5. DOSE-RESPONSE CHARACTERIZATION

Previous sections of this integrated summary focused on characterizing the hazards of and exposure to dioxin-like compounds. In order to bring these issues together and provide an adequate characterization of risk, the relationships of exposure to dose and, ultimately, to response must be evaluated. Key questions to be asked include: (1) What can be said about the shape of the dose-response function in the observable range and what does this imply about dose-response in the range of environmental exposures? and (2) What is a reasonable limit (critical dose or point of departure [POD]) at the lower end of the observable range and what risk is associated with this exposure? In addition, one can address the issue of extrapolation beyond the range of the data in light of the answers to the above questions. Although extrapolation of risks beyond the range of observation in animals and/or humans is an inherently uncertain enterprise, it is recognized as an essential component of the risk assessment process (NAS/NRC, 1983). The level of uncertainty is dependent on the nature (amount and scope) of the available data and on the validity of the models that have been used to characterize dose-response. These form the bases for scientific inference regarding individual or population risk beyond the range of current observation (NAS/NRC, 1983, 1994).

Dose-response analysis can be implemented in a variety of ways in risk assessment, depending on the extent and quality of the available data. At the basic level, dose-response information comes from a comparison of doses or levels at which there are no observed adverse effects with those at which the lowest adverse effect is observed. Such an analysis can be enhanced through the application of mathematical models to interpolate between empirically measured data points (plus incorporating their statistical variability), with the option for extrapolation below these data points subject to model shape assumptions when going beyond the range of known data. One such form of modeling is the benchmark dose (BMD) analysis, where a mathematical model is used to calculate the dose necessary to elicit a predetermined response rate (e.g., an effective dose [ED] for a 1% response: ED_{01}). Ultimately, the development and use of physiologically-based pharmacokinetic PBPK models and biologically-based dose response models goes beyond the mathematical replication of data points by linking the model to relevant and measurable biological parameters in the species of interest, and potentially between species (Kim et al., 2002).

These dose-response concepts are developed in Part II, Chapter 8, where the body of literature concerning dose-response relationships for TCDD is presented. Among other things, this chapter addresses the important concept of selecting an appropriate metric for cross-species

1 scaling of dose and presents the results of empirical modeling for many of the available data sets

2 on TCDD exposures in humans and in animals. Although not all human observations or animal

3 experiments on TCDD are amenable to this level of dose-response modeling, more than 200 data

4 sets were evaluated for shape, leading to an effective dose value expressed as a percent response

5 being presented for each endpoint being evaluated.

6 The analysis of dose-response relationships for TCDD, considered within the context of

7 toxic equivalency, mechanism of action, and background human exposures, helps elucidate the

8 common ground and the boundaries of the science and science policy components inherent in

9 this risk characterization for the broader family of dioxin-like compounds. For instance, the

10 dose-response relationships provide a basis to infer a POD for extrapolation for cancer and

11 noncancer risk for a complex mixture of dioxin-like congeners given the assumption of toxic

12 equivalency as discussed in Part II, Chapter 9, Section 9.6. Similarly, these relationships provide

13 insight into the shape of the dose-response at the POD, which can help inform choices for

14 extrapolation models for both TCDD and total TEQ. Dose-response modeling also provides a

15 perspective on the relationship between the level at which effects are seen in experimental

16 systems or epidemiologic studies and background exposures and body burdens for dioxin and

17 related compounds.

18 In evaluating the dose-response relationships for TCDD as a basis for assessing this

19 family of compounds, both empirical dose-response modeling approaches and mode of action

20 based approaches have been developed and applied (see Part II, Chapter 8, Section 8.3 and 8.4;

21 Portier et al., 1996; Kim et al., 2003). Empirical models have advantages and disadvantages

22 relative to more ambitious mechanism-based models. Empirical models provide a simple

23 mathematical model that adequately describes the pattern of response for a particular data set;

24 they can also provide the means for hypothesis testing and interpolation between data points. In

25 addition, they can provide qualitative insights into underlying mechanisms. However, the major

26 disadvantage of empirical models is their inability to quantitatively link data sets in a

27 mechanistically meaningful manner. On the other hand, mechanism-based modeling can be a

28 powerful tool for understanding and combining information on complex biological systems. Use

29 of a truly mechanism-based approach can, in theory, enable more reliable and scientifically sound

30 extrapolations to lower doses and between species. However, any scientific uncertainty about the

31 mechanisms that the models describe is inevitably reflected in uncertainty about the predictions

32 of the models.

33 PBPK models have been validated in the observable response range for numerous

34 compounds in both animals and humans. The development of PBPK models for disposition of

TCDD in animals has proceeded through multiple levels of refinement, with newer models showing increasing levels of complexity by incorporating data for disposition of TCDD and its molecular actions with the AhR and other proteins, as well as numerous physiological parameters (Part II, Chapter 1). These models have provided insights into key determinants of TCDD disposition in treated animals. Development of such models continues and the current generation of dioxin PBPK models are being submitted for publication (DeVito et al., personal communication). Pharmacokinetic models have been extended to generate predictions for early biochemical consequences of tissue dosimetry of TCDD, such as induction of CYP1A1, and are being developed to address the impacts of enzyme induction (e.g., CYP1A2) on TCDD storage and half-life. It is anticipated that these enhanced PBPK models will improve the understanding of early phase human distributional and half-life kinetic data. However, extension of these models to more complex responses is more uncertain at this time, particularly regarding selection of the appropriate tissue metric to link to the effect(s) under consideration. Differences in interpretation of the mechanism of action embodied in these pharmacodynamic models lead to varying estimates of dose-dependent behavior for similar responses. The shape of the dose-response curves governing extrapolation to low doses are determined by these hypotheses and assumptions.

At this time, the knowledge of the mechanism of action of dioxin, receptor theory, and the available dose-response data do not firmly establish a scientific basis for replacing a linear procedure for estimating cancer potency. Consideration of this same information indicates that the use of different procedures to estimate the risk of exposure for cancer and noncancer endpoints may not be appropriate. Both the cancer and noncancer effects of dioxin appear to result from qualitatively similar modes of action. Initial steps in the process of toxicity are the same, and many early events appear to be shared. Thus, the inherent potential for low dose significance of either type of effect (cancer or noncancer) should be considered equal and evaluated accordingly. In the observable range around 1% excess response, the quantitative differences are relatively small. Below this response, the different mechanisms can diverge rapidly. The use of predicted biochemical responses as dose metrics for toxic responses is considered a potentially useful application of these models. However, greater understanding of the linkages between these biochemical effects and toxic responses is needed to reduce the potentially large uncertainty associated with these predictions.

5.1. DOSE METRIC(S)

One of the most difficult issues in risk assessment is determining the dose metric to use for animal-to-human extrapolations. An appropriate animal-to-human extrapolation of tissue dose is required to provide significant insight into differences in sensitivity among species. As noted in Section 1.3, the most appropriate dose metric should reflect both the magnitude and frequency of exposure, and it should be clearly related to the toxic endpoint of concern by a well-defined mechanism. However, this is often difficult, because human exposures with observable responses may be very different from highly controlled exposures in animal experiments. In addition, comparable exposures may be followed by very different pharmacokinetics (absorption, distribution, metabolism and/or elimination) in animals and humans. Finally, the sequelae of exposure in the form of a variety of responses related to age, organ, and species sensitivity complicate the choice of a common dose metric. Despite these complexities, relatively simple default approaches, including body surface or body weight scaling of daily exposures, have often been recommended (U.S. EPA, 1992a, 1996; ATSDR, 1999).

As discussed in Section 1.3, dose can be expressed in a number of ways. For TCDD and other dioxin-like compounds, attention has focused on the consideration of dose expressed as daily intake (ng/kg/day), body burden (ng/kg), or AUC (DeVito et al., 1995; Aylward et al., 1996). The concept of physiological time (lifetime of an animal) complicates the extrapolation, as the appropriate scaling factor is uncertain for toxic endpoints. Because body burden incorporates differences between species in TCDD half-life (these differences are large between rodent species and humans [see Part II, Chapter 8, Table 8.2]), this dose metric appears to be the most practical for many effects of this class of compounds (DeVito et al., 1995).

Average lifetime body burden is best suited for steady-state conditions, with difficulties arising when this dose metric is applied to the evaluation of acute exposures, such as those occurring in the 1976 accidental exposure in Seveso, Italy (Bertazzi and di Domenico, 1994). In cases such as this one, increased body burden associated with the acute exposure event is expected to decline (half-life for TCDD is approximately 7 years) until it begins to approach a steady-state level associated with the much smaller daily background intake. In general, daily excursions in human exposure are relatively small and have minor impact on average body burden. Instead, PBPK models suggest that human body burdens increase over time and begin to approach steady-state after approximately 25 years with typical background doses. Occupational exposures represent the middle ground where daily excursions during the working years can significantly exceed daily background intakes for a number of years, resulting in elevated body burdens.

1   The relationship between occupational exposures and body burden and between body

2 burden and AUC are demonstrated in Figure 5-1. This figure graphs two hypothetical body

3 burden scenarios during the 70-year lifespan of an individual. The first is a continuation to 70

4 years of age of the background body burden scenario discussed—with caveats and

5 assumptions— in Part I, Volume 3, Chapter 5. In this scenario, an infant is breast-fed for 6

6 months by a mother who has a background dioxin body burden level and is subsequently exposed

7 to the average current level of dioxin in the food supply (1 pg/kg/day). This background scenario

8 leads to a 70 year lifetime area under the curve (AUC) of 184 ng/kg*Y, equivalent to a lifetime

9 average body burden (LABB) of 2.6 ng/kg (~184/70 years).

10   In the second scenario, the same individual incurs an additional occupational exposure

11 between 20 and 30 years of age of 100 pg/kg/day—100 times background—which then ceases.

12 The buildup of dioxin body burden is evident in the peak level and shark fin appearance. AUC in

13 this occupational scenario is 3911 ng/kg*Y, and LABB is 55.9 ng/kg. Note that in the

14 occupational scenario the AUC and LABB are only 21 times background.

15   Table 5-1 and Figure 5-2 summarize literature on average levels of dioxin TEQs in the

16 background human population and peak levels in commonly cited epidemiological cohorts.

17 Table 5-1 collates data on tissue lipid levels (ppt lipid adjusted) in populations, principally from

18 serum, and tabulates either current levels for the background population or back-calculated peak

19 levels for the exposed cohorts. Figure 5-2 graphs the estimated range and central tendency of the

20 total TEQ_{DFP} body burden (ng/kg whole body), combining the range of measured 2,3,7,8-TCDD

21 values with the estimate of the background non-2,3,7,8-TCDD TEQ level from the U.S.

22 population in the late 1980s/early 1990s. TEQ levels are calculated for PCDD, PCDF, and

23 PCBs, based on TEQ_{DFP}-WHO_{98} values, and assume a constant 25% body fat ratio when

24 converting from serum lipid ppt to ng/kg body burden. Total TEQ values for the Hamburg

25 cohort women were calculated by the authors, but did not include a dioxin-like PCB contribution.

26 Seveso values reported by Needham et al. (1999) are based on stored serum samples from

27 subjects undergoing medical examinations contemporaneous with the exposure and were not

28 back-calculated. Additional information consistent with Figure 5-2 has recently been published

29 (Eskenazi et al., 2004) that demonstrate similar Seveso Zones A and B initial levels, with an

30 important further measurement of background 2,3,7,8-TCDD (20.2 ppt serum lipid) and other

31 congener TEQ contributions (80.2 ppt) in the unexposed background population (non-ABR

32 women) in this time period.

33   As discussed earlier, using background total body burden (TEQ_{DFP}-WHO_{98}) as a point of

34 comparison, these often-termed "highly exposed" populations have peak body burdens that are

1 relatively close to general population backgrounds at the time. When compared with background

2 body burdens of the late 1980s, many of the median values and some of the mean values fall

3 within a range of one order of magnitude (factor of 10) and all fall within a range of two orders

4 of magnitude (factor of 100). General population backgrounds at the time are likely to have been

5 higher than present background body burdens.

6 One uncertainty in comparing peak body burdens is the use of a first-order elimination

7 rate with an overall half-life of 7.1 years. Recent evidence suggests that the elimination of

8 TCDD may be dependent on the level of exposure, in addition to an early distributional or

9 sequestration phase. Populations with high exposures may have half-lives significantly less than

10 7.1 years. Relatively rapid early elimination was noted in two highly exposed Austrian women

11 (initial half-lives of ~1.5 and 2.9 years; Geusau et al., 2002). Supportive data are also available

12 through an analysis of the Seveso populations (Michalek et al., 2002). In this analysis, a period

13 of fast elimination within the first 0.27 years after the exposure in Seveso was observed, followed

14 by a period of slower elimination between 3 and 16.35 years from exposure. The mean TCDD

15 half-life in the first 0.27 years after exposure in the Seveso cohort was 0.34 years in males (n=6)

16 and 0.43 years in females (n=10). From 3 years onward in the Seveso cohort, the half-life in

17 males was 6.9 years (n=9) and 9.6 years in females (n=13). For Ranch Handers, the half-life was

18 7.5 years (n=97) between 9 and 33 years after exposure. This analysis indicates that dioxin body

19 burdens and elimination kinetics may be more complex at higher doses than represented by a

20 single first-order half-life, including issues of tissue distribution and dose-dependent elimination.

21 This is consistent with the limited data available in rodents that also indicates a dose-dependent

22 elimination.

23 There are a number of physiologically-based pharmacokinetic models of TCDD in both

24 experimental animals and humans. Several of the rodent models assume that the elimination rate

25 of TCDD is a constant (Wang et al., 1997; 2000; Emond et al., 2004). One model by Anderson

26 et al. (1993) has a dose dependent doubling of the elimination rate which is dependent upon Ah

27 receptor occupancy. Kohn et al. (1993; 1996) has the elimination rate increasing in proportion to

28 body weight and includes an increased elimination of TCDD from the liver at high doses due to

29 hepatocyte cell death. The Carrier et al. (1995a, b) model describes a dose-dependent

30 elimination of TCDD and other dioxins due to a dose-dependent hepatic sequestration of these

31 chemicals. While these models use different approaches, they all provide reasonable fits to the

32 available experimental data.

33 Attempts to develop pharmacokinetic models for TCDD in humans have also resulted in

34 a variety of mathematical descriptions of the elimination rate. Maruyama et al. (2002, 2003)

have assumed that the elimination rate is constant. Van der Molen et al. (1998; 2000) multiply a constant elimination rate by the ratio of liver fat/body fat. This results in an overall change in the elimination of TCDD based on body composition and body weight. Gentry et al. (2003) and Clewell et al. (2004) describe the elimination of TCDD in proportion to hepatic CYP1A2 expression. Aylward et al. (2004) modified the Carrier et al. (1995a, b) model to include an elimination of dioxins directly into the large intestine based on lipid partitioning. This model provided reasonable fits to data from Seveso patients as well as three Austrian patients. Finally, Michalek et al. (2002) used a classical pharmacokinetic approach to describe the Seveso data. This work suggests that there is an early distribution phase that results in a rapid loss of TCDD from the blood (half-life of 0.37 years) followed by a prolonged terminal elimination phase (half-life approximately 6.9 years).

Hence, there are a number of pharmacokinetic models available that describe the absorption, distribution and elimination of TCDD in animals and humans. While these models provide reasonable fits to the available data, they employ a wide range of descriptions of the elimination of TCDD. Some assume first order elimination, while others assume dose-dependent pharmacokinetics. Others suggest that body composition significantly influences the elimination of dioxins. Presently, it is difficult to determine which of these model structures provides the most accurate description of the pharmacokinetics of TCDD and other dioxins.

Advances in understanding the dose-dependency of the pharmacokinetics of TCDD and related chemicals will improve our ability to describe the relationship between exposure, dose and response. The development of more accurate models may affect both exposure group assignment in epidemiology studies and the calculation of dose-response curves, although the magnitude and direction of these postulated impacts remains to be quantified. Estimates of back-calculated doses are important because the ability to detect effects in epidemiologic studies is dependent on a sufficient difference between control and exposed populations. Using published first-order back-calculation procedures, the relatively small difference (< 10–100-fold) in body burden between exposed and controls in the dioxin epidemiology studies makes exposure characterization in the studies a particularly serious issue. This point also strengthens the importance of measured blood or tissue levels in the epidemiologic analyses, despite the uncertainties associated with calculations extending the distribution of measured values to the entire cohort and assumptions involved in back-calculations.

As a bounding exercise on the impact of half-lives on back-extrapolated exposure estimates, EPA has compared the impacts of varying half-life values on back-calculated peak and AUC results. This scenario is constructed by calculating the peak body burden 20 years prior to a

1   terminal level for various half-lives versus a 7.1 year fixed half-life, assuming first order kinetics

2   ($C_t = C_0 e^{-rt}$). A constant dosing regimen is then constructed to simulate an occupational exposure

3   that would achieve these same peak body burdens following 10 years exposure, maintaining the

4   same half-life as in the 20 year follow-up.   For each half-life value, a different dose level is

5   necessary and was mathematically derived to reach the required peak level after ten years

6   occupational exposure.

7   In this occupational scenario, peak and AUC ratios ($AUC_{variable\ half-life}/AUC_{7.1years}$) varied in

8   a non-linear manner depending on the input half-life. Half-life values of 4 years and longer had

9   low, single digit numerical impacts on the peak and AUC ratios compared to the 7.1 year half-life

10   results (e.g., at a 4 year half-life, the ratio for the peak value = 4.6, the AUC ratio = 3.8; at a 5

11   year half-life, the ratio for peak = 2.3, AUC = 2). At half-lives below 4 years, peak and AUC

12   ratios rose dramatically to approximately 1 and 2 orders of magnitude for 3 and 2 year half-lives,

13   respectively. The terminal body burden did not influence the ratio because the mathematical

14   function remained constant. More complex PBPK models, where half-life varies with body

15   burden, are under development and will be more influenced by the terminal body burden for each

16   individual. This bounding exercise suggests that impacts on back-calculated peak and AUC

17   values may become significant if the models predict prolonged periods with half-lives of less

18   than 4 years.

19   **5.1.1. Calculations of Effective Dose**

20   Comparisons across multiple endpoints, multiple species, and multiple experimental

21   protocols are too complicated to be made on the basis of the full dose-response curve. As

22   discussed above, comparisons of this sort can be made by either choosing a given exposure and

23   comparing the responses or choosing a particular response level and comparing the associated

24   exposures. In the analyses contained in Chapter 8, Section 8.3, and elsewhere in the

25   reassessment, emphasis is placed on comparing responses using estimated exposures associated

26   with a given level of excess response or risk. To avoid large extrapolations, this common level

27   of excess risk was chosen such that for most studies the estimated exposure is in or near the

28   range of the exposures seen in the studies being compared, with extra weight given to the human

29   data. A common metric for comparison is the effective dose, which is the dose resulting in an

30   excess response over background in the studied population. This excess response rate can be

31   calculated as a fraction of the minimum to maximum response (e.g., 1% increase in risk).

32   Alternatively, for continuous data the dose can be calculated as the amount necessary to move an

33   additional percentage of distribution of the response past a predetermined "effect" level. EPA

1 has suggested this approach in calculating BMDs (Allen et al., 1994) and in its proposed

2 approaches to quantifying cancer risk (U.S. EPA, 1996, 1999, 2003).

3   Although effective dose evaluation at the 10% response level (ED_{10} or lower bound on

4 ED_{10} [LED_{10}]) is somewhat the norm, given the power of most chronic toxicology studies to

5 detect an effect, this level is actually higher than those typically observed in the exposed groups

6 in studies of TCDD impacts on humans. To illustrate, lung cancer mortality has a background

7 lifetime risk of approximately 4% (smokers and nonsmokers combined), so that even a relative

8 risk of 2.0 (two times the background lifetime risk) represents approximately a 4%, or 4 in 100,

9 increased lifetime risk (see Chapter 8 for a comprehensive elaboration of formulae). On the basis

10 of this observation, and recognizing that many of the TCDD-induced endpoints studied in the

11 laboratory include 1% effect levels in the experimental range, Chapter 8 presents effective doses

12 of 1%, or $ED_{01,}$ and 10%, or ED_{10}, values.

13   The use of effective dose values below 10% is consistent with the Agency's guidance on

14 the use of mode of action in assessing risk, as described in the proposed carcinogen risk

15 assessment guidelines (U.S. EPA, 1996, 1999, 2003) and in the evaluation framework discussed

16 in Section 3.3, in that the observed range for many "key events" for TCDD extends down to or

17 near the 1% response level. Determining the dose at which key events for dioxin toxicity begin

18 to be seen in a heterogeneous human population provides important information for decisions

19 regarding risk and safety.

20

21 **5.2. EMPIRICAL MODELING OF INDIVIDUAL DATA SETS**

22   As described in Chapter 8, Section 8.3, empirical models have advantages and

23 disadvantages relative to more ambitious mechanism-based models. Empirical models provide a

24 simple mathematical model that adequately describes the pattern of response for a particular data

25 set and that can also provide the means for hypothesis testing and interpolation between data

26 points. In addition, they can provide qualitative insights into underlying mechanisms. However,

27 the major disadvantage is their inability to quantitatively link data sets in a mechanistically

28 meaningful manner.

29   Data available for a number of biochemical and toxicological effects of TCDD and for its

30 mechanism of action indicate that there is good qualitative concordance between responses in

31 laboratory animals and humans (see Table 2-1). In addition, as described below, human data on

32 exposure and cancer response appear to be qualitatively consistent with animal-based risk

33 estimates derived from carcinogenicity bioassays. These and other data presented throughout this

34 reassessment would suggest that animal models are generally an appropriate basis for estimating

human responses to dioxin-like compounds. Nevertheless, there are clearly differences in exposures and responses between animals and humans, and recognition of these is essential when using animal data to estimate human risk. The level of confidence in any prediction of human risk depends on the degree to which the prediction is based on an accurate description of these interspecies extrapolation factors. See Chapter 8, Section 8.3, for a further discussion of this point.

Almost all dioxin research data are consistent with the hypothesis that the binding of TCDD to the AhR is the first step in a series of biochemical, cellular, and tissue changes that ultimately lead to toxic responses observed in both experimental animals and humans (see Part II, Chapter 2, Section 2.3). Therefore, an analysis of dose-response data and models should use, whenever possible, information on the quantitative relationships among ligand (i.e., TCDD) concentration, receptor occupancy, and biological response. However, it is clear that multiple dose-response relationships are possible when considering ligand receptor-mediated events. For example, dose-response relationships for relatively simple responses, such as enzyme induction, may not accurately predict dose-response relationships for complex responses such as developmental effects and cancer.

Cell- or tissue-specific factors may determine the quantitative relationship between receptor occupancy and the ultimate response. Indeed, for TCDD there are much experimental data from studies using animal and human tissues to indicate that this is the case. This serves as a note of caution, as empirical data on TCDD are interpreted in the broader context of complex exposures to mixtures of dioxin-like compounds as well as to nondioxin-like toxicants.

As for other chemical mechanisms where high biological potency is directed through the specific and high-affinity interaction between chemical and critical cellular target, the supposition of a response threshold for receptor-mediated effects is a subject for scientific debate. The basis of this controversy has been summarized by Sewall and Lucier (1995).

Based on classic receptor theory, the occupancy assumption states that the magnitude of biological response is proportional to the occupancy of receptors by drug molecules. The "typical" dose-response curve for such a receptor-mediated response is sigmoidal when plotted on a semilog graph or hyperbolic if plotted on an arithmetic plot. Implicit in this relationship is low-dose linearity (0–10% fractional response) through the origin. Although the law of mass action predicts that a single molecule of ligand can interact with a receptor, thereby inducing a response, it is also widely held that there must be some dose that is so low that receptor occupancy is trivial and, thus, no perceptible response is obtainable.

1   Therefore, the same receptor occupancy assumption of the classic receptor theory is

2   interpreted by different parties as support for and against the existence of a threshold. It has been

3   stated that the occupancy assumption cannot be accepted or rejected on experimental or

4   theoretical grounds (Goldstein et al., 1974). To determine the relevance of receptor interaction

5   for TCDD-mediated responses, one must consider (1) alternatives as well as limitations of the

6   occupancy theory, (2) molecular factors contributing to measured endpoints, (3) limitations of

7   experimental methods, (4) contribution of measured effect to a relevant biological/toxic

8   endpoint, and (5) background exposure.

9   Throughout this reassessment, each of these considerations has been explored within the

10   current context of the understanding of the mechanism of action of TCDD, of the methods for

11   analysis of dose-response for cancer and noncancer endpoints, and of the available data sets of

12   TCDD dose and effect for several rodent species, as well as humans who were occupationally

13   exposed to TCDD at levels exceeding the exposure of the general population.

14

15   **5.2.1. Cancer**

16   As discussed in Section 2.2.1.4, TCDD is characterized as carcinogenic to humans when

17   using a weight-of-evidence approach, and is a carcinogen in all species and strains of laboratory

18   animals tested. The epidemiological database for TCDD, described in detail in Part II, Chapter

19   7a, suggests that exposure may be associated with increases in all cancers combined and

20   respiratory cancer and with the possibility of elevated risks at other sites. Although there are

21   sufficient data in animal cancer studies to model dose-response for a number of tumor sites, as

22   with many chemicals it is generally difficult to find human data with sufficient information to

23   model dose-response relationships. For TCDD, three studies of human occupational exposure

24   have sufficient information to perform a quantitative dose-response analysis: Becher et al. (1998)

25   (the Hamburg cohort); Ott and Zober (1996) (the BASF cohort); and Steenland et al. (2001) (the

26   NIOSH cohort).

27   The all-cancer mortality ED_{01}/LED_{01} results from these three studies are detailed in Part

28   II, Chapter 8, Section 8.3, and tabulated and graphed in Table 5-2, along with the bioassay results

29   for liver cancer in female Sprague-Dawley rats (Kociba et al., 1978). Table 5-2 includes only the

30   results and mathematical formulae that were published by the primary authors in the peer-

31   reviewed literature. These calculations and formulae were chosen because they are based on the

32   full primary data set and not on secondary analyses using summary results. In order to graph

33   results for the occupational cohort studies, the central points for data ranges were requested from,

1 and kindly provided by, the authors (Drs. Steenland, Zober and Becher) and are included in the table.

2 Slightly different approaches are used for modeling cancer in humans than are used for

3 modeling in animal studies. The modeling approach used in the analysis of the human

4 epidemiology data for all cancers combined and lung cancer involves applying the estimated

5 human body burden-to-cancer response and estimating parameters in a mathematical risk model

6 for each data set. For the three occupational cohort studies, exposure subgroups were defined by

7 the authors using measured and then back-extrapolated TCDD levels in a subset of workers to

8 inform exposure calculations for the remainder of the cohort. None of the studies sampled

9 TCDD blood serum levels for more than a fraction of its cohort, and these samples were

10 generally taken decades after the last known exposure. In each study, serum fat or body fat levels

11 of TCDD were back-calculated using a first-order model. The assumed half-life of TCDD used

12 in the model varied from study to study.

13 Steenland et al. and Becher et al. used the measured and back-extrapolated TCDD

14 concentrations to refine and quantitate job exposure matrices, which were then used to estimate

15 dioxin cumulative dose for each member of their entire cohort. Ott and Zober (1996a) used

16 regression procedures with data on time spent at various occupational tasks to estimate TCDD

17 levels for all members of the cohort. The cohorts were then divided into exposure groups on the

18 basis of the estimated TCDD levels. As noted, central measures of the ranges from the primary

19 data were provided to the Agency by the authors, removing the need to estimate this parameter

20 from the upper and lower range points in the literature.

21 Risk outcomes in these cohorts were expressed as standardized mortality ratios (SMRs)

22 or rate ratios. SMRs are calculated by comparing the cancer rates in the subcohorts to the age-

23 and gender-matched general community in that time period. SMR results are usually expressed

24 as a ratio, with SMR = 100 set as the community, or expected, cancer death rate. Rate ratios are

25 calculated from within cohort data using the lowest exposed group as the control value for both

26 dose and risk. Although the lowest exposed group is defined to have a risk equal to unity (rate

27 ratio = 1), this low group may not, in fact, have an SMR equal to the general community (it could

28 be either lower or higher).

29 The three occupational cohort studies provide best fit dose-response models within the

30 range of their data. These models and the resulting formulae allow for the calculation of

31 ED_{01}/LED_{01} values, from which a linear extrapolation can be performed, consistent with the

32 EPA's draft cancer guidelines. There are several assumptions and uncertainties involved in

33 modeling these data, including extrapolation of dosage (both in back-calculation and in

elimination kinetics), the type of extrapolation model employed, and whether the origin point should be fixed (i.e., SMR = 100) or allowed to float.

Based on the model formulae using the full data set as provided in the primary literature (Steenland et al., 2001; Ott and Zober, 1996; Becher et al., 1998; detailed in Chapter 8), the calculated ED_{01} central estimates for all cancers combined range from 1.4 to 62 ng TCDD/kg LABB (Table 5-3). The lower bounds on these doses (based on a modeled 95% CI) range from 0.71 ng TCDD/kg to 30.5 ng TCDD/kg (not available for models published by Becher et al., 1998, due to the absence of statistical parameter measures). A parallel measure of unit excess risk per one part per trillion TCDD body burden above background (assumed 5 ppt) is also tabulated. These values are strongly dependent on the study chosen and the model used, and it must be recognized that the risks posed to some members of the population from TCDD may be zero, depending on the model chosen to extrapolate results below the range of observation. Male and female values do not match because of differences in the input variable of background lifetime all-cancer mortality risk.

Analysis of model results indicates that the power model applied to the Steenland et al. (2001) data leads to unreasonably high risks at low exposure levels, based on calculations of the attributable risk that this model would predict from background dioxin levels in the general population. This result is due to the very steep slope of this power curve at low environmental levels. The steep dose-response curve also makes the power model very sensitive to the background dose that is incorporated into the calculations and the location of the calculation point on the dose-response curve. Exclusion of the Steenland et al. power model reduces the ED_{01} range to 6–62 ng TCDD/kg LABB and the LED_{01} range to 11.5–31 ng TCDD/kg LABB (lower confidence values were unavailable for the Becher et al. 1998 data). For the purposes of this assessment, the piecewise linear formula published by Steenland et al. (2001) is the preferred model from this data set.

These epidemiologically derived ED_{01} values are summarized in Table 5-4 (additional details in Part II, Chapter 8), along with the resulting cancer slope factors. The results of the Kociba et al. (1978) cancer bioassay are also included in Table 5-4 for comparison purposes, using the Goodman and Sauer (1992) revision to the liver tumor pathology results. Dose-response modeling for this bioassay used the EPA Benchmark Dose software and multistage model to calculate the ED_{01}/LED_{01}. The similarity between the cancer bioassay ED_{01} results in rodents (Kociba et al. 1978) and the human epidemiology results is noteworthy when the exposure metric is based on lifetime average body burden (LABB). LABB is calculated as the AUC divided by lifetime years, and it equilibrates tissue doses across species.

1   The epidemiological data and dose-response models have stimulated considerable
2   contemporary interest and statistical analysis, particularly the option of performing a pooled or
3   meta-analysis on the entire occupational cohort data set. In reviewing this literature, care should
4   be taken to note which published analyses form the basis for the statistical tests, the recent
5   provision of data-derived central dose estimates for the ranges given in the literature (courtesy of
6   the primary authors), and the availability of more detailed primary dose-response literature
7   (Steenland et al., 2001; Becher et al., 1998), which supercede studies used previously (Aylward
8   et al., 1996; Flesch-Janys et al., 1998). For instance, the dose-response pattern for the NIOSH
9   cohort summary data, as published by Aylward et al. (1996), demonstrates a different high dose
10   point from the more recent and detailed analysis of the full dataset, as published by Steenland et
11   al. (2001).
12   Starr (2001, 2003) reviewed meta-analysis data and results that were included in the
13   external review draft of the EPA dioxin reassessment, and the analysis performed by Crump et al.
14   (2003; see below). The draft EPA meta-analysis was based on summary results published by
15   Aylward et al. (1996; NIOSH), Ott and Zober (1996; BASF), and Flesch-Janys et al. (1998).
16   Exposure range midpoints were either obtained from the original publication (Aylward et al.,
17   1996) or were based on a log-normal fit to the data ranges to estimate the midpoint (for Ott and
18   Zober, 1996; Flesch-Janys et al., 1998). On the basis of these earlier data sets and the application
19   of a linear model, Starr concluded that the assumption of a fixed origin at an SMR = 100 should
20   be rejected on statistical grounds. Although a significantly increased cancer risk was evident in
21   these cohorts, the overall results using an unconstrained linear model (not fixed to the SMR =
22   100 point) were concluded to be consistent with the null hypothesis of no dose-response
23   relationship between TCDD and the cancer rate.
24   In a subsequent dioxin meta-analysis performed as part of the Joint European
25   Commission on Food Additives, Crump et al. (2003) performed similar and expanded statistical
26   analyses on a more recent data set using data-derived central estimates of exposure levels for Ott
27   and Zober (1996; Hamburg cohort) and from Steenland et al. (2001; NIOSH cohort). Fitting a
28   linear model to the data again indicated that the baseline SMR = 100 assumption could be
29   rejected, based on statistical tests.
30   Goodness of fit trend tests for this linear model were statistically significant both with the
31   background SMR set equal to 100 and with the background SMR estimated (p=0.01). A further
32   series of trend tests were performed by successively removing the highest cumulative exposure to
33   determine the lowest exposure for which there remained statistically significant evidence for an
34   effect. This progressive analysis of the data was considered by Crump et al. to provide a more

robust test for trends than a linear goodness of fit test. The analysis demonstrated an increase in total cancer at cumulative TEQ serum levels that would result from a lifetime average intake of 7 pg TEQ/kg body weight/day (assuming 50% uptake, $t_{1/2}$ 7.6 years, 25% body fat), with no trend for increase at 6 pg/kg/day.

The pooled analysis of the Ott and Zober (1996), Flesch-Janys et al. (1998), and Steenland et al. (2001) data yielded ED_{01} estimates of 51 ng/kg body burden (baseline SMR fixed at 100) and 91 ng/kg body burden (baseline SMR estimated), corresponding to ED_{01} daily intake estimates of 25 and 45 (95% CI = 21–324) pg/kg/day, respectively, above current background TCDD-TEQ for all cancers combined (calculated using the half-life and absorption assumptions in Crump et al.). These results are consistent with the range of ED_{01}s in Part II, Chapter 8, and Tables 5-3 and 5-4. On the basis of their results and comparison to other published analyses, Crump et al. (2003) concluded that they could not see a clear choice between their ED_{01} estimate of 45 pg/kg/day and the Steenland et al. (2001) estimate of 7.7 pg/kg/day, citing advantages to each study.

The choice of model is central to the above statistical analyses of the individual studies and the meta-analysis. The epidemiological data are not sufficient to mandate the selection of any particular model shape. The published literature includes power, linear, piecewise linear, and multiplicative models (see Table 5-2). The EPA's draft carcinogen risk assessment guidelines (U.S. EPA, 1999) propose applying a standard curve-fitting procedure within the range of the data (e.g., Benchmark Dose software), recognizing that more elaborate models will be appropriate for more complex information and that, ultimately, biologically based pharmacokinetic models would be preferred.

The curve-fitting procedure is used to determine a POD, generally at the 10% response level, but where more sensitive data are available, a lower point for linear extrapolation can be used to improve the assessment (e.g., 1% response for dioxin, ED_{01}). Extrapolation from the POD to lower doses is conducted using a straight line drawn from the POD to the origin—zero incremental dose, zero incremental response—to give a probability of extra risk. The linear default is selected on the basis of the agent's mode of action when the linear model cannot be rejected and there is insufficient evidence to support an assumption of nonlinearity. Additional important uncertainties in the human epidemiological data are discussed in Part II, Chapter 8, Section 8.3, and include the representativeness and precision of the dose estimates that were used, the choice of half-life and whether it is dose dependent, and potential interactions between TCDD and smoking or other toxicants.

For the animal data, both empirical and mechanistic models have been applied to examine cancer dose-response. Portier et al. (1984) used a simple multistage model of carcinogenesis with up to two mutation stages affected by exposure to model the five tumor types observed to be increased in the 2-year feed study by Kociba et al. (1978) (Sprague-Dawley rats) and the eight tumor types observed to be increased in the 2-year gavage cancer study conducted by NTP (1982a) (Osborne-Mendel rats and B6C3F$_1$ mice). The findings from this analysis, which examined cancer dose-response within the range of observation, are presented in Part II, Chapter 8, Table 8.3., which is reproduced with slight modifications as Table 5-5. All but one of the estimated ED$_{01}$s are above the lowest dose used in the experiment (approximately 1 ng TCDD/kg/day in both studies) and are thus interpolations rather than extrapolations. The exception, liver cancer in female rats from the Kociba study, is very near the lowest dose used in this study and is only a small extrapolation (from 1 ng TCDD/kg/day to 0.77 ng TCDD/kg/day). Steady-state body burden calculations were also used to derive doses for comparison across species. Absorption was assumed to be 50% for the Kociba et al. (feed experiment) and 100% for the NTP study (gavage experiment).

The shapes of the dose-response curves as determined by Portier et al. (1984) are also presented in Table 5-5. The predominant shape of the dose-response curve in the experimental region for these animal cancer results is linear. This does not imply that a nonlinear model such as the quadratic or cubic—or for that matter a "J-shaped" model—would not fit these data. In fact, it is unlikely that in any one case a linear model or a quadratic model could be rejected statistically. These studies had only three experimental dose groups; hence, these shape calculations are not based on sufficient doses to guarantee a consistent estimate, and they should be viewed with caution.

The ED$_{01}$ steady-state body burdens range from a low value of 14 ng/kg, based on the linear model associated with liver tumors in female rats, to as high as 1190 ng/kg, based on a cubic model associated with thyroid follicular cell adenomas in female rats. Lower bounds on the steady-state body burdens in the animals range from 10 ng TCDD/kg to 224 ng/kg. The corresponding estimates of daily intake level at the ED$_{01}$ obtained from an empirical linear model range from 0.77 to 43 ng TCDD/kg body weight/day, depending on the tumor site, species, and sex of the animals investigated. Lower confidence bounds on the estimates of daily intake level at the ED$_{01}$ in the animals range from 0.57 to 14 ng TCDD/kg body weight/day.

In addition, using a mechanistic approach to modeling, Portier and Kohn (1996) combined the biochemical response model by Kohn et al. (1993) with a single initiated-phenotype two-stage model of carcinogenesis to estimate liver tumor incidence in female

Sprague-Dawley rats from the 2-year cancer bioassay by Kociba et al. (1978). By way of comparison, the ED_{01} estimate obtained from this linear mechanistic model was 0.15 ng TCDD/kg body weight/day, based on intake, which is equivalent to 2.7 ng TCDD/kg steady-state body burden. No lower bound on this modeled estimate of steady-state body burden was provided.

As discussed in Part II, Chapter 8, Section 8.2, the use of different dose metrics can lead to widely diverse conclusions. For example, the ED_{01} intake for the animal tumor sites presented above ranges from less than 1 to tens of ng/kg/day, and the lowest dose with an increased tumorigenic response (thyroid tumors) in a rat is 1.4 ng TCDD/kg/day (NTP, 1982a). The daily intake of dioxins in humans is estimated at approximately 1 pg TEQ/kg/day. This implies that humans are exposed to doses 1400 times lower than the lowest tumorigenic daily dose in rat thyroid. However, 1.4 ng TCDD/kg/d in the rat leads to a steady-state body burden of approximately 25 ng TCDD/kg, assuming a half-life of TCDD of 25 days and absorption from feed of 50%[2]. If the body burden of dioxins in humans is approximately 20 ng TEQ/kg lipid, or 5 ng TEQ/kg body weight (assuming about 25% of body weight is lipid), "average" humans are exposed to about five times less TCDD than the minimal carcinogenic dose for the rat. The difference between these two estimates is entirely due to the approximately 100-fold difference in the half-life of TCDD in humans and rats. At least for this comparison, if cancer is a function of average levels in the body, the most appropriate metric for comparison is the average or steady-state body burden, because this accounts for the large differences in animal and human half-lives.

Comparisons of human and animal ED_{01}s from Part II, Chapter 8, Section 8.3, for cancer response on a body burden basis show similar potential for the carcinogenic effects of TCDD. In humans, cancer ED_{01}s ranged from approximately 6 ng/kg to 62 ng/kg (excluding the Steenland et al., 2001, power model). This is similar to the empirical modeling estimates from the animal studies, which ranged from 14 ng/kg to 1190 ng/kg (most estimates were in the range of 14 to 500 ng/kg). The lower bounds on the human body burdens at the ED_{01}s (based on a modeled 95% CI) ranged from 11.5 ng TCDD/kg to 31 ng TCDD/kg (again, the lower values that would have resulted from the Becher et al., 1998, analysis could not be included because error bounds on the models were unavailable). Lower bounds on the steady-state body burdens in the animals ranged from 10 ng TCDD/kg to 224 ng/kg. The estimate for the single mechanism-based model presented earlier (2.7 ng/kg) is below the lower end of the human ED_{01} estimates.

---

[2] Steady-state body burden (ng/kg) = (daily dose (ng/kg/day) * (half-life)/Ln(2)) (f), where f is the fraction absorbed from the exposure route (unitless) and half-life is the half-life in days.

1   Using human and animal cancer ED_{01}s, their lower bound estimates, and the value of 2.7

2   ng TCDD/kg from the single mechanism-based model, slope factors and comparable risk

3   estimates for a human background body burden of approximately 5 ng TEQ/kg (20 ng TEQ/kg

4   lipid) can be calculated using the following equations:

5   Slope factor (per pg TEQ/kgBW/day) = risk at ED_{01} / intake (pg TEQ/kgBW/day)

6   associated with human equivalent steady-state body burden at $ED_{01,}$ where:

7

8   Risk at ED_{01} = 0.01; and

9

10   Intake (pg TEQ/kg BW/day) = [body burden at ED_{01} (ng TEQ/kg)* Ln(2)] * 1000 (pg/ng)

11    $$\text{half-life (days) x f} \qquad\qquad (5\text{-}1)$$

12

13   half-life = 2593 days in humans and 25 days in rats (see Table 8.1 in Part II, Chapter 8)

14   f = fraction of dose absorbed; assumed to be 0.8 (80%)

15   and

16   Upper bound on excess risk at human background body burden = (human   (5-2)

17   background body burden (ng/kg))(risk at ED_{01})/lower bound on human

18   equivalent steady-state body burden (ng/kg) at ED_{01}, where:

19   Risk at ED_{01} = 0.01

20

21   Use of these approaches reflects methodologies being developed within the context of the

22   revised draft carcinogen risk assessment guidelines (U.S. EPA, 1999, 2003). Under these draft

23   guidelines (EPA, 2003, section 5.4), risk estimates may be based on linear extrapolation or

24   nonlinear hazard quotients, depending on the mode of action, accompanied by a statement on the

25   extent of extrapolation generally expressed as the margin of exposure (MOE = POD/exposure).

26   The formulae used in this quantitative linear analysis for dioxin are approximate for a number of

27   the cancer slope factors derived from human data in Table 5.4 because of the calculation of risk

28   for 1pg TCDD/kg body weight/day above background, the use of lifetable analysis to derive the

29   expected cancer rates, and the changing gradient of the dose-response curves as body burden

30   increases, especially for the power formulae. As discussed below, these methods can be

31   compared to previous approaches using the linearized multistage (LMS) procedure to determine

32   whether the chosen approach has significantly changed the estimation of slope. The estimates of

33   ED_{01}/LED_{01} represent the human-equivalent body burden for 1% excess cancer risk based on

34   exposure to TCDD and are assumed for purposes of this analysis to be equal for TCDD

equivalents (total TEQ). This assumption is based on the toxic equivalency concept discussed throughout this report and in detail in Part II, Chapter 9. All cancer slope factors can be compared to the Agency's previous slope factor of 1.6×10^{-4} per pg TCDD/kg body weight/day, which is equivalent to 1.6×10^{5} per mg TCDD/kg body weight/day (U.S. EPA, 1985).

5.2.1.1. *Estimates of Slope Factors and Risk at Current Background Body Burdens Based on Human Data*

Traditionally, EPA has relied on central estimates of risk from epidemiological studies rather than on upper bound estimates, which can exhibit substantial statistical spread in these results. This practice developed because epidemiological data were most often from high-end occupational exposures—as with the principal dioxin literature—where the data were likely to provide upper estimates of cancer slope and where all excess cancer increases were attributed to the single exposure of interest, amidst a variety of other potential carcinogenic exposures. For the analyses conducted herein, the Agency has presented both central (e.g., ED_{01}) and upper bound (e.g., LED_{01}) estimates where these are available.

The estimates of slope factors (risk per pg TCDD/kg body weight/day) calculated from the human ED_{01}s presented in Part II, Chapter 8, Table 8.3.1, range from 5.1×10^{-3} if the ED_{01} for all cancer deaths in the Hamburg cohort is used to 0.57×10^{-3} if the ED_{01} for all cancer deaths in the smaller BASF cohort is used. All of the other slope factors for all cancer deaths in the three cohorts fall within this range (Table 5-4). The meta-analysis by Crump et al. (2003) leads to similar results, with the reported ED_{01} of 46 ng/kg (95% lower bound = 31 ng/kg) BB, resulting in a cancer slope factor of 0.65 (95% upper confidence limit = 0.97) x 10^{-3} risk per pg TCDD/kgBW/day (adopting the EPA assumptions of baseline SMR = 100, halflife = 7.1 years, 80% absorption; alternatively, adopting a floating SMR results in a CSF = 0.37 (0.69) x 10^{-3}).

There is no compelling reason to choose one slope factor over the next from among those calculated, given that each study had particular strengths and weaknesses (See Part II, Chapter 7a). The results cluster around a cancer slope factor of 10^{-3} risk/pgTCDD/kg body weight/day above background, which represents EPA's most current upper bound slope factor for estimating human cancer risk based on human data. By inference, this risk value could also apply to total TEQ intake. As described in Section 4.4.2, current intakes in the United States are approximately 1 pg TEQ_{DFP}-WHO_{98}/kg body weight/day, and body burdens are approximately 5 ng TEQ_{DFP}-WHO_{98}/kg body weight (which equates to a serum level of approximately 20 pg/g lipid). Uncertainties associated with these estimates from human studies are discussed in Part II, Chapter 8, Section 8.3, and in Becher et al. (1998).

1   These estimates compare well with the published estimates of cancer slope and risk for
2   the Hamburg and NIOSH cohorts by Becher et al. (1998) and Steenland et al. (2001),
3   respectively. The risk estimates by Becher et al. were derived from data on TCDD exposure to
4   male workers with a 0 or 10-year latency. These estimates range from 1.3×10^{-3} to 5.6×10^{-3} per
5   pg TCDD/kg body weight/day, and were calculated using German background cancer rates. The
6   fraction of dioxin assumed absorbed is not stated by Becher et al. but, presumably, if the
7   absorption fraction was set at 100%, this would contribute to the slight differences to the EPA
8   values in Table 5.5. The Steenland et al. calculations were performed for either no lag or a 15-
9   year lag. The authors calculated a lifetime all cancer excess risk above background of between 5
10   x 10^{-4} (piecewise linear) to 9.4 x 10^{-3} (power model) per pgTCDD/kg/day. The Steenland et al.
11   results are lower than those presented in Table 5-4 because the authors assumed 50% absorption
12   and a lower additional dose (i.e., incorporating a two-fold doubling of dose over background into
13   the Steenland et al. results reproduces their calculations).

14   In both analyses, all excess cancers are attributed to TCDD exposure, despite significant
15   levels of other dioxin-like compounds in blood measurements. Notable, though, is the Becher et
16   al. determination of a very similar slope coefficient for total TEQ and TCDD, based on their
17   measured data, which is consistent with the TEF methodology. The results from Steenland et al.
18   are more consistent with a reduced cancer slope factor when based on TEQ. Although risk
19   estimates using TCDD alone in these cohorts might suggest an overestimate of risk because dose
20   is underestimated, no evidence for this has emerged from the analysis because TCDD dominates
21   the total TEQ in these occupational cohorts.

22

23   **5.2.1.2.** *Estimates of Slope Factors and Risk at Current Background Body Burdens Based*
24   *on Animal Data*

25   Upper bound slope factors (per pg TCDD/kg body weight/day) for human cancer risk
26   calculated from lower bounds on ED_{01}s (LED_{01}s) for the animal cancers presented in Table 5-5
27   range from 3×10^{-3} to 0.1×10^{-3}, that is, from 19 times greater than the previous upper bound
28   estimate on cancer slope (1.6×10^{-4} [U.S. EPA, 1985]) to less than 50% of this value. The
29   highest slope factor is derived from the same study as the 1985 estimate; that is, the slope factor
30   derived from the female liver cancer in the Kociba et al. (1978) study continues to give the
31   highest slope factor.

32

5.2.1.2.1. *Reconciling the Portier (1984) and EPA (1985) slope estimates.* In attempting these comparisons, two issues became apparent. First, the body burden and the intake at the ED_{01} from Portier et al. (1984) does not result in the same slope factor as EPA's (U.S. EPA, 1985). Despite the use of the same study results, a slope factor of 1.8×10^{-5} per pg TCDD/kg body weight/day results when using the LMS approach in Portier et al. (1984), which is approximately a factor of 10 lower than EPA's estimate of the slope (U.S. EPA, 1985). The differences are attributable to the aims of the respective calculations at the time. Portier et al. calculated "virtually safe doses" assuming that rodent and human doses scaled on a mg/kg basis, and they used the original tumor counts from the study. EPA, on the other hand, used (body weight)$^{2/3}$ to arrive at a human equivalent dose and the pathology results from a reread of the original Kociba study (U.S. EPA, 1980). In addition, EPA adjusted tumor counts for early mortality in the study. The factor to adjust for (body weight)$^{2/3}$ scaling in the rat is 5.8. The correction for early mortality can be accounted for with a factor of 1.6 (this is the ratio of the intake values at the ED_{01} with and without the early mortality correction). If the Portier et al. slope factor (1.8×10^{-5} per pg TCDD/kg body weight/day) is multiplied by these two factors, a slope of 1.7×10^{-4} per pg TCDD/kg body weight/day is calculated. This is essentially equivalent to the EPA estimate of 1.6×10^{-4} per pg TCDD/kg body weight/day. Reconciling these issues is important to ensuring appropriate comparisons of slope factor estimates.

5.2.1.2.2. *Calculating a revised estimate of cancer slope from Kociba et al. (1978).* Of greater consideration is the calculation of slope factor estimates using current methods of analysis that recognize the importance of the dose metric and the differences in half-life of dioxins in the bodies of laboratory animals and humans (see Part II, Chapter 8, Section 8.2, for detailed discussion). The major difference between the approaches used to calculate risks in the mid-1980s (Portier et al., 1984; U.S. EPA, 1985) and the current approach is the use of body burden as the dose metric for animal-to-human dose equivalence. The decision to use body burden accounts for the approximately 100-fold difference between half-lives of TCDD in humans and rats (2593 days vs. 25 days [see Part II, Chapter 8, Table 8.1]).

The use of equation 5-1 results in an estimated body burden at the LED_{01} of 6.1 ng TEQ/kg, derived from the EPA (U.S. EPA, 1985) Kociba et al. tumor counts. This compares favorably with the Portier estimate of 10 ng TEQ/kg found in Table 5-5. The difference is entirely accounted for by the early deaths adjustment by EPA. Use of these body burdens at the LED_{01} results in slope factor estimates of 3.3×10^{-3} per pg TCDD/kg body weight/day and 4.9×10^{-3} per pg TCDD/kg body weight/day for the Portier at al. (1984) (10 ng/kg) and the newly

derived body burden (6.1 ng/kg), respectively. Again, the difference is due solely to the adjustment for early mortality, which EPA considers a better estimate of upper bound lifetime risk than the unadjusted estimate. EPA's revised slope factor (4.9×10^{-3} per pg TCDD/kg body weight/day) would be 31 times greater than the slope factor from 1985.

However, a second issue with the modeling of the Kociba et al. data relates to the use of the appropriate tumor counts. As mentioned in Section 2.2, Goodman and Sauer (1992) reported a second re-evaluation of the female rat liver tumors in the Kociba et al. study using the latest pathology criteria for such lesions. Results of this review are discussed in more detail in Part II, Chapter 6, Section 6.2. The review confirmed only approximately one-third of the tumors seen in the previous review (U.S. EPA, 1980). Although this finding did not change the determination of carcinogenic hazard, because TCDD induced tumors in multiple sites in this study, it does have an effect on evaluation of dose-response and on estimates of risk. Because neither the original EPA slope factor estimate (U.S. EPA, 1985) nor that of Portier et al. (1984) reflect this reread, it is important to factor these results into the estimate of the ED_{01} and slope factor.

Using the LMS procedure used by EPA in 1985 and the tumor counts as reported in Part II, Chapter 6, Table 6.2, the revised slope factor is reduced by approximately 3.6-fold to yield a slope factor of 4.4×10^{-5} per pg TCDD/kg body weight/day. However, because the original estimates used a (body weight)$^{2/3}$ scaling, an adjustment must also be made to remove this interspecies scaling factor in order to obtain a correct result when comparing with body burden as the interspecies metric. When dose is adjusted and equation 5-1 is used, an LED_{01} of 22.2 ng TEQ/kg and a slope factor of 1.4×10^{-3} per pg TCDD/kg body weight/day are derived. This represents EPA's most current upper bound slope factor for estimating human cancer risk based on animal data. It is 8.7 times larger than the slope factor calculated in U.S. EPA (1985). This number reflects the increase in slope factor based on the use of the body burden dose metric (31 times greater) and the Goodman and Sauer (1992) pathology (3.6 times less). These results can also be obtained using EPA's Benchmark Dose software and entering adjusted tumor counts and dose data to obtain a $BMDL_{01}$ from which an LED_{01} body burden of 22 ng/kg can be derived (see Tables 5-2, 5-4).

5.2.1.3. *Estimates of Slope Factors and Risk at Current Background Body Burdens Based on a Mechanistic Model*

As discussed above, Portier and Kohn (1996) combined the biochemical response model of Kohn et al. (1993) with a single initiated-phenotype two-stage model of carcinogenesis to estimate liver tumor incidence in female Sprague-Dawley rats from the Kociba et al. (1978)

1   bioassay. The model is described in more detail in Part II, Chapter 8, Section 8.4. This model

2   adequately fit the tumor data, although it overestimated the observed tumor response at the

3   lowest dose in the Kociba et al. study. The shape of the dose-response curve was approximately

4   linear, and the estimated ED_{01} value for this model was 1.3 ng/kg/day. The corresponding body

5   burden giving a 1% increased effect was 2.7 ng/kg.

6   The model authors believe that the use of CYP1A2 as a dose metric for the first mutation

7   rate is consistent with its role as the major TCDD-inducible estradiol hydrolase in liver and with

8   its hypothesized role in the production of estrogen metabolites leading to increased oxidative

9   DNA damage and increased mutation (Yager and Liehr, 1996; Hayes et al., 1996; Dannan et al.,

10   1986; Roy et al., 1992). Although no lower bound estimate of the ED_{01} is calculated, a

11   maximum likelihood estimate of the slope factor of 7.1×10^{-3} per pg TCDD/kgBW/day can be

12   calculated. This estimate represents an example of the type of modeling based on key events in a

13   mode of action for carcinogenesis that is consistent with the future directions in dose-response

14   modeling described in EPA's revised proposed cancer risk assessment guidelines (U.S. EPA,

15   1999). Although a number of uncertainties remain regarding structure and parameters of the

16   model, the slope estimate is consistent with those derived from humans and animals. More

17   details on this model can be found in Part II, Chapter 8, Section 8.4.

18   An alternative mechanistic model has been proposed (Conolly and Andersen, 1997). This

19   model was developed for focal lesion growth, based on two types of initiated cells and applying

20   the negative selection mechanism for hepatic tumor promotion proposed by Jirtle et al. (Jirtle and

21   Meyer, 1991; Jirtle et al., 1991). In this model, even though the two types of initiated cells

22   express the same biochemical marker, they respond differently to promotional stimulation in the

23   liver. The model presumes that a promotional stimulus to the liver is countered by mito-

24   inhibitory signals generated by the liver to constrain proliferation. One set of mutated cells is

25   sensitive to this mito-inhibition, whereas the other set of mutated cells is insensitive and

26   responds only to the promotional stimulus. The result is that, under increasing doses of the

27   promoter, one group of focal lesions is decreasing in size—and hence, number of cells—whereas

28   the other group is increasing in size.

29   The Conolly and Andersen model is different from the Portier and Kohn (1996) model in

30   that it can result in U-shaped dose-response curves for the total number and mean size of

31   observable focal lesions without using U-shaped parametric forms for the mutation rates or the

32   birth rates. Conolly and Andersen did not apply their model to cancer risk estimation. Presently,

33   there are insufficient experimental data to support or refute the use of either the Portier and Kohn

34   or the Conolly and Andersen model.

1

5.2.2. Noncancer Endpoints

The analysis of noncancer endpoints following dioxin exposure uses the same dose metrics as for the preceding cancer analysis, although with increased emphasis on LOAELs and NOAELs. Summarized here are noncancer results based on the 200+ ED_{01} calculations performed in Part II, Chapter 8, combined with a tabulation (Table 5-6; Appendix A) of the lower range of measured, empirical, LOAEL/NOAEL results. Noncancer endpoints following dioxin exposure present similar—lower for some effects—PODs as compared to cancer ED_{01}s, with many of the PODs falling in a range of ~10–50 ng/kg BB and lower still for subclinical endpoints.

Before presenting these results, consideration should be give to a number of difficulties and uncertainties associated with comparing the same or different endpoints across species, such as differences in sensitivity of endpoints, times of exposure, exposure routes, and species and strains; the use of multiple or single doses; and variability between studies even for the same response. The estimated ED_{01}s may be influenced by experimental design, suggesting that caution should be used when comparing values from different designs. Caution should also be used when comparing studies that extrapolate ED_{01}s outside the experimental range. Furthermore, it may be difficult to compare values across endpoints. For example, the human health risk for a 1% change of body weight may not be equivalent to a 1% change in enzyme activity. Similarly, a 1% change in response in a population for a dichotomous endpoint is different from a 1% change in a continuous endpoint, where the upper bound of possible values may be very large, leading to a proportional increase in what constitutes the 1% effect level. Finally, background exposures are often not considered in these calculations simply because they were not known.

Part II, Chapter 8, presents estimated ED_{01}s for more than 200 data sets. These data sets were categorized by exposure regimen (single exposure vs. multiple exposures), effect (biochemical, hepatic, tissue, immune, and endocrine) and developmental stage (adult vs. developmental). The Hill model was fit to a majority of the data sets. This model not only provides estimates of the ED_{01}, it also provides insight into the shape of the dose-response curve in the form of a shape parameter. The shape parameter, or the Hill coefficient, can be used to determine whether the dose-response curve is linear or threshold-like. An analysis of the shape parameters for the different response categories implies that many dose-response curves are consistent with linearity over the range of doses tested. This analysis does not imply that the curves would be linear outside this range of doses, but it does inform the choices for

1 extrapolation. This is particularly true when body burdens or exposures at the lower end of the

2 observed range are close to body burdens or exposures of interest for humans, which is the case

3 with dioxin-like chemicals and biochemical effects.

4   Several general trends were observed and discussed in Part II, Chapter 8, relating to the

5 ED_{01} results. The lowest ED_{01}s tended to be for biochemical effects, followed by hepatic

6 responses, immune responses, and responses in tissue weight. However, there was a wide range

7 of ED_{01}s within each category. For example, in the immune category, there was a range of

8 almost six orders of magnitude in the ED_{01} estimates. In addition, some of the lowest ED_{01}

9 estimates were for changes in immune function in adult mice, with ED_{01}s ranging from 2 to 25 ng

10 TCDD/kg. Overall shape parameter data suggest that biochemical responses to TCDD are more

11 likely to be linear within the experimental dose range. The more complex responses are more

12 likely to assume a nonlinear shape. Nonetheless, a large number (> 40%) of the more complex

13 responses have shape parameters that are more consistent with linearity than with nonlinearity.

14   Table 5-6 summarizes the range of experimental LOAEL, NOAEL, and ED_{01} values for

15 critical endpoints from animal studies. The published data supporting these values are presented

16 in Appendix A. These endpoints were chosen because they are considered adverse (e.g.,

17 developmental or reproductive toxicity) or are on the critical path for cancer and noncancer

18 effects. In addition, these effects were chosen because the body burdens at which the effects

19 occur are approximately 50 ng/kg or lower. The use of ED_{01}s and NOAELs and/or LOAELs in

20 this analysis provides a "point of departure" for a discussion of margins of exposure for a variety

21 of health endpoints. No one endpoint has been chosen as the "critical effect," as is often done in

22 RfD calculations. For the effects listed in Table 5-6 and Appendix A, the MOE is approximately

23 10 or less. In some cases, particularly for ED_{01} values for the developmental toxicities of TCDD

24 in rats (Mably et al., 1992a-c; Gray et al., 1997a, b; Faqi et al., 1998; Markowski et al., 2001), the

25 MOE is less than 1. These estimates of the MOE assume a background human body burden of 5

26 ng TEQ/kg body weight.

27   Results from the analysis of ED_{01}s and an examination of LOAELs in additional studies

28 suggest that noncancer effects can occur at body burden levels in animals equal to or less than

29 body burdens calculated for tumor induction in animals. This is especially true when considering

30 biochemical changes that may be on the critical path for both noncancer and cancer effects, such

31 as enzyme induction or impacts on growth factors or their receptors. Although human noncancer

32 effects were not modeled in Part II, Chapter 8, the observation of effects in the Dutch studies

33 (discussed in Section 2.2.2 in this document) suggest that subtle but important noncancer human

1   effects may be occurring at body burden levels equivalent to those derived for many

2   biochemical—and some clearly adverse—effects in animals.

3

5.3. MODE-OF-ACTION–BASED-DOSE-RESPONSE MODELING

5   As described in Part II, Chapter 8, Section 8.3, mechanism-based modeling can be a

6   powerful tool for understanding and combining information on complex biological systems. Use

7   of a truly mechanism-based approach can, in theory, enable reliable and scientifically sound

8   extrapolations to lower doses and between species. However, any scientific uncertainty about the

9   mechanisms that the models describe is inevitably reflected in uncertainty about the predictions

10   of the models. The assumptions and uncertainties involved in the mechanistic modeling

11   described in Chapter 8 are discussed at length in that chapter and in cited publications.

12   The development and continued refinement of PBPK models of the tissue dosimetry of

13   dioxin has provided important information concerning the relationships between administered

14   dose and dose-to-tissue compartments (Part II, Chapter 8, Section 8.2). Aspects of these models

15   have been validated in the observable response range for multiple tissue compartments, species,

16   and class of chemical. These models will continue to provide important new information for

17   future revisions of this health assessment document. Such information will likely include

18   improved estimates of tissue dose for liver and other organs where toxicity has been observed,

19   improved estimates of tissue dose(s) in humans, and improved estimates of tissue dose for

20   dioxin-related compounds.

21   In this reassessment, the development of biologically based dose-response models for

22   dioxin and related compounds has led to considerable and valuable insights regarding both

23   mechanisms of dioxin action and dose-response relationships for dioxin effects. These efforts,

24   described in some detail in Part II, Chapter 8, Section 8.3, have provided additional perspectives

25   on traditional methods such as the linearized multistage procedure for estimating cancer potency

26   or the uncertainty factor approach for estimating levels below which noncancer effects are

27   unlikely to occur. These methods have also provided a biologically based rationale for what had

28   been primarily statistical approaches. The development of models like those in Chapter 8 allows

29   for an iterative process of data development, hypothesis testing, and model development.

30

5.4. SUMMARY OF DOSE-RESPONSE CHARACTERIZATION

32   All humans tested contained detectable body burdens of TCDD and other dioxin-like

33   compounds that are likely to act through the same mode of action. The receptor modeling theory

34   outlined in Chapter 8 indicates that xenobiotics that operate through receptor binding

1 mechanisms, such as dioxin, will follow a linear dose-response binding in the 1–10% receptor

2 occupancy region. This theoretical basis suggests—and this is supported by empirical

3 findings—that the proximal biochemical and transcription reactions for dioxins, such as effects

4 on DNA transcription and enzyme induction, may also follow linear dose-response kinetics.

5 More distal toxic effects could be linear or sublinear/threshold depending on (1) the toxic

6 mechanism, (2) location on the dose-response curve, and (3) interactions with other processes

7 such as intracellular protein binding and co-factor induction/repression.

8   Empirical data provide dose-response shape information down to approximately the 1%

9 effect level for many toxic endpoints. Many examples of adverse effects experienced at these

10 low levels have too much data variability to clearly distinguish on a statistical basis (goodness of

11 fit) between dose-response curve options and whether dose-response follows linear,

12 supra/sublinear, power curve, or threshold kinetics. Toxic effects seen only at higher doses are

13 presumably more likely to result from multiple cellular perturbations and are thus less likely to

14 follow linear relationships.

15   Empirical dose-response data from cancer studies—both human epidemiological and

16 bioassays—do not provide consistent or compelling information supportive of either threshold or

17 supralinear models (see Tables 2-3 and 5-2) and are insufficient to move from EPA's default

18 linear extrapolation policy in the proposed carcinogen risk assessment guidelines (U.S. EPA,

19 1996, 1999, 2003). This policy indicates that, for cancer dose-response, the data are to be

20 modeled within the observed range and a POD calculated from which a linear extrapolation to

21 the origin is generated. For noncancer endpoints, EPA proposes using an MOE approach, rather

22 than an RfD approach, due to the inability to determine levels that are likely to be without

23 appreciable effects of lifetime exposure to the population (including susceptible subpopulations)

24 for all adverse effects, particularly given the current level of background exposure and human

25 body burdens. Data on background levels of dioxins, furans and coplanar PCBs (see Part I,

26 Volume 3, and Section 4.4 in this document) indicate that current levels in humans are already

27 substantially along the dose-response curve. Thus, theoretical issues regarding increases from

28 zero body burden levels are moot, and assessments must consider both background and

29 additional increments of dose to this background level.

30   MOEs between population levels and the empirically observed (not modeled) 1% effect

31 levels for a number of biochemical/toxic endpoints are on the order of less than 1 to 2 orders of

32 magnitude. Thus, the extrapolation between observed effects and background levels is not large,

33 with any increments to background further advancing along the dose-response curve through or

34 toward the observed range. This further reduces the level of uncertainty when evaluating the

1 significance of MOEs. It is possible that any additional exposure above current background body
2 burdens will be additive to ongoing responses. The magnitude of the additional response will be
3 a function of the toxic equivalency of the incremental exposure. This observation, the relatively
4 small MOE for "key events" potentially on the pathway to cancer and noncancer effects, and the
5 high percentage of observed linear responses suggest that a proportional model should be used
6 when extrapolating beyond the range of the experimental data. Short of extrapolating linearly
7 over one to two orders of magnitude to estimate risk probabilistically for cancer and noncancer
8 effects in the face of the uncertainties described above, a simple MOE approach may be useful to
9 decision makers when discussing risk management goals. However, this decision would have to
10 be based on a policy choice, because this analysis does not strongly support either approach.

11 Because human data for cancer dose-response analysis were available and because of a
12 strong desire to stay within the range of responses estimated by these data, the risk chosen for
13 determining a POD was the 1% excess risk. Doses and exposures associated with this risk (the
14 ED_{01}s) were estimated from the available data using both mechanistic and empirical models.
15 Comparisons were made on the basis of body burdens to account for differences in half-life
16 across the numerous species studied.

17 In humans, restricting the analysis to log-linear models resulted in cancer ED_{01}s ranging
18 from 6.0 ng/kg to 62 ng/kg. These were similar to the estimates from empirical modeling of the
19 animal studies, which ranged from 14 ng/kg to 1190 ng/kg (most estimates were in the range of
20 14 to 500 ng/kg), and 2.7 ng/kg for the single mechanism-based model. Lower bounds on these
21 ED_{01} estimates were used to calculate upper bound slope factors and risk estimates for average
22 background body burdens.

23 Table 5-4 summarizes the ED_{01}/LED_{01} and slope factor calculations for the occupational
24 cohort and bioassay studies. The slope factor calculations are performed by linearly
25 extrapolating the ED/LED_{01} values to the background response rates, consistent with procedures
26 outlined in the draft proposed guidelines for carcinogen risk assessment (U.S. EPA, 1996, 1999,
27 2003). A slope factor estimate of approximately 1×10^{-3} per pg TCDD/kg body weight/day
28 represents EPA's most current upper bound slope factor for estimating human cancer risk based
29 on human data. A slope factor of 1.4×10^{-3} per pg TCDD/kg body weight/day represents EPA's
30 most current upper bound slope factor for estimating human cancer risk based on animal data.
31 Details on the specific procedures and calculations are provided in the footnotes. Additional
32 details on the study characteristics and dose-response data and graphs are available in Section 5.2
33 and Table 5-2. The Agency, although fully recognizing the range and the public health-
34 conservative nature of the slope factors that make up the range, suggests the use of 1×10^{-3} per

1   pg TEQ/kg body weight/day as an estimator of upper bound cancer risk for both background

2   intakes and incremental intakes above background.

3   Upper bound slope factors allow the calculation of the high end (greater than 95%) of the

4 probability of cancer risk in the population. This means that there is a greater than 95% chance

5 that cancer risks will be less than the upper bound. Use of the ED_{01} rather than the LED_{01} to

6 provide more likely estimates based on the available epidemiological and animal cancer data

7 result in slope factors and risk estimates that are within a factor of 2 from the upper bound

8 estimates. Even though there may be individuals in the population who might experience a

9 higher cancer risk on the basis of genetic factors or other determinants of cancer risk not

10 accounted for in epidemiologic data or animal studies, the vast majority of the population is

11 expected to have less risk per unit of exposure, and some may have zero risk. On the basis of

12 these slope factor estimates (per pg TEQ/kg body weight/day), upper bound cancer risk at

13 average current background body burdens (5 ng TEQ/kg body weight) exceed 10^{-3} (1 in 1000).

14 Current background body burdens reflect higher average intakes from the past (approximately 3

15 pg TEQ/kg body weight/day). For a very small percentage of the population (< 1%), estimated

16 upper bound risks may be two to three times higher than this upper bound, based on average

17 intake, if their individual cancer risk slope is represented by the upper bound estimate and they

18 are among the most highly exposed (among the top 5%), based on dietary intake of dioxin and

19 related compounds.

20   Estimates for noncancer endpoints show greater variability. In general, when compared

21 on a body burden basis, the noncancer endpoints displayed lower ED_{01}s and NOAELs and/or

22 LOAELs for short-term exposures versus longer-term exposures and for simple biochemical

23 endpoints versus more complex endpoints such as tissue weight changes or toxicity. A number

24 of significant, adverse, noncancer responses occurred at LOAEL/NOAEL/ED_{01}s of < 10–50

25 ng/kg, levels that are similar to the ED_{01}s estimated for cancer effects (see Tables 5-4, 5-6 and

26 Appendix A). The mechanism-based models for noncancer endpoints gave a lower range of

27 ED_{01}s (0.17 to 105 ng/kg) when compared to the broader noncancer data set. Although most of

28 these estimates were based on a single model, the estimate from a different model—the hepatic

29 zonal induction model—gave an ED_{01} for CYP1A2 induction of 51 ng/kg and, hence, was within

30 the same range.

31   Although highly variable, these estimates suggest that any choice of body burden of more

32 than 100 ng/kg as a POD would likely yield > 1% excess risk for some endpoint in humans,

33 including those with clear clinical significance. Also, choosing a POD of less than 1 ng/kg

34 would likely be an extrapolation below the range of these data. Any choice in the middle range

1   of 1 to 100 ng/kg would be supported by the analyses, although the data provide the greatest

2   support in the range of 10 to 50 ng/kg. This range of body burdens should also provide a useful

3   point of comparison when evaluating impacts of risk management on average body burdens in

4   the general population or on estimates of impact of incremental exposures above background on

5   individual body burdens at various ages.

Table 5-1. Peak serum dioxin levels in the background population and epidemiological cohorts

Cohort	No.	Total TEQ (ppt lipid)			2,3,7,8-TCDD (ppt lipid)	PCBs	Non-2,3,7,8-TCDD TEQ (ppt lipid)	Comment
		Lower	Central Tendency	Upper	Central Tendency	Mean TEQ	Central Tendency	Comment
CDC comparison population, USA 1995–1997; CDC (2000)	316	2[a]	25.4 mean[b]	50[a]	2.1 mean 1.9 median (95% UCL = 4.2)	5.3 (est.)[b]	23.3 mean	TEQ_{DFP}-WHO_{98}; serum; missing PCBs 105, 118, 156 estimated
Background, Dioxin Assessment, USA ~1990s	pooled results	30	52.8 mean 55 median	70	5.2 mean SD ~1.32[c]	18.8 mean 20 median	47.6 mean	TEQ_{DFP}-WHO_{98}; serum, adipose, breast milk[d]
Back-calculated								
Ranch Hand, low; Ketchum et al. (1999)	276				52.3 median (range 27–94)			serum
Ranch Hand, high; Ketchum et al. (1999)	283				195.7 median (range 94–3,290)			serum
Hamburg cohort, women; Flesch-Janys et al. (1999)	$65_{2,3,7,8}$ 64_{TEQ}	19.3	811.2 mean[e] 172.8 median[e]	6789.1	506.8 mean 125.8 median (range 2.4–6397.4)		304.4 mean[e]	I-TEQs, dioxin and furan TEQ only; serum
NIOSH, Fingerhut et al. (1991b), NTIS	253				2,000 mean (range[f] 2–32,000)			serum
BASF, severe chloracne; Ott et al. (1993)	56				1008 geom. mean (range[g] 20–13360)			serum

Table 5-1. Peak serum dioxin levels in the background population and epidemiological cohorts (continued)

| Cohort | No. | Total TEQ (ppt lipid) | | | 2,3,7,8-TCDD (ppt lipid) | PCBs | Non-2,3,7,8-TCDD TEQ (ppt lipid) | Comment |
		Lower	Central Tendency	Upper	Central Tendency	Mean TEQ	Central Tendency	
BASF, moderate chloracne; Ott et al. (1993)	59				420.8 geom. mean (range[g] 2.72–4915)			serum
BASF, no chloracne; Ott et al. (1993)	139				38.4 geom. mean (range[g] 2.72–2981)			serum
Seveso Zone A; Landi et al. (1998)	7				230 geom. mean 325.9 median (range 41.2–399.7)			serum
Seveso Zone A, medical; Needham et al. (1999)[h]	296				381–489 median (range 1.5–56,000)			Samples taken 1976, not back-calculated; serum; using ½ DL
Seveso Zone B; Landi et al. (1998)	51				47.5 geom. mean 52.5 median (range 5.3–273)			serum
Seveso Zone B, medical; Needham et al. (1999)[h]	80				87–147 median (range 1.8–725)			Samples taken 1976, not back-calculated; serum; using ½ DL
Seveso Zone R, medical; Needham et al. (1999)[h]	48				15–89 median (range 1–545)			Samples taken 1976; not back-calculated; serum; using ½ DL
Seveso NonABR; Landi et al. (1998)	52				4.9 geom. mean 5.5 median (range 1.0–18.1)			serum

Table 5-1. Peak serum dioxin levels in the background population and epidemiological cohorts (continued)

Cohort	No.	Total TEQ (ppt lipid)			2,3,7,8-TCDD (ppt lipid)	PCBs	Non-2,3,7,8-TCDD TEQ (ppt lipid)	Comment
		Lower	Central Tendency	Upper	Central Tendency	Mean TEQ	Central Tendency	
Dutch Accident; Hooiveld et al. (1996)	14				1841.8 arith. mean 1433.8 geom. mean (range 301–3683)			serum
Dutch Main Production; Hooiveld et al. (1996)	5				608.2 arith. mean 285.9 geom. mean (range 17–1160)			serum

[a] Estimated from ATSDR (1999b) Calcasieu comparison population graph.

[b] CDC data scaled upward to adjust for missing data on PCB congeners 105, 118 and 156 by matching to PCB congener ratios measured in the early 1990s.

[c] SD approximated from unweighted estimate.

[d] Weighted average levels for the subset of serum lipid TEQs were 4.54 ng/kg for 2,3,7,8-TCDD and 55.4 ng/kg for total TEQ (PCB contribution not adjusted for missing congeners).

[e] PCDD- and PCDF-derived TEQ only, using I-TEFs.

[f] Lower interval on current level.

[g] Range estimated from exponential log distribution graph.

[h] Ranges for median values for Seveso result from age groupings in original publication (Needham et al., 1999; Tables 1, 2, 5)

Table 5-2. Published cancer epidemiology and bioassay data and dose-response formulae

Study	Exposure groups	Central estimate of range (ng/kg fat x years)[a]	All cancer deaths observed (latency)	
Hamburg cohort, Becher et al. (1998)	0–1 1–4 4–8 8–16 16–64 64+ µg/kg fat*Years n = 1189 male; measured = 275; cancer deaths = 124	0 2000 5657 11314 32000 96000 Harmonic mean, 1.5 x upper limit	1.00 RR 1.12 (0-yr lag)[b] 1.42 P trend = 0.03 1.77 1.63 2.19 Power: $p=0.026$ RR = $(0.00017x+1)^{0.326}$ Additive: $p=0.031$ RR = $1+0.000016\,x$ Multiplicative: $p=0.043$ RR = $\exp(0.00000869\,x)$	
NIOSH cohort, Steenland et al. (2001)	<335 335–<520 520–<1212 1212–<2896 2896–<7568 7568–<20455 >20455 ppt lipid *Years n = 3538 male; measured = 199; cancer deaths = 256	260 402 853 1895 4420 12125 59838 Median	1.00 RR 1.26 (15-yr lag) 1.02 1.43 1.46 1.82 1.62 Power: $p=0.003$ RR = $(x/\text{background})^{0.097}$ Piecewise linear, <40000:[c] RR = $\exp(0.000015\,x)$	
BASF cohort, Ott and Zober (1996)	<0.1 0.1–0.99 1.0–1.99 2.0+ µg/kg bw. peak; n = 243 male; measured = 138; cancer deaths = 31	598 19407 55057 148800 Arithmetic mean	0.80 SMR 1.2 (0-yr lag) 1.4 2.0 Conditional risk ratio = 1.22 (95% CI 1.00–1.50)[d] RR = $\exp(0.00000503\,x)$	

Table 5-2. Published cancer epidemiology and bioassay data and dose-response formulae (continued)

	Study	Exposure groups	Central estimate of range (ng/kg fat x years)[a]	All cancer deaths observed (latency)	
1 2 3 4 5 6 7	S-D Rats, Kociba et al. (1978); Goodman and Sauer (1992) pathology	0 0.001 0.01 0.1 µg/kg/day	0 540 1700 8100 ng/kg lipid, not AUC	2/86 Tumors 1/50 9/50 18/45	

8
9 [a] Central estimates provided courtesy of Drs. Steenland, Zober, and Becher.
10 [b] RR data provided only for the zero-lag analysis in Becher et al. (1998)
11 [c] Coefficient for the piecewise linear model (0.000015) provided by Dr. Steenland. The initial slope in the
12   piecewise regression is applicable only to 40,000 ng/kg lipid years.
13 [d] Slope factor calculated from the conditional risk ratio, CR=1.22; see Chapter 8

1 **Table 5-3. All cancer risk in humans through age 75[a]**

2

Study	Model and Sex	ED_{01}	95% CI (lower, upper)	Unit excess risk for 1 ppt body burden above background
Steenland et al. (2001)	power male	1.38	0.71, 8.95	0.0079 (0.0027, 0.0132)
	power female	1.84	0.92, 14.9	0.0064 (0.0022, 0.0107)
	piecewise linear male	18.6	11.5, 48.3	0.00052 (0.00020, 0.00084)
	piecewise linear female	23.1	14.3, 59.8	0.00042 (0.00016, 0.00067)
Becher et al. (1998)	power-male	5.971		0.0018
	power-female	7.58		0.0014
	additive-male	18.22		0.00055
	additive-female	22.75		0.00044
	multiplicative-male	32.16		0.0003
	multiplicative-female	39.82		0.00024
Ott and Zober (1996)	multiplicative-male	50.9	25.0, ∞	0.00019 (0, 0.00039)
	multiplicative-female	62.1	30.5, ∞	0.00015 (0, 0.00032)

11
12 [a] Units are constant body burden in ng/kg not adjusted for lipid: see Part III, Chapter 8, Table 8-2, for details.
13

Table 5-4. Summary of all site cancer ED_{01} and slope factor calculations

Study	ED_{01} (LED_{01}) (ng/kg)	Cancer slope factor for 1 pg/kg/day above background[a] (UCL)
Hamburg cohort, Becher et al. (1998), power	6	5.1 E-3
Hamburg cohort, Becher et al. (1998), additive	18.2	1.6 E-3
Hamburg cohort, Becher et al. (1998), multiplicative	32.2	0.89 E-3
NIOSH cohort, Steenland et al. (2001), piecewise linear[b]	18.6 (11.5)	1.5 E-3 (2.5 E-3)
BASF cohort, from Ott and Zober (1996), multiplicative	50.9 (25.0)	0.57 E-3 (1.2 E-3)
Sprague-Dawley rats, Kociba et al.(1978); Goodman and Sauer (1992), pathology	31.9 (22)[c] BMD dose 38 (27.5) BMD adipose	0.97 E-3 (1.4 E-3) 0.8 E-3 (1.1 E-3)

[a] Assumes 25% of body weight is lipid; 80% of dioxin dose is absorbed from the normal diet in humans; the TCDD half-life is 7.1 years in humans. Background all cancer mortality rate calculated through lifetable analysis to 75 years. Summary results are for male all cancer risk, because the male lifetime (to 75 years) all cancer risk is greater than for females, leading to correspondingly higher cancer slope factors. As detailed in Part III, Chapter 8, $RelRisk_{(ED01)} = 0.99 + 0.01/Risk_{(0\ dose)}$. Based on the manner in which the dose-response data were calculated using Cox Regression rate ratio analyses, risks are given as cancer slope factors for 1 pg/kg/day above background, assumed 5 ppt TCDD in lipid.

[b] Steenland et al. (2001) power model results are not included, as this formula predicts unreasonably high attributable risks at background dioxin levels in the community due to the steep slope of the power curve formula at very low levels.

[c] Modeled using U.S. EPA Benchmark Dose Software, version 1.2, with either dose or adipose concentration as the metric. Absorption from food pellets in animals is assumed to be 50%. BMD = 0.00176849 ug/kg/day. BMDL = 0.00122517 ug/kg/day. Therefore, rat LED_{01} = 1.2251 x 25 x 0.5/ln2 = 22 ng/kg; human equivalent LED_{01} = 22 x ln2 x 1000/2593/0.8 = 7.38 pg/kg/day; slope factor = 0.01/7.38 = 1.4 E-3 risk/pg/kg/day.

Table 5-5. Doses yielding 1% excess risk (95% lower confidence bound) based upon 2-year animal carcinogenicity studies using simple multistage (Portier et al., 1984) models[a]

Tumor	Shape	ED_{01} Animal intake for 1% excess risk in ng/kg/day (95% lower confidence bound)	ED_{01} Steady-state body burden in ng/kg at ED_{01} (95% lower confidence bound)
Liver cancer in female rats (Kociba)	Linear	0.77 (0.57)	14 (10)
Squamous cell carcinoma of the tongue in male rats (Kociba)	Linear	14.1 (5.9)	254 (106)
Squamous cell carcinoma of the nasal turbinates or hard palate in male rats (Kociba)	Cubic	41.4 (1.2)	746 (22)
Squamous cell carcinoma of the lung in female rats (Kociba)	Cubic	40.4 (2.7)	730 (48)
Squamous cell carcinoma of the nasal turbinates or hard palate in female rats (Kociba)	Linear	5.0 (2.0)	90 (36)
Thyroid follicular cell adenoma in male rats (NTP)	Linear	4.0 (2.1)	144 (76)
Thyroid follicular cell adenoma in female rats (NTP)	Cubic	33.0 (3.1)	1190 (112)
Liver adenomas and carcinomas in female rats (NTP)	Quadratic	13.0 (1.7)	469 (61)
Liver adenomas and carcinomas in male mice (NTP)	Linear	1.3 (0.86)	20.6 (13.6)
Liver adenomas and carcinomas in female mice (NTP)	Linear	15.1 (7.8)	239 (124)
Thyroid follicular cell adenomas and carcinomas in female mice (NTP)	Linear	30.1 (14.0)	478 (222)
Subcutaneous tissue sarcomas in female mice (NTP)	Lin-Cubic	43.2 (14.1)	686 (224)
Leukemias and lymphomas in female mice (NTP)	Linear	10.0 (5.4)	159 (86)

[a] Reprinted with slight modifications from Part II, Chapter 8, Table 8.3.2.

Table 5-6. Body burdens for critical endpoints in animals with human equivalent daily intake

Animal	Endpoint	Study	Estimated body burden (ng/kg)			Human equiv.[a] intakes (pg/kg/day)
			LOAEL	NOAEL	ED_{01}	
Rats	Cancer	Kociba et al. (1978)	180	18	32	60; 6; 11
Rhesus monkeys	Fetal mortality	Bowman et al. (1989)	90	21	NC	30; 7
	Developmental neurotoxicity	Schantz et al. (1992)	21	–	NC	7
	Endometriosis	Rier et al. (1993)	21	–	NC	7
Rats	Reproductive tox. (multigenerational)	Murray et al. (1979)	180	18	NC	60; 6
Rats	Developmental/ reproductive toxicity	Mably et al. (1992)	38	–	0.34	13; 0.1
		Gray et al. (1997)	30	–	0.08	10; 0.03
		Faqi et al. (1998)	25	–	0.6	8; 0.2
		Ohsako et al. (2001)	30	8	NC	10; 3
Rats	Developmental immunotoxicity	Gehrs and Smialowicz (1999)	60	–	NC	20
Rats	Developmental Neurotoxicity	Markowski et al. (2001)	108	36[b]	0.7	36; 12; 0.2
Mice	Immunological effects (adult)	Burleson et al. (1996)	6	3	NC	2; 1
		Smialowicz et al. (1994)	300	–	2.9	100; 1
		Narasimhan et al. (1994)	100	50[b]	1.5	33; 17; 0.5
		Vecchi et al. (1983)	1200	–	7	401; 2
Rats	Thyroid effects	Sewall et al. (1995)	76	22	26	25; 7; 8
Mice	CYP1A1/1A2 enzyme induction	DeVito et al. (1994)	24	–	22	8; 7
		Diliberto et al. (2001)	2.8	–	67	0.9; 22
		Vogel et al. (1997)	5.1	0.51	0.003	1.6; 0.16; 0.001
		Narasimhan et al (1994)	25	10	3	8; 3; 2; 1
Rats	CYP1A1/1A2 enzyme induction	van Birgelen et al. (1995)	243	–	19	81; 6
		Schrenk et al. (1994)	72	–	26	24; 9
		Sewall et al. (1995)	8	2	3.5	3; 0.7; 1
		Walker et al. (1999)	76	–	59	25; 20

Table 5-6. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

[a] Human equivalent intakes were estimated according to the following equation: daily intake (pg/kg/day) = (body burden (ng/kg)*Ln2*1000)/(t½*absorption) where t½ = 2593 days and absorption fraction = 0.8 (Poiger and Schlatter 1986; see Section II). Corresponding human equivalent intake values are arranged in sequence from the previous three columns.

[b] NOAEL values are based on the highest individual dose group in which there are no statistically significant changes. Statistically significant dose response trends plus apparent declines are also evident at all dose levels—20 and 60 ng/kg orally—in all fixed-ratio test groups in Markowski et al. (2001) and in the 50 ng/kg dose group in Narasimhan et al. (1994).

- - = no NOAEL value, as effects seen in the lowest dose group in the study.

NC = Not calculated due to insufficient dose response information (less than three doses and a control) or due to presentation of the data in graphical form without tabulation of mean and variance estimates.

Note: This table is reproduced in Appendix A with explanatory details of study design, results, and calculation procedures, formulae, and assumptions.
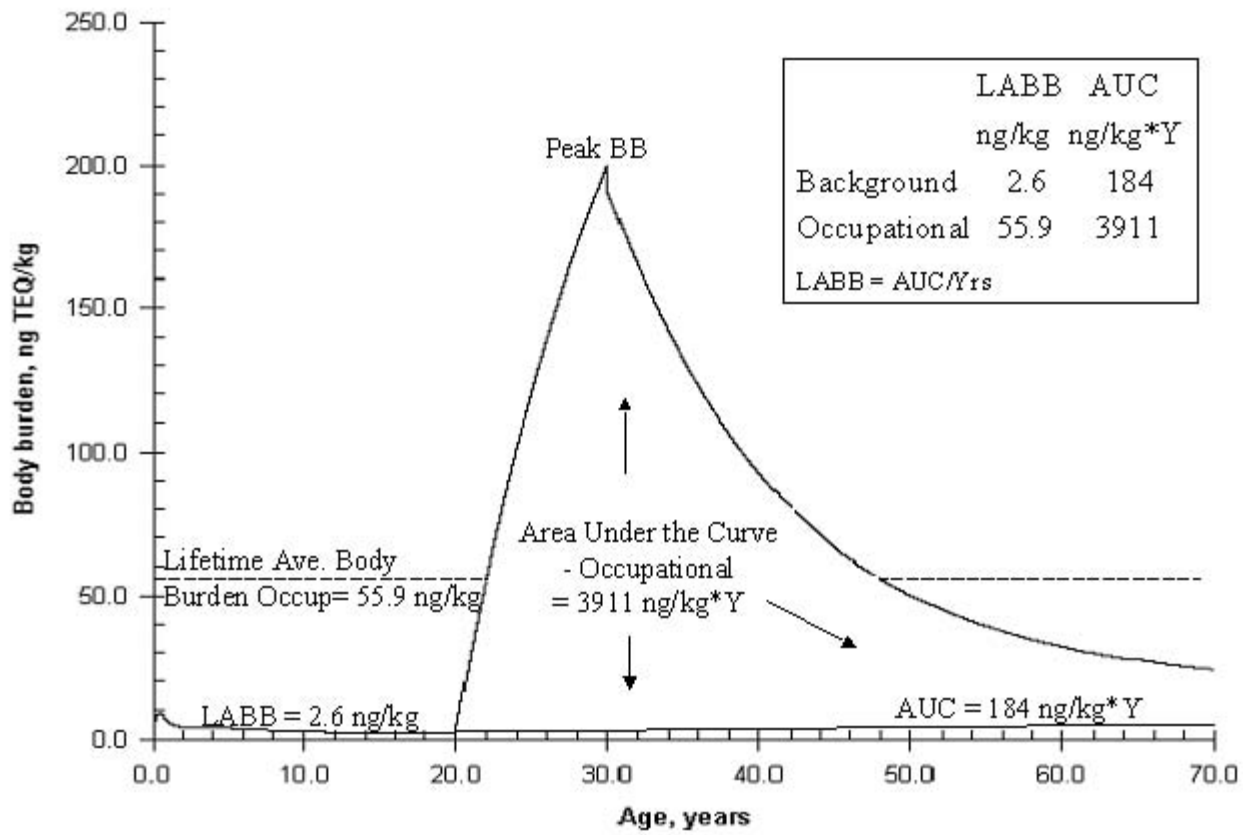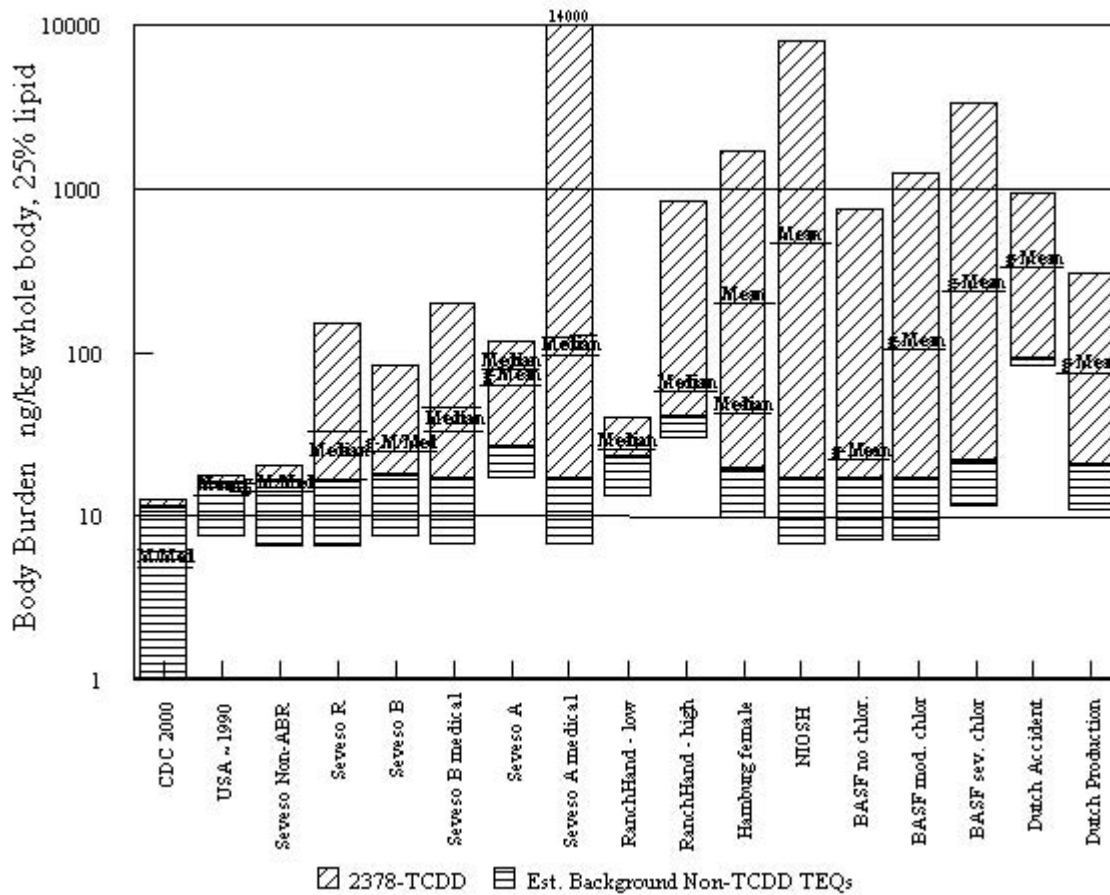
Figure 5-1. Comparison of lifetime average body burden and area under the curve in hypothetical background and occupational scenarios.

Figure 5-2. **Peak dioxin body burden levels in background populations and epidemiological cohorts (back-calculated) (See Table 5-1).** For the background U.S. populations (CDC; USA ~1990s), the bars represent the range of total TEQ measured in the population. The lower shaded portion represents the variability from non-2,3,7,8-TCDD-derived TEQs, the upper shaded portion the variability in the 2,3,7,8-TCDD. Note that the respective bar sizes do not represent the total non-2,3,7,8-TCDD TEQ or 2,3,7,8-TCDD contributions, because a portion of each of these contributions is contained within the region between the x-axis and bottom of the bar, namely the minimum estimated body burden. For each of the back-calculated epidemiological cohort exposures, the bar was estimated on the basis of the combination of two distributions: the 2,3,7,8-TCDD levels measured in the respective cohort plus the estimated range of background non-2,3,7,8-TCDD-derived TEQs from the U.S. population. The lower estimate is the combination of the lower 2,3,7,8-TCDD and lower non-2,3,7,8-TCDD TEQ contributions; the shading junction represents the variability in background U.S. population non-2,3,7,8-TCDD levels that have been added to this bar; the mean/median/geometric mean indicators represent the addition of the measured 2,3,7,8-TCDD central estimate with the mean background U.S. population non-2,3,7,8-TCDD TEQ level (~47.6 ppt lipid, 11.9 ng/kg body burden at 25% body fat); and the upper limit is the combination of the upper 2,3,7,8-TCDD and upper non-2,3,7,8-TCDD TEQs.