around the characterization of these compounds as among the most toxic "man-made" chemicals ever studied. These compounds, which are generally unwanted by-products of chemical reactions, are extremely potent in producing a variety of effects in experimental animals based on traditional toxicology studies at levels hundreds or thousands of times lower than most synthetic chemicals of environmental interest. In addition, human studies demonstrate that exposure to dioxin and related compounds is associated with subtle biochemical and biological changes

whose clinical significance is as yet unknown and, at higher levels, with chloracne, a serious skin condition. Laboratory studies suggest that exposure to dioxin-like compounds may be associated with other serious health effects, including cancer. Human data, while limited in their ability to answer questions of hazard and risk, are consistent with some observations in animals. The ability to determine the expression in humans of adverse effects noted in laboratory studies or to detect these effects in human population studies is dependent on the dose absorbed and the intrinsic sensitivity of humans to these compounds. The large data base on exposure coupled with toxicity data from animal experiments, as well as more limited human information, forms the basis for the risk characterization of dioxin and related compounds.

A large variety of sources of dioxin have been identified and others may exist. Because dioxin-like chemicals are persistent and accumulate in biological tissues, particularly in animals, the major route of human exposure is through ingestion of foods containing minute quantities of dioxin-like compounds. This results in widespread, low-level exposure of the general population to dioxin-like compounds. Certain segments of the population may be exposed to additional increments of exposure by being in proximity to point sources or because of dietary practices.

Dioxin-like compounds are released to the environment in a variety of ways and in varying quantities, depending on the source. Despite a growing body of literature from laboratory, field, and monitoring studies examining the environmental fate and environmental distribution of CDDs, CDFs, and PCBs, the fate of these environmentally ubiquitous compounds is not yet fully understood. The available information suggests that the presence of dioxin-like compounds in the environment has occurred primarily as a result of industrial practices and is likely to reflect changes in release over time. Further work to confirm declining concentrations in environmental samples and to relate these data to human exposures will be required.

The principal identified sources of environmental release of CDDs and CDFs may be grouped into four major types: combustion and incineration sources; chemical

manufacturing/processing sources; industrial/municipal processes; and reservoir sources. PCBs were produced in relatively large quantities for use in such commercial products as dielectrics, hydraulic fluids, plastics, and paints. They are no longer produced in the United States but continue to be released to the environment through the use and disposal of these products. A similar situation exists for the commercially produced PBBs that are produced for a number of uses such as flame retardants. Additional measurement data will be needed to gain an adequate appreciation for the nature and magnitude of major U.S. sources and releases of CDDs, CDFs, and polyhalogenated biphenyls.

CDDs, CDFs, and PCBs have been found throughout the world in practically all media, including air, soil, water, sediment, fish and shellfish, and agricultural food products such as meat and dairy products. The highest levels of these compounds are found in soils, sediments, and biota; very low levels are found in water and air. The widespread occurrence observed, particularly in industrialized countries, is not unexpected, considering the numerous sources that emit these compounds into the environment and the overall resistance of these compounds to biotic and abiotic transformation. The levels of dioxin and related compounds in environmental media and in food in North America are based on few samples and must be considered quite uncertain. However, they seem reasonably consistent with levels measured in a number of studies in Western Europe and Canada. The consistency of these levels across industrialized countries provides reassurance that the U.S. estimates are reasonable. Collection of additional data to reduce uncertainty in U.S. estimates of dioxin-like compounds in the environment and in food represents an important data need.

This assessment adopts the hypothesis that the primary mechanism by which dioxin-like compounds enter the terrestrial food chain is via atmospheric deposition. Dioxin and related compounds enter the atmosphere directly through air emissions or indirectly, for example, through volatilization from land or water or from resuspension of particles. Deposition can occur directly onto soil or onto plant surfaces. At present, it is unclear whether atmospheric deposition represents primarily current contributions of dioxin and related compounds from all media reaching the atmosphere or whether it is past emissions of dioxin and related compounds that persist and recycle in the environment. Understanding the relationship between these two scenarios will be particularly important in understanding the

relative contributions of individual point sources of these compounds to the food chain and in assessing the effectiveness of control strategies focused on either current or past emissions of dioxins in attempting to reduce the levels in food.

Throughout this document, concentrations of dioxin and related compounds have been presented as TCDD equivalents (TEQs). Total TEQs are the sum of the products of concentrations of individual dioxin-like compounds in a complex environmental mixture times the corresponding TCDD toxicity equivalence factor (TEF) for that compound [Total TEQs = $\Sigma\ C_{congener} \times TEF_{congener}$]. The strengths and weaknesses as well as the uncertainties associated with the TEF/TEQ approach have been discussed in this chapter. As noted, the use of the TEQ approach is fundamental to the evaluation of this group of compounds and, as such, represents a key assumption on which many of the conclusions in this characterization hinge.

The term "background" exposure has been used throughout this reassessment to describe exposure of the general population that is not exposed to readily identifiable point sources of dioxin-like compounds. Data on human tissue levels suggest that body burden levels among industrialized nations are reasonably similar (Schecter, 1991). These data can also be used to estimate background exposure through the use of pharmacokinetic models. Using this approach, exposure levels to 2,3,7,8-TCDD in industrialized nations are estimated to be about 0.3-0.6 pg TCDD/kg body weight/day[1]. This is generally consistent with the estimates derived using diet-based approaches to estimate total TCDD intake. Pharmacokinetic approaches have not been applied to estimate exposures to CDDs or CDFs other than TCDD, which contribute substantially to the body burden of dioxin-like compounds. Estimates of exposure to dioxin-like CDDs and CDFs based on dietary intake are in the range of 1-3 pg TEQ/kg body weight/day. Estimates based on the contribution of dioxin-like PCBs to toxicity equivalents raise the total to 3-6 pg TEQ/kg body weight/day. This range is used throughout this characterization as an estimate of average background exposure to dioxin-like CDDs, CDFs, and PCBs. This average background exposure leads to body burdens in the human population that average 40-60 pg TEQ/g lipid (40-60 ppt)

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[1]Since 2,3,7,8-TCDD is the reference compound for the TEF/TEQ approach, 1.0 pg TCDD = 1.0 pg TEQ.

when all dioxins, furans, and PCBs are included. High-end estimates of body burden of individuals in the general population (approximately the top 10% of the general population) may be greater than three times higher.

In addition to general population exposure, some individuals or groups of individuals may also be exposed to dioxin-like compounds from discrete sources or pathways locally within their environment. Examples of these "special" exposures include occupational exposures, direct or indirect exposure to local populations from discrete sources, exposure to nursing infants from mother's milk, or exposures to subsistence or recreational fishers. These exposures have been discussed previously in terms of increased exposure due to dietary habits (see Exposure Document) or due to occupational conditions or industrial accidents (see Chapter 7). Although exposures to these populations may be significantly higher than to the general population, they usually represent a relatively small percentage of the total population. Inclusion of their levels of exposure in the general population estimates would have little impact on average population estimates. Simply evaluating these exposures as average daily intakes prorated over a lifetime might obscure the potential significance of elevated exposures for these subpopulations, particularly if exposures occur for a short period of time during critical windows of biological sensitivity.

The scientific community has identified and described a series of common biological steps that are necessary for most if not all of the observed effects of dioxin and related compounds in vertebrates, including humans. Binding of dioxin-like compounds to a cellular protein called the "Ah receptor" represents the first step in a series of events attributable to exposure to dioxin-like compounds, including biochemical, cellular, and tissue-level changes in normal biological processes. Binding to the Ah receptor appears to be necessary for all well-studied effects of dioxin but is not sufficient, in and of itself, to elicit these responses. This reassessment concludes that the effects elicited by exposure to 2,3,7,8-TCDD are shared by other chemicals that have a similar structure and Ah receptor-binding characteristics. Consequently, the biological system responds to the cumulative exposure of Ah receptor-mediated chemicals rather than to the exposure to any single dioxin-like compound.

Based on our understanding of dioxin mechanism(s) to date, it is accurate to say that interaction with the Ah receptor is necessary, that humans are likely to be sensitive to many of the effects of dioxin demonstrable in laboratory animals, and that there is likely to be a variation between and within species and between tissues in individual species based on differential responses "downstream" from receptor binding. Further analyses of dioxin action may provide more insight into the mechanisms by which TCDD and related compounds produce effects that are of particular public health concern. A major challenge for the future will be the establishment of experimental systems in which complex biological phenomena associated with these effects are amenable to study at the molecular level.

The concept of toxicity equivalence based on a unifying mechanism of action within this class of compounds and the use of toxicity equivalence factors as described in this document and elsewhere have been extensively reviewed and are widely used. While some uncertainty remains with regard to the additivity of complex mixtures of these compounds and with the impacts of co-exposure to nondioxin-like compounds, the use of this approach is consistent with the Agency's guidance on the evaluation of complex mixtures in the absence of data on the impact of the actual mixture. This approach to the evaluation of dioxin and related compounds, while considered an interim procedure to be used in the absence of more specific data, is an integral part of this reassessment. Additional validation studies to reduce uncertainty in the use of TEFs/TEQs will be very important.

There is adequate evidence based on all available information, including studies in human populations as well as in laboratory animals and from ancillary experimental data, to support the inference that humans are likely to respond with a broad spectrum of effects from exposure to dioxin and related compounds, if exposures are high enough. These effects will likely range from adaptive changes at or near background levels of exposure to adverse effects with increasing severity as exposure increases above background levels.

Enzyme induction, changes in hormone levels, and indicators of altered cellular function represent examples of effects of unknown clinical significance and which may or

may not be early indicators of toxic response. Induction of activating/metabolizing enzymes at or near background levels, for instance, may be adaptive or may be considered adverse since induction may lead to more rapid metabolism and elimination of potentially toxic compounds, or may lead to increases in reactive intermediates and may potentiate toxic effects. Demonstration of examples of both of these situations is available in the published literature.

Clearly adverse effects, including perhaps cancer, may not be detectable until exposures exceed background by one or two orders of magnitude. The mechanistic relationships of biochemical and cellular changes seen at very low levels of exposure to production of adverse effects detectable at higher levels remain uncertain and controversial.

Individual species vary in their sensitivity to any particular dioxin effect. However, the evidence available to date indicates that humans most likely fall in the middle of the range of sensitivity for individual effects among animals rather than at either extreme. In other words, evaluation of the available data suggests that humans, in general, are neither extremely sensitive nor insensitive to the individual effects of dioxin-like compounds. Human data provide direct or indirect support for evaluation of likely effect levels for several of the end points discussed in previous sections, although the influence of variability among humans remains difficult to assess. Discussions in previous chapters have highlighted certain prominent, biologically significant effects of TCDD and related compounds. These biochemical, cellular, and organ-level end points have been shown to be affected by TCDD, but specific data on these end points do not generally exist for other congeners. Despite this lack of congener-specific data, there is reason to infer that these effects may occur for all dioxin-like compounds, based on the concept of toxicity equivalence.

Some of the effects of dioxin and related compounds, such as enzyme induction, changes in hormone levels, and indicators of altered cellular function, have been observed in laboratory animals and humans at or near levels to which people in the general population are exposed. Other effects are detectable only in highly exposed populations, and there may or may not be a likelihood of response in individuals experiencing lower levels of exposure. Evaluation of effects in this health assessment document is based on the concept that lipid-adjusted serum levels approximate the body burden of dioxin and related compounds and that

there will be a dose-response relationship between effects and body burden. Adverse effects associated with temporary increases in dioxin blood levels based on short-term high-level exposures, such as those that might occur in an industrial accident or in infrequent contact with highly contaminated environmental media, may be dependent on exposure coinciding with a window of sensitivity of biological processes. It is reasonable to assume that developing organisms may be particularly sensitive to adverse impacts from temporary increases above average background exposure levels. Such exposures may also lead to higher tissue levels over the long term because of the long half-life for elimination of dioxin and related compounds.

In TCDD-exposed men, subtle changes in biochemistry and physiology, such as enzyme induction, altered levels of circulating reproductive hormones, or reduced glucose tolerance, have been detected in a limited number of available studies. These findings, coupled with knowledge derived from animal experiments, suggest the potential for adverse impacts on human metabolism and developmental and/or reproductive biology and, perhaps, other effects in the range of current human exposures. Given the assumption that TEQ intake values represent a valid comparison with TCDD exposure, some of these adverse impacts may be occurring at or within one order of magnitude of average background TEQ intake or body-burden levels (equal to 3-6 to 60 pg TEQ/kg body weight/day or 40-60 to 600 ppt in lipid). As body burdens increase within and above this range, the probability and severity as well as the spectrum of human noncancer effects most likely increase. It is not currently possible to state exactly how or at what levels humans in the population will respond, but the margin of exposure (MOE) between background levels and levels where effects are detectable in humans in terms of TEQs is considerably smaller than previously estimated.

Average human daily intakes of TCDD are in the range of 0.3-0.6 pg TCDD/kg body weight/day. Using the TEQ approach, average human daily intakes of dioxin and related compounds, including the dioxin-like PCBs, are in the range of 3-6 pg TEQ/kg body weight/day. This intake results in average body burdens estimated to be in the range of 30-

60 pg TEQ/g lipid (30-60 ppt) or 5-10 ng TEQ/kg body weight. Subtle changes in biochemistry and physiology described above and discussed in detail in previous chapters are seen with TCDD exposures at or just several fold above these average TEQ levels. Since exposures within the general population are thought to be log-normally distributed, individuals at the high end of the general population range (with body burdens estimated to be three, and perhaps as high as seven, times higher than the average) may be experiencing some of these effects. These facts and assumptions lead to the inference that some more highly exposed members of the general population or more highly exposed, special populations may be at risk for a number of adverse effects, including developmental toxicity based on the inherent sensitivity of the developing organism to changes in cellular biochemistry and/or physiology, reduced reproductive capacity in males based on decreased sperm counts, higher probability of experiencing endometriosis in women, reduced ability to withstand an immunological challenge, and others. This inference that more highly exposed members of the population may be at risk for various noncancer effects is supported by observations in animals, by some human information from highly exposed cohorts, and by scientific inference.

The deduction that humans are likely to respond with noncancer effects from exposure to dioxin-like compounds is based on the fundamental level at which these compounds affect cellular regulation and the broad range of species that have proven to respond with adverse effects. Since, for example, developmental toxicity following exposure to TCDD-like congeners occurs in fish, birds, and mammals, it is likely to occur at some level in humans. It is not currently possible to state exactly how or at what levels people will respond with adverse impacts on development or reproductive function. Fortunately, there have been few human cohorts identified with TCDD exposures in the high end of the exposure range, and when these cohorts have been examined, few clinically significant effects were detected. The lack of adequate human information and the focus of most currently available epidemiologic studies on occupationally TCDD-exposed adult males make difficult the evaluation of the inference that noncancer effects associated with exposure to dioxin-like compounds may be occurring. It is important to note, however, that when exposures to very high levels of dioxin-like compounds have been studied, such as in the Yusho and Yu-Cheng cohorts, a

spectrum of adverse effects has been detected in men, women, and children. Some have argued that to deduce that a spectrum of noncancer effects will occur in humans in the absence of better human data overstates the science; most scientists involved in the reassessment as authors and reviewers have indicated that such inference is reasonable given the weight of the evidence from available data. As presented, this logical conclusion represents a testable hypothesis that may be evaluated by further data collection.

The likelihood that noncancer effects may be occurring in the human population at environmental exposure levels is often evaluated using a margin of exposure approach. A MOE is calculated by dividing the human-equivalent animal lowest observed adverse effect level or no observed adverse effect level with the human exposure level. MOEs in the range of 100 to 1,000 are generally considered adequate to rule out the likelihood of significant effects occurring in humans based on sensitive animal responses. The average levels of intake of dioxin-like compounds in terms of TEQs in humans described above would be well within a factor of 100 of levels representing lowest observed adverse effect levels in laboratory animals exposed to TCDD or TCDD equivalents. For several of the effects noted in animals, a MOE of less than a factor of 10, based on intake levels or body burdens, is likely to exist.

The previous basis for MOE calculations was the observation that exposure in the range of 1-10 ng TEQ/kg/day represented a no observed adverse effect level for a sensitive noncancer end point in laboratory animals and, therefore, that an intake of up to 10 pg TEQ/kg/day might represent an adequate MOE for all other noncancer effects in humans. Recent data suggest that "high-end" average exposures in the general population are likely to approach this intake level and that several effects, both subtle and frank, can be demonstrated to occur in animals at intake values significantly lower than 1-10 ng TEQ/kg/day. This information, coupled with limited human data suggesting measurable effects, which may or may not be considered adverse, at or near average background intake levels, makes it highly unlikely that a margin of exposure of 100 or more currently exists for these effects at background intake levels, at least for some members of the human population. Whether the current MOE is adequate to protect public health is beyond the purview of this document and represents a risk management decision. The reassessment points to the need to continue to

monitor trends in human intake and body burden for dioxin and related compounds. If levels are declining, the relationship of background body burdens to observed effect levels in animal and human studies will need to be reevaluated.

Another approach that has been used to evaluate the likelihood of noncancer effects of environmental chemicals is the reference dose (RfD). The EPA has frequently defined a reference dose for toxic chemicals to represent a scientific estimate of the dose below which no appreciable risk of noncancer effects is likely to occur following chronic exposures. In the case of dioxin and related compounds, calculation of an RfD based on human and animal data and including standard uncertainty factors to account for species differences and sensitive subpopulations would likely result in reference intake levels on the order of 10 to 100 times below the current estimates of daily intake in the general population. For most compounds where RfDs are applied, the compounds are not persistent and background exposures that are generally low are not taken into account. Dioxin and related compounds present an excellent example of a case where background levels in the general population are likely to have significance for evaluation of the relative impact of incremental exposures associated with a specific source. Since RfDs refer to the total chronic dose level, the use of the RfD in evaluating incremental exposures in the face of a background intake exceeding the RfD would be inappropriate and make the calculation of an Rfd for dioxin-like compounds of doubtful significance.

In addition to the concern for various noncancer health end points discussed above, the potential immunotoxicity of dioxin and related compounds represents a special situation. Impairment of the immune system can be considered an adverse outcome in its own right, being responsible for induced pathologies. At the same time, immunotoxicity can function as a modulator of the disease process. It has been clearly established that TCDD is immunotoxic and that it can impair normal immune function in laboratory animals at very low levels (see Table 9-5). Epidemiological studies provide conflicting evidence for the immunotoxicity of these compounds in humans. Few changes in the immune system in humans associated with dioxin body burdens have been detected when exposed adult males have been studied. It is possible that humans may be less sensitive than certain animal models to dioxin immunotoxicity, or that available studies have lacked the power or the

specificity to evaluate the impact of immunotoxic responses to dioxin and related compounds in humans. Despite the possibility that these compounds may be immunotoxic at some level in humans, the impact of dioxin and related compounds on the immune system and implications for characterizing risk are largely unknown at this time.

With regard to carcinogenicity, a weight-of-the-evidence evaluation suggests that dioxin and related compounds (CDDs, CDFs, and dioxin-like PCBs) are likely to present a cancer hazard to humans. While major uncertainties remain, efforts of this reassessment to bring more data into the evaluation of cancer potency have resulted in a risk-specific dose estimate (1×10^{-6} risk or one additional cancer in one million exposed) of approximately 0.01 pg TEQ/kg body weight/day. This risk-specific dose estimate represents a plausible upper bound on risk based on the evaluation of animal and human data. "True" risks are not likely to exceed this value, may be less, and may even be zero for some members of the population.

Based on bioavailability and uptake studies, a cancer hazard is likely by oral, inhalation, and dermal routes of exposure. As daily doses through these routes and subsequent body burdens approach those seen in occupational studies, the uncertainty of the hazard characterization is reduced. The epidemiological data alone are not yet deemed sufficient to characterize the cancer hazard of this class of compounds as being "known." However, combining suggestive evidence of recent epidemiology studies with the unequivocal evidence in animal studies and inferences drawn from mechanistic data supports the characterization of dioxin and related compounds as likely cancer hazards, that is, likely to produce cancer in some humans under some conditions. It is important to distinguish this statement of cancer hazard from the evaluation of cancer risk. The extent of cancer risk will depend on such parameters as route and level of exposure, overall body burden, dose to target tissues, individual sensitivity, and hormonal status.

The current evidence suggests that both receptor binding and most early biochemical events such as induction of CYP1A1 and CYP1A2, as described in Chapter 8, are likely to demonstrate low-dose linearity. The mechanistic relationship of these early events to the

complex process of carcinogenesis remains to be established. If these findings imply low-dose linearity in biologically based cancer models under development, then the probability of cancer risk will be linearly related to exposure to TCDD at low doses. Until the mechanistic relationship between early cellular responses and the parameters in biologically based cancer models is better understood, the shape of the dose-response curve for cancer in the low-dose region can only be inferred with uncertainty. Associations between exposure to dioxin and certain types of cancer have been noted in occupational cohorts with average body burdens of TCDD approximately two orders of magnitude (100 times) higher than average TCDD body burdens in the general population. The average body burden in these occupational cohorts is within one to two orders of magnitude (10 to 100 times) of average background body burdens in the general population in terms of TEQ. Thus, there is no need for large-scale low-dose extrapolations. Nonetheless, the relationship of apparent increases in cancer mortality in these populations to calculations of general population risk remains uncertain.

With regard to average intake, humans are currently exposed to background levels of dioxin-like compounds on the order of 3-6 pg TEQ/kg body weight/day, including dioxin-like PCBs. This is more than 500-fold higher than the EPA's 1985 risk-specific dose associated with a plausible upper-bound, one in a million (1×10^{-6}) risk of 0.006 pg TEQ/kg body weight/day and several hundredfold higher than revised risk-specific dose estimates presented in Chapter 8 of this reassessment. Plausible upper-bound risk estimates for general population exposures to dioxin and related compounds, therefore, may be as high as 10^{-4} to 10^{-3} (one in ten thousand to one in a thousand).

The fact that dioxin-like compounds are ubiquitous in the environment may have further implications for low-dose risk assessment. Special populations may receive identifiable, incremental exposures, based on proximity to specific sources or specific human activity patterns such as consumption of higher amounts of foods containing average or higher levels of dioxin-like compounds. The additive background model of Crump et al. (1976) implies that the addition of an incremental dose to an existing background exposure would support the use of a dose response model containing the assumption of linearity. This assumption is particularly appropriate, in the absence of more definitive data on dose response, if the exposure range (i.e., background exposure plus the added incremental

exposure) is within one to two orders of magnitude (10 to 100 times) of the range of observation of purported dioxin-induced tumors in highly exposed humans. In other words, the proximity of background exposures to the range of observation of tumors in animals and humans provides added support for the assumptions of additivity to background and linearity of response.

TCDD has been clearly shown to increase malignant tumor incidence in laboratory animals. In addition, a number of studies analyzed in Chapter 8 elucidate other biological effects of dioxin related to the process of carcinogenesis. These studies have been used to develop biologically based models of the pharmacokinetics of dioxin, of binding to the Ah receptor, and of induction of various proteins that may be involved in the carcinogenic process. In addition, bioassay data on TCDD reported by Kociba have been analyzed using the two-stage clonal expansion model of carcinogenesis. There is evidence to suggest that hormones and growth factors may be involved in TCDD carcinogenesis. The role of such factors warrants additional study. Ideally, a biologically based model for cancer induction by TCDD should explicitly consider hormonal influences. Initial attempts to construct a biologically based model for certain dioxin effects as a part of this reassessment will need to be continued and expanded to accommodate more of the available biology and to apply to a broader range of potential health effects associated with exposure to dioxin-like compounds.

Based on all of the data reviewed in this reassessment and scientific inference, a picture emerges of TCDD and related compounds as potent toxicants in animals with the potential to produce a spectrum of effects. Some of these effects may be occurring in humans at very low levels and some may be resulting in adverse impacts on human health.

The potency and fundamental level at which these compounds act on biological systems are analogous to several well-studied hormones. Dioxin and related compounds have the ability to alter the pattern of growth and differentiation of a number of cellular targets by initiating a series of biochemical and biological events resulting in the potential for a spectrum of responses in animals and humans. Despite this potential, there is currently no

clear indication of increased disease in the general population attributable to dioxin-like compounds. The lack of a clear indication of disease in the general population should not be considered strong evidence for no effect of exposure to dioxin-like compounds. Rather, lack of a clear indication of disease may be a result of the inability of our current data and scientific tools to directly detect effects at these levels of human exposure. Several factors suggest a need to further evaluate the impact of these chemicals on humans at or near current background levels. These are the weight of the evidence on exposure and effects, an apparently low margin of exposure for noncancer effects, and potential for additivity to background processes related to carcinogenicity.

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The following information is provided to assist you in locating information contained in the two external review drafts for dioxin.

Health Assessment Document for
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)
and Related Compounds
(EPA/600/BP-92/001a, 001b, 001c)

Volume I of III (EPA/600/BP-92/001a):

Chapter 1.	Disposition and Pharmacokinetics
Chapter 2.	Mechanisms of Toxic Actions
Chapter 3.	Acute, Subchronic, and Chronic Toxicity
Chapter 4.	Immunotoxic Effects
Chapter 5.	Reproductive and Developmental Toxicity
Chapter 6.	Carcinogenicity of TCDD in Animals

Volume II of III (EPA/600/BP-92/001b):

Chapter 7.	Epidemiology/Human Data
Chapter 8.	Dose-Response Relationships

Volume III of III (EPA/600/BP-92/001c):

Chapter 9.	Risk Characterization (Note: This third volume of the 3-volume set integrates health and exposure information on dioxin and related compounds; approx. 100 pages.)

Estimating Exposure to Dioxin-Like Compounds
(EPA/600/6-88/005Ca, 005Cb, 005Cc)

Volume I of III (EPA/600/6-88/005Ca):	Executive Summary (Note: This first volume of the 3-volume set summarizes the exposure information on dioxin and related compounds; approx. 100 pages.)
Volume II of III (EPA/600/6-88/005Cb):	Properties, Sources, Occurrence, and Background Exposure
Volume III of III (EPA/600/6-88/005Cc):	Site-Specific Assessment Procedures

Reassessment of Dioxin - External Review Drafts - How to Order

If you wish to receive copies of any of the volumes of the draft dioxin reassessment, please complete the bottom of this page and mail, fax, or phone the Center for Environmental Research Information (CERI) (see address and phone numbers below). Due to the large size of the reassessment (over 2,000 pages in length) and the expense of printing and mailing, please check only the document that you actually need from the following list.

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OR

____ Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and Related Compounds, Volumes I, II, and III, EPA/600/BP-92/001a, 001b, 001c.
(Note: The full document is 3 volumes and approximately 1,100 pages.)

AND/OR

____ Executive Summary of the Exposure Document, EPA/600/6-88/005Ca (paper)

* ____ Executive Summary of the Exposure Document, EPA/600/6-88/005Caa (disk)

(Note: This is Volume I of the 3-volume set; it summarizes the exposure information on dioxin and related compounds; approximately 100 pages.)

OR

____ Estimating Exposure to Dioxin-Like Compounds, Volumes I, II, and III, EPA/600/6-88/005Ca, Cb, Cc.
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