6. RISK CHARACTERIZATION

Characterizing risks from dioxin and related compounds requires the integration of complex data sets and the use of science-based inferences regarding hazard, mode of action, dose response, and exposure. It also requires consideration of incremental exposures in the context of an existing background exposure that, for the majority of the population, is independent of local sources and dominated by exposure through the food supply. Finally, this characterization must consider risks to special populations and developmental stages (subsistence fishers, children, etc.) as well as to the general population. It is important that this characterization convey the current understanding of the scientific community regarding these issues, highlight uncertainties in this understanding, and specify where assumptions have been used or inferences made in the absence of data. Although characterization of risk is inherently a scientific exercise, it must by nature go beyond empirical observations and draw conclusions in untested areas. In some cases, these conclusions are, in fact, untestable, given the current capabilities in analytical chemistry, toxicology, and epidemiology. This situation should not detract from one's confidence in the conclusions of a well-structured and well-documented characterization of risk, but it should serve to confirm the importance of considering risk assessment as an iterative process that benefits from evolving methods and data collection and is subject to change as the knowledge base improves.

Dioxin and related compounds can produce a wide variety of effects in animals and may produce many of the same effects in humans.

There is adequate evidence, based on all the available information, as discussed in Parts I and II of this Reassessment and in this Integrated Summary, to support the inference that the potential exists for humans to respond with a broad spectrum of effects from exposure to dioxin and related compounds, depending on the magnitude and duration of exposure. This inference is based on the similarities in receptor and receptor binding and their sequellae observed in animals and in humans. Effects will likely range from detection of biochemical changes at or near background levels of exposure to detection of adverse effects with increasing severity as body burdens increase above background levels. Data presented in Part II, Chapter 8, and illustrated in Table 5-6 and Appendix A support this general conclusion.

Enzyme induction, changes in hormone levels, and indicators of altered cellular function seen in humans and laboratory animals represent effects of unknown clinical significance but that may be early indicators of toxic response. Induction of activating/metabolizing enzymes at or

near background levels, for instance, may be adaptive and, in some cases, beneficial, or it may be considered adverse. Induction may lead to more rapid metabolism and elimination of potentially toxic compounds, or it may lead to increases in reactive intermediates and may potentiate toxic effects. Examples of both of these situations are available in the published literature, and events of this type formed the basis for a biologically based model discussed in Part III, Section 5.

Subtle effects, such as the impacts on neurobehavioral and developmental outcomes in laboratory animals and humans, the thyroid function and immune system alterations seen in the Dutch children exposed to background levels of dioxin and related compounds, or the changes in circulating reproductive hormones in men exposed to TCDD, illustrate the types of responses that support the finding of subtle yet arguably adverse effects at or near background body burdens. Clearly adverse effects, including, perhaps, cancer, may not be detectable until exposures contribute to body burdens that exceed current background by one or two orders of magnitude (10 or 100 times). MOEs in this range are considerably less than those typically seen for environmental contaminants of toxicologic concern, particularly when the health endpoint is cancer, as observed in epidemiologic studies.

Clear mechanistic relationships between biochemical and cellular changes seen at or near background body burden levels and production of adverse effects detectable at higher levels remain uncertain, but modes of action consistent with available data have been discussed in several chapters in Part II. Information on these mechanistic relationships and modes of action is useful in hazard characterization, and data are accumulating to suggest refined mode of action hypotheses for further testing.

It is well known that individual species vary in their sensitivity to any particular dioxin effect. Laboratory rodents (typically strains of rats and mice) are not necessarily the most sensitive responders for several well-studied effects. However, the evidence available to date indicates that humans most likely fall in the middle rather than at either extreme of the range of sensitivity for individual effects among animals. In other words, evaluation of the available data suggests that humans, in general, are neither extremely sensitive nor insensitive to the individual effects of dioxin-like compounds.

Human data provide direct or indirect support for evaluation of likely effect levels for several of the endpoints observed in laboratory studies (e.g., cancer and neurobehavioral and endocrine endpoints), although the influence of variability among humans remains difficult to assess. Discussions have highlighted certain prominent, biologically significant effects of TCDD and related compounds. In TCDD-exposed men, subtle changes in biochemistry and physiology, such as enzyme induction, altered levels of circulating reproductive hormones, or reduced

glucose tolerance and, perhaps, diabetes, have been detected in a limited number of epidemiologic studies.

These findings, coupled with the knowledge derived from animal experiments, suggest the potential for adverse impacts on human metabolism and developmental and/or reproductive biology and, perhaps, other effects in the range of current human exposures. These biochemical, cellular, and organ-level endpoints have been shown to be affected by TCDD, but specific data on these endpoints do not generally exist for other congeners. Despite this lack of congener-specific data, there is reason to infer that these effects may occur for all dioxin-like compounds, based on the concept of toxic equivalency.

In this document, dioxin and related compounds are characterized as developmental, reproductive, immunological, endocrinological, and carcinogenic hazards. The deduction that humans are likely to respond with noncancer effects from exposure to dioxin-like compounds is based on the finding that these compounds impact cellular regulation at a fundamental level and on the demonstration of adverse effects among a broad range of species. For example, because developmental toxicity following exposure to TCDD-like congeners occurs in fish, amphibians, reptiles, birds, and mammals, it is likely to occur at some level in humans.

It is not currently possible to state exactly how or at what levels individuals will respond with specific adverse impacts on development or reproductive function, but the analyses of the Dutch cohort data and laboratory animal studies suggest that some effects may occur at or near background levels. Fortunately, there have been few human cohorts identified with TCDD exposures high enough to raise body burdens significantly over background levels (see Table 5-1 and Figure 5-2 in this document), and when these cohorts were examined, relatively few clinically significant effects were detected. However, the power of these studies to detect these effects remains an issue. The lack of sufficient exposure gradients and adequate human information and the focus of most currently available epidemiologic studies on occupationally TCDD-exposed adult males make it difficult to evaluate the inference that noncancer effects associated with exposure to dioxin-like compounds may be occurring in the broader human population. It is important to note, however, that when exposures to very high levels of dioxin-like compounds have been studied—such as in the Yusho and Yu-Cheng cohorts—a spectrum of adverse effects have been detected in men, women, and children. Many of these effects are similar to what has been observed not only in small laboratory animals, but in wildlife and in nonhuman primates.

Some have argued that in the absence of better human data, deducing that a spectrum of noncancer effects will occur in humans overstates the science; however, most of the scientists

involved as authors and reviewers in the reassessment have indicated that such inference is reasonable, given the weight of evidence from available data. As presented, this logical conclusion represents a testable hypothesis that may be evaluated by further data collection. EPA, its federal colleagues, and others in the general scientific community are continuing to fill critical data gaps, which will reduce our uncertainty regarding both hazard and risk characterization for dioxin and related compounds. However, as discussed by EPA's SAB (U.S. EPA, 2001b) "neither knowledge breakthroughs nor fully developed techniques for producing more unbiased risk assessments can be expected to be available in the near future."

Dioxin and related compounds are structurally related and elicit their effects through a common mode of action.

The scientific community has identified and described a series of common biological steps that are necessary for most, if not all, of the observed effects of dioxin and related compounds in vertebrates, including humans. Binding of dioxin-like compounds to a cellular protein called the aryl hydrocarbon receptor (AhR) represents the first step in a series of events attributable to exposure to dioxin-like compounds, including biochemical, cellular, and tissue-level changes in normal biological processes. Binding to the AhR appears to be necessary for all well-studied effects of dioxin, but it is not sufficient in and of itself to elicit these responses.

There remains some uncertainty as to whether every dioxin response is AhR-mediated. Some data from the use of sensitive biological tools, such as AhR-deficient ($AhR^{-/-}$) mice, suggest a small residual of effects from exposure to TCDD, and, thus, we cannot rule out receptor-independent alternative pathways. However, these reported non-AhR-mediated responses occur in animals at doses that are orders of magnitude higher than current human exposures and require much higher doses than other AhR-mediated effects in animals. Thus, these putative non-AhR-mediated mechanisms are unlikely to impact any of the assumptions made in this reassessment.

Exposure of animals—and in some cases humans—to chemicals whose structure and AhR binding characteristics are similar to those of 2,3,7,8-TCDD can elicit similar effects. In the past 5 years, significant data have accumulated that support the concept of toxic equivalence, a concept that is at the heart of risk assessment for the complex mixtures of dioxin and related compounds encountered in the environment. These data have been analyzed and summarized in Part II, Chapter 9. This chapter was added to EPA's dioxin reassessment to address questions raised by the SAB in 1995. The SAB suggested that, because the TEQ approach was a critical component of risk assessment for dioxin and related compounds, the Agency should be explicit

in its description of the history and application of the process and go beyond reliance on the Agency's published reference documents on the subject (U.S. EPA, 1987, 1989a).

The analyses in Parts II and III of this document demonstrate that, although variability in the data underpinning the scientific judgments regarding toxic equivalency exists, when data are restricted to longer exposure and in vivo data, the empirical analysis strongly supports the judgment of experts in setting TEF values. This is particularly true for the use of TEFs for assessing the animal cancer endpoint but will likely apply even more strongly to noncancer effects as additional congener-specific data are collected. A focus on the five congeners that make up greater than 80% of human body burden on a TEQ basis reveals rather robust data sets, which form the basis for assigned TEFs. This focus reduces the impact of the uncertainties in TEFs assigned to less-studied congeners. In its recent review (U.S. EPA, 2001b), EPA's SAB agreed that the general framework for calculating TEFs and applying them to obtain a TEQ is well described in Part II, Chapter 9. The Board recognized that uncertainties remained regarding toxicities of joint exposures that are not dominated by well-studied congeners, and recommended further development of the TEF methodology (e.g., development of probability density functions around experimental results to assist future expert judgment in reviewing and revising TEFs) (see Finley et al., 2003).

EPA and the international scientific community have adopted toxic equivalency of dioxin and related compounds as prudent science policy.

Dioxin and related compounds always exist in nature as complex mixtures. As discussed in the exposure document, these complex mixtures can be characterized through analytic methods to determine concentrations of individual congeners. Dioxin and related compounds can be quantified and biological activity of the mixture can be estimated using relative potency values and an assumption of dose additivity. Such an approach has evolved over time to form the basis for the use of TEQ in risk assessment for this group of compounds. Although such an approach is dependent on critical assumptions and scientific judgment, it has been characterized by the SAB as a "useful, interim" way to deal with the complex mixture problem, and it has been accepted by numerous countries and several international organizations. Alternative approaches, including the assumption that all congeners carry the toxic equivalency of 2,3,7,8-TCDD or that all congeners other than 2,3,7,8-TCDD can be ignored, have been rejected as inadequate for risk assessment purposes.

Significant additional literature is now available on the subject of toxic equivalency of dioxin and related compounds, as summarized (through 2000) in Part II, Chapter 9. An

international evaluation of all of the available data (van den Berg et al., 1998) reaffirmed the TEQ approach and provided the scientific community with the latest values for TEFs for PCDDs, PCDFs, and dioxin-like PCBs. Consequently, we can infer with greater confidence that humans will respond to the cumulative exposure of AhR-mediated chemicals. This reassessment recommends that the WHO_{98} TEF scheme be used to assign toxic equivalency to complex environmental mixtures for assessment and regulatory purposes. Further research is needed to address remaining uncertainties inherent in the current approach, in particular those regarding the impact of actual exposures compared to measured body burdens of highly persistent congeners and the continuing debate regarding the role of other Ah-agonists in the diet on the toxicity of dioxin-like compounds. WHO has suggested that the TEQ scheme be reevaluated on a periodic basis and that TEFs and their application to risk assessment be reanalyzed to account for emerging scientific information. EPA supports this suggestion and intends to participate in future re-evaluations.

Complex mixtures of dioxin and related compounds are highly potent, "likely" carcinogens.

A weight-of-evidence evaluation suggests that mixtures of dioxin and related compounds (CDDs, CDFs, and dioxin-like PCBs) are strong cancer promoters and weak direct or indirect initiators and that they are likely to present a cancer hazard to humans. Because dioxin and related compounds always occur in the environment and in humans as complex mixtures of individual congeners, it is appropriate that the characterization apply to the mixture. According to the Agency's revised proposed guidelines for carcinogen risk assessment, the descriptor "likely to be carcinogenic to human" is appropriate when the available tumor effects and other key data are adequate to demonstrate carcinogenic potential to humans (U.S. EPA, 1999, 2003) yet are not sufficient to infer a cause-and-effect relationship.

"Adequate data" are recognized to span a wide range. Even though the database from cancer epidemiologic studies remains a point of scientific discussion, it is the view of this reassessment that this body of evidence is supported by the laboratory data that indicate that TCDD increases cancer mortality of several types. Although not all confounders were ruled out in any one study, positive associations between surrogates of dioxin exposure, either length of occupational exposure or proximity to a known source combined with some information based on measured blood levels, and cancer have been reported.

These epidemiologic data strongly suggest a role for dioxin exposure to contribute to a carcinogenic response but are not sufficient to confirm a causal relationship between exposure to

dioxin and increased cancer incidence. Available human studies alone cannot demonstrate whether a cause-and-effect relationship between dioxin exposure and increased incidence of cancer exists. Therefore, evaluation of cancer hazard in humans must include an evaluation of all of the available animal and in vitro data as well as the data from exposed human populations.

The data for complex mixtures of dioxin and related compounds represent a case that, according to discussions in the draft guidelines, would approach the strong-evidence end of the adequate data spectrum. Epidemiologic observations of an association between exposure and cancer responses (TCDD); unequivocal positive responses in both sexes, multiple species, multiple sites, and different routes in lifetime bioassays or initiation-promotion protocols or other shorter-term in vivo systems such as transgenic models (TCDD plus numerous PCDDs, PCDFs, dioxin-like PCBs); and mechanistic or mode-of action data that are assumed to be relevant to human carcinogenicity, including, for instance, initiation-promotion studies (PCDDs, PCDFs, dioxin-like PCBs) all support the description of complex mixtures of dioxin and related compounds as likely to be human carcinogens. On the basis of these observations, complex environmental mixtures of TCDD and dioxin-like compounds should be characterized as "likely" carcinogens, with the degree of certainty of the characterization being dependent on the constituents of the mixture, when known. For instance, the hazard potential, although "likely," would be characterized differently for a mixture whose TEQ was dominated by octaCDD as compared with one dominated by pentaCDF.

As discussed in Section 2.2.1.5, under EPA's current approach for carcinogen risk assessment, individual congeners can also be characterized as to carcinogenic hazard. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is best characterized as "carcinogenic to humans." This means that, on the basis of the weight of all of the evidence (human, animal, mode of action), TCDD meets the criteria that allow EPA and the scientific community to accept a causal relationship between TCDD exposure and cancer hazard. The guidance suggests that "carcinogenic to humans" is an appropriate descriptor of human carcinogenic potential when there is an absence of conclusive epidemiologic evidence to clearly establish a cause-and-effect relationship between human exposure and cancer but there is compelling evidence of carcinogenicity in animals and mechanistic information in animals and humans demonstrating similar modes of carcinogenic action. The "carcinogenic to humans" descriptor is suggested for TCDD because all of the following conditions are met:

- There is strong and consistent evidence from occupational epidemiologic studies for an association between TCDD exposure and increases in cancer at all sites, in lung cancer

and, perhaps, at other sites, but the data are insufficient on their own to support a causal association. This point was discussed in detail by the International Agency for Research on Cancer (IARC, 1997).

- There is extensive carcinogenicity in both sexes of multiple species at multiple sites.

- There is general agreement that the mode of TCDD's carcinogenicity is as an AhR-dependent promoter and proceeds through gene expression and/or a modification of the action of a number of receptor and hormone systems involved in cell growth and differentiation, such as the epidermal growth factor receptor and the estrogen receptor.

- The human AhR and the rodent AhR are similar in structure and function and, once activated, both bind to the same DNA response elements, designated DREs.

- Human and rodent tissue and organ cultures respond to TCDD and related chemicals in a similar manner and at similar concentrations. TCDD has the ability to transform immortalized human and rodent cells that then have demonstrable tumorigenicity.

Other individual dioxin-like compounds are characterized as "likely to be carcinogenic to humans" primarily because of the lack of epidemiological evidence associated with their carcinogenicity, although the inference based on toxic equivalency is strong that they would behave in humans as TCDD does. Other factors, such as the available congener-specific chronic bioassays, also support this characterization. For each congener, the degree of certainty is dependent on the available congener-specific data and their consistency with the generalized mode of action that underpins toxic equivalency for TCDD and related compounds.

Although uncertainties remain regarding quantitative estimates of upper-bound cancer risk from dioxin and related compounds, efforts of this reassessment to bring more data into the evaluation of cancer potency have resulted in evaluation of the slope of the dose-response curve at the low end of the observed range (using the LED_{01}) using a simple proportional (linear) model and a calculation of both upper-bound risk and MOE based on human equivalent background exposures and associated body burdens. Evaluation of shape parameters (used to estimate degree of linearity or nonlinearity of dose-response within the range of observation) for biochemical effects that can be hypothesized as key events in a generalized dioxin mode-of-action model do

not argue for significant departures from linearity below a calculated ED_{01}, extending down to at least one to two orders of magnitude lower exposure.

Risk estimates for intakes associated with background body burdens or incremental exposures based on this slope factor represent a plausible upper bound on risk, based on the evaluation of animal and human data. The slope factors, based on the most sensitive cancer responses calculated by authors of peer-reviewed publications and presented in Part II, Chapter 8, and Section 5 for both animals and humans, fall in a range of approximately 0.6×10^{-3} to 5×10^{-3} per pg TEQ/kg body weight/day.

The ranges of estimates of upper-bound cancer potency calculated from the human and animal data overlap. The range above is bounded on the upper end by the estimate of slope from the Hamburg cohort epidemiology study and on the lower end by the estimates from the Ott and Zober epidemiology study, with the NIOSH piece-wise linear epidemiology model and the reanalyzed Kociba rat study falling intermediate in this range. Consequently, the Agency, although fully recognizing this range and the public health-conservative nature of the slope factors that make up the range, suggests the use of 1×10^{-3} per pg TEQ/kg body weight/day as an estimator of upper-bound cancer risk for both background intakes and incremental intakes above background.

This decision reflects the weight given to the individual estimates from the human studies and the comparability of the revised estimate from the animal data. A recently published meta-analysis (Crump, 2003) is consistent with this estimate. In addition, this decision reflects the judgment that, because ED_{01} estimates require little extrapolation from the range of observation and current body burdens are within a factor of 10 of the ED_{01} estimates, use of a linear model is both consistent with the data and unlikely to require more than an order of magnitude extrapolation. This bounding on extrapolation would apply to both estimates of risk at current background exposures and to additional increments above current background. Application of upper-bound slope factors allows the calculation of a high-end bounding estimate of the probability of cancer risk in the population. This means that there is greater than a 95% chance that "true" population cancer risks will be less than the upper-bound estimate.

Use of the human ED_{01}s rather than the LED_{01}s to provide more likely upper-bound estimates based on the available epidemiological data is a matter of EPA science policy and compares well with upper-bound animal cancer data. Use of either ED_{01} or LED_{01} results in slope factors and risk estimates that are within a factor of 2; well within the inherent uncertainty of these estimates. Although there may be individuals within a population who may experience a higher cancer risk on the basis of genetic factors or other determinants of cancer risk not

accounted for in epidemiologic data or animal studies, the vast majority of the population is expected to have less risk per unit of exposure than the bounding estimate would suggest, and some may have zero risk.

On the basis of these slope factor estimates (per pg TEQ/kg body weight/day), upper-bound risks at average current background body burdens (5 ng TEQ/kg body weight) that result from historical average intakes of approximately 3 pg TEQ/kg body weight/day may exceed 10^{-3} (1 in a 1000). A very small percentage of the population (< 1%) has estimated risks that are a few times higher than an upper bound based on average intake if their individual cancer risk slope is represented by the upper bound estimate and they are among the most highly exposed (among the top 5%), based on dietary intake of dioxin and related compounds. This estimate of the range of upper-bound risk for the general population has increased by approximately an order of magnitude from the estimate described at background exposure levels in EPA's earlier draft of this reassessment (10^{-4}–10^{-3}) (U.S. EPA, 1994). This has occurred because, despite the fact that average intakes and body burdens are going down, estimates of upper-bound risk per unit dose have gone up by a factor of approximately 6 over the Agency's 1985 estimate and the range of exposure through the diet has been characterized.

EPA's approach to the development of an upper-bound estimate on cancer risk is consistent with its own past practices described above and with FDA's approach. In its recent report (U.S. EPA, 2001b), the SAB agreed that the treatment of the range of upper-bound risks obtained for the general population in this assessment is consistent with past EPA practice. FDA's past estimates of a risk-specific dose associated with a one-in-a-million risk (0.057 pg/kg body weight/day) (FDA 1990) have been based on animal data and have differed from EPA's only in minor ways regarding tumor counts and in the approach to cross-species scaling. In 1992, while EPA's reassessment was underway, FDA's risk-specific dose was adopted by the U.S. Public Health Service's Committee to Coordinate Environmental Health and Related Programs (CCEHRP) as the risk-specific dose for TEQ. In 1998, ATSDR used this risk-specific dose as a line of support for its policy guideline on dioxin and dioxin-like compounds in soil.

WHO and a number of individual countries have taken a different science-policy approach and have treated dioxins as nongenotoxic carcinogens and assumed that a safety factor approach, based on noncancer effects observed at lower doses than cancer in animals, would be adequate to account for concerns for both cancer and noncancer effects. This approach assumes that there is a virtual threshold for cancer effects above those for many noncancer effects. This position has been reiterated as recently as June 2001 by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The differences between EPA (plus a number of other U.S. federal

agencies) and these international organizations in their approach to assessing potential cancer risk reflect differences in science policy.

Despite EPA's use of the epidemiology data to describe an upper bound on cancer risk, the peer panels who met to review earlier drafts of the cancer epidemiology chapter suggested that the epidemiology data alone were not adequate to support the characterization of dioxin and related compounds as "known" human carcinogens but that the results from the human studies were largely consistent with observations from laboratory studies of dioxin-induced cancer and, therefore, should be weighed in the assessment. Other scientists, including those who attended the peer panel meetings, felt either more or less strongly about the weight of evidence from cancer epidemiology studies, representing the range of opinions that still exists on the interpretation of these studies. Similar opinions were expressed in the comments documented in the SAB's reports in 1995 and in 2001 (U.S. EPA, 1995, 2001b).

In its reevaluation of the cancer hazard of dioxin and related compounds, IARC (1997) found that whereas the epidemiologic database for 2,3,7,8-TCDD was still "limited," the overall weight of the evidence provided by human, animal and mechanistic data was sufficient to characterize 2,3,7,8-TCDD as a Category 1 "known" human carcinogen. Other related members of the class of dioxin-like compounds were considered to have "inadequate" epidemiologic data to factor into hazard categorization. A similar classification of 2,3,7,8-TCDD as a "known" carcinogen has been published within the context of the Department of Health and Human Services' report on carcinogens (NTP, 2001). Here, too, the characterization is based on the weight of the human, animal, and mode of action information in humans and animals.

Therefore, given that 2,3,7,8-TCDD is contained in complex mixtures of dioxin and related compounds and that the TEQ approach has been adopted as a reasonable approach to assessing risks of these complex mixtures, it is also reasonable to apply estimates of upper-bound cancer potency derived from epidemiology studies where 2,3,7,8-TCDD was associated with excess cancer risk to complex mixtures of dioxin and related compounds.

The current evidence suggests that both receptor binding and most early biochemical events such as enzyme induction demonstrate linearity of dose-response within the range of observation. The mechanistic relationship of these early events to the complex process of carcinogenesis remains uncertain, although modes of dioxin action have been proposed. If these findings imply low-dose linearity in biologically based cancer models under development, then the probability of cancer risk may also be linearly related to exposure to TCDD. Until the mechanistic relationship between early cellular responses and the parameters in biologically

based cancer models is better understood, the shape of the dose-response curve for cancer below the range of observation can be inferred only with uncertainty.

Initial attempts to construct a biologically based model for certain dioxin effects as described in this reassessment will need to be continued and expanded to accommodate more of the available biology and to apply to a broader range of potential health effects associated with exposure to dioxin-like compounds. Associations between exposure to dioxin and certain types of cancer have been noted in occupational cohorts with average body burdens of TCDD approximately one to three orders of magnitude (10 to 1000 times) higher than average TCDD body burdens in the general population. In terms of TEQ, the average body burden in these occupational cohorts level is within one to two orders of magnitude (10 to 100 times) of average background body burdens in the general population (see Table 5-1 and Figure 5-2). Thus, there is no need for large-scale, low-dose extrapolations when applying models based on curve-fitting empirical data in order to evaluate background intakes and body burdens, and there are few if any data to suggest large departures from linearity in this somewhat narrow window between the lower end of the range of observation and the range of general population background exposures. Nonetheless, the relationship of apparent increases in cancer mortality in these worker populations to calculations of general population risk remains a source of uncertainty.

Use of a "margin of exposure" approach to evaluate risk for noncancer and cancer endpoints.

The likelihood that noncancer effects may be occurring in the human population at environmental exposure levels has received increased attention in recent years and is a major focus of this reassessment. This likelihood is often evaluated using an MOE approach. An MOE is calculated by dividing a "point of departure" at the low end of the range of observation in human or animal studies (the human-equivalent LOAEL, NOAEL, BMD, or effective dose [EDxx]) by the comparable surrogate of human exposure at the level of interest. It differs from a reference dose (RfD), which establishes a level of exposure below which the Agency considers it unlikely that any adverse effects will occur. The Agency has used the MOE approach for a number of years in its noncancer assessment of the safety of pesticides. The MOE concept has also been incorporated into the *Draft Final Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2003) as an alternative approach to dose-response analysis if the shape of the dose-response curve is uncertain. These draft cancer guidelines recommend differing approaches and default assumptions for linear versus nonlinear cancer data, where linear data can be approximated through the cancer slope factor and nonlinear data through an RfD and Hazard

Index approach. For both linear and nonlinear approaches to cancer characterization, the Agency recommends a statement of the extent of extrapolation of risk estimates from observed data to exposure levels of interest and its implications for certainty or uncertainty in quantifying risk. The extent of this extrapolation can be expressed as a *margin of exposure* (MOE).

As the exposure of interest approaches the range of observation of effects and MOEs get smaller, reaching any conclusion regarding the certainty of no harm is much more difficult and relies heavily on scientific judgment regarding the adequacy of the available data. In order for a decision relying on the MOE to be adequately protective of health, information is provided to allow the decisionmaker, to the extent information allows, to take into account the nature of the effect at the POD; the shape and slope of the dose-response curve; the adequacy of the overall database to assess human hazard; interindividual variability in the human population with regard to exposure, metabolism, and toxic response; and other factors. Background exposures should be factored into the calculation. Considering MOEs based on estimates of incremental exposure alone divided by the human exposure of interest is not considered to give an accurate portrayal of the implications of that exposure unless background exposures are insignificant.

One of the difficulties in assessing the potential health risk of exposure to dioxins is that background exposures are often a significant component of total exposure when based on TEQ. The average levels of background intake and current average body burdens of dioxin-like compounds in terms of TEQs in the general population (1 pg TEQ/kg body weight/day and 5 ng TEQ/kg body weight, respectively) are within a factor of 10 of human-equivalent levels associated with NOELS, LOAELs, or ED_{01} values derived from studies in laboratory animals exposed to TCDD or TCDD equivalents for both cancer and noncancer toxic effects (see Table 5-6 and Appendix A). Therefore, in many cases, the MOE compared to background using these toxic endpoints is a factor of 10 or less. These estimates and others are presented and discussed in Part II, Chapter 8.

As discussed in Chapter 8, these data, although variable, suggest that choosing a human-equivalent body burden associated with an ED_{01} value above 100 ng/kg as a point of departure would likely yield a greater than 1% excess risk for some toxicity endpoint in humans. Also, choosing a POD below 1 ng/kg would likely be an extrapolation below the range of these data. Given the nature of the data and the range of uncertainty around individual data sets, any choice for a 1% effect point of departure in the middle range of 1 ng/kg to 100 ng/kg would be supported by the analyses, although the data provide the greatest support for defining a point of departure consistent with principles of safety assessment in the range of 10 ng/kg to 50 ng/kg. This range also includes body burdens consistent with the empirically derived NOAELs and

LOAELs for many of the effects that have traditionally been used as a POD for safety assessment by WHO, JECFA, and ATSDR.

Although somewhat dependent on experimental design or the model chosen to derive the ED_{01}, NOAEL, and LOAEL values, this range provides a perspective on the nature and variety of effects that have been evaluated within approximately an order of magnitude, from biochemical markers of exposure to more clearly adverse effects in animals. This range of body burdens should also provide a useful point of comparison when evaluating impacts of risk management on average body burdens in the general population or on estimates of impact of incremental exposures above background on the range of individual body burdens at various ages.

Because of the relatively high background levels as compared to effect levels, the Agency is not recommending the derivation of a reference dose (RfD) for dioxin and related compounds. Although RfDs are often useful because they represent a health risk goal below which there is likely to be no appreciable risk of noncancer effects over a lifetime of exposure, their primary use by the Agency is to evaluate increments of exposure from specific sources when background exposures are low. Any RfD that the Agency would recommend using a traditional approach for setting an RfD using uncertainty factors to account for limitations of knowledge is likely to be below—perhaps significantly below (by a factor of 10 or more)—current background intakes and body burdens. Because exceeding the RfD is not a statement of risk, comparing an incremental exposure to an RfD when the RfD has already been exceeded by average background exposures has little value for evaluating possible risk management options. In addition, the calculation of an RfD (with its traditional focus on a single "critical" effect) distracts from the large array of effects associated with similar body burdens of dioxin.

The Agency's SAB, in its comments on an earlier draft of this document, remarked that there might be value in calculating an RfD, despite a recognition of these concerns. The RfD could be used for purposes of comparison with other chemical-specific RfDs, to ensure that proper emphasis was given to noncancer effects and to set a goal for future exposure reductions. These comments notwithstanding, the Agency feels that all of these ends can be accomplished without the establishment of an RfD.

As discussed earlier, a range of values has been presented that indicates that dioxin and related compounds can produce effects, some of which are indicative of a biological response to dioxin exposure and some of which are arguably adverse, at or near current background body burdens or intake levels. Several of the studies within this range could logically be chosen as the "critical" effect upon which an RfD could be set. No one effect provides the obvious choice, as evidenced by approaches taken by WHO, JECFA and ATSDR, all of which chose different

effects upon which to base their tolerable or minimal risk levels. A range of ED_{01}s has been described in Chapter 8 and a summary of NOAELs, LOAELs, and ED_{01}s for low-dose effects is presented in Table 5-6 and Appendix A.

Depending on the choice of the endpoint, a composite uncertainty factor would need to be determined in order to set an RfD. This composite uncertainty factor should account for, at a minimum, pharmacodynamic aspects of cross-species scaling (traditionally, a factor of 3)—because pharmacokinetic factors are assumed to be accounted for by cross-species scaling on the basis of body burden—and interindividual human variability (traditionally, a factor of 10). In addition, selection of a LOAEL within the range would suggest an additional factor of uncertainty as large as 10. Recently published results also indicate neurobehavioral impacts on adult rats exposed perinatally at levels that yield body burden ED_{01}s below current average human body burdens and as low as the lowest noncancer effects previously evaluated (Markowski et al., 2001). In addition, many of the developmental reproductive effects observed in rats (Mably et al., 1992a-c) have ED_{01} values less than current background exposures. These results suggest that there may be additional database needs regarding risks to children. The above considerations would traditionally yield a composite uncertainty factor in the range of 30 to 100 or more.

Coupled with the relatively narrow range of possible "critical" effects discussed above, the range of plausible composite uncertainty factors make the selection of any particular value as the Agency's RfD more difficult than usual and probably unnecessary, particularly in light of the fact that any value that the Agency might choose using traditional approaches would be below current background body burden or intake levels.

When evaluating incremental exposures associated with specific sources, knowing the increment relative to background may help in understanding the impact of the incremental exposure. For instance, it would be misleading to focus on only the incremental exposure in evaluating the potential impact on human health when a relatively large background body burden of dioxin already exists in the exposed population. In these circumstances, the incremental exposure needs to be evaluated in the context of these background levels to aid in determining whether these incremental exposures have regulatory significance. This approach would parallel the Agency's approach to evaluating lead exposures. Other parallel science and management issues between dioxin-like compounds and lead are under discussion within the Agency. Providing guidance on the how to judge the significance of incremental increases to background using the MOE approach is beyond the science scope of the reassessment and will have to be addressed elsewhere by EPA. However, it is clear, in light of relatively high background

exposures, that the MOE approach is more useful than an RfD for characterizing dioxin noncancer risks.

Other national and international bodies have chosen to define "safe" or "tolerable" levels for dioxin and related compounds (e.g., WHO, 1998; ATSDR, 1999a; SCF, 2000). These estimates cluster within a factor of 4 of current average intake levels, although estimates in the past have spanned many orders of magnitude. Some commenters on earlier drafts of this reassessment have suggested that EPA's approach is inconsistent with these efforts and overly "conservative." Two distinctions can help in understanding these apparent differences. First, in its reassessment, EPA has not tried to establish a tolerable or acceptable level of risk. Rather, it has tried to provide a science-based description of hazard and potential risk without making a policy judgment of acceptability. Second, whether one is providing a risk descriptor or an acceptable risk determination, a number of judgments need to be made as one moves from experimental observation to conclusion. Apparently subtle differences in these judgments can result in significantly different conclusions. These differences in judgment fall into three major areas: (1) the original focus on cancer rather than noncancer effects as the primary endpoint of regulatory concern and the assumption by some that all nongenotoxic compounds have thresholds below which cancer risk is minimal or nonexistent; (2) the use of intake as the cross-species dose metric despite the large difference in half-life in animals versus humans (for TCDD, for instance, the difference between rats and humans is over a factor of 100); and (3) the size of the "safety" factor or "uncertainty" factors used to derive a "safe or "tolerable" level.

The latter factor is currently the most widely divergent. More recent assessments have taken noncancer endpoints into account and have applied a range of uncertainty factors. For instance, ATSDR (1999a) set a minimal risk level (MRL), which is defined similarly to EPA's RfD, for dioxin and related compounds of 1.0 pg TEQ/kg body weight/day. The ATSDR assessment is based on the results of Schantz et al. (1992), a study that is included in Table 5-6 and Appendix A. ATSDR used intake as the interspecies dose metric and a composite uncertainty factor of 90, accounting for intraindividual human variability (10), a minimal LOAEL/NOAEL (3), and residual pharmacodynamic differences (3).

Hypothetically, had ATSDR relied on the TCDD body burdens measured during this series of rhesus monkey experiments (see Bowman et al., 1989) and had all other factors been equal, the MRL would likely have been determined to be in the range of 0.07 pg TEQ/kg body weight/day (see Table 5-6 and Appendix A), or more than 10 times lower than the existing ATSDR MRL and current average intake levels. The ATSDR assessment, however, selects a

single "critical" effect from among a number of choices and uses "traditional" uncertainty factors, but it uses intake rather than body burden as the dose metric.

Several recent assessments have recognized the value of body burden rather than daily intake as the preferred dose metric. WHO (1998) has set a tolerable daily intake (TDI) of 1–4 pg TEQ/kg body weight/day using a range of effects and body burden and has indicated that, although current exposures in that range are "tolerable" (a decision taking into account risk management in addition to traditional hazard assessment), efforts should be made to ultimately reduce intake levels to the lower end of the range and perhaps further. Findings in this reassessment and comments made by the SAB (U.S. EPA, 2001b) are consistent with this recommendation. The WHO assessment relied on an evaluation of the most sensitive effects that are considered adverse (hormonal, reproductive, and developmental effects) and were seen at low doses in animal studies (rats and monkeys). Body burden was used as a dose metric, and a composite uncertainty of 10 was recommended to account for a number of factors, including the use of a LOAEL rather than a NOAEL, differences in animal-to-human susceptibility, and differences in half-lives of elimination for the different components of the TEQ mixture.

In May 2001, the European Commission Scientific Committee on Food (SCF, 2000) established a tolerable weekly intake of 14 pg TEQ/kg body weight/week (equivalent to a TDI of 2 pg TEQ/kg body weight/day), based on several new studies, which are also now included in EPA's range of low-dose effects, and on a composite uncertainty factor of 9.6. This factor accounts for interindividual variability in toxicokinetics (a factor of 3.2) and marginal effects close to a NOAEL (a factor of 3). The committee concluded that no uncertainty factor needed to be applied for differences in toxicodynamics between experimental animals and humans and for interindividual variation among humans. In June 2001, WHO JECFA determined a provisional tolerable monthly intake (PTMI) of 70 pg TEQ/kg body weight/month (equivalent to 2.33 pg TEQ/kg body weight/day), based on an approach similar to that used by the SCF. The same two studies and safety factors of 3.2 or 9.6 were used, but two models were used to extrapolate the maternal body burden at the NOEL/LOEL of the studies. The committee chose the PTMI as the mid-point of the range of values from its analysis.

It should be clear from the discussion above that there is a consensus that sensitive animal responses falling within a relatively narrow range of body burdens can be used as a POD for regulatory guidance, but the choice of individual studies varies. The EPA assessment is the only one to bound the full range of effects (from arguably adaptive and questionably adverse to arguably adverse to clearly adverse) observed through the application of a uniform modeling approach, as well as through evaluating experimental LOAELs and NOAELs. There is also an

emerging consensus that body burden should often be used as a cross-species dose metric. This has implications for ATSDR's current MRL derivation. Finally, there is no consensus on the size or nature of uncertainty factors to be applied. Traditional approaches that might be applied by EPA or that have been applied by ATSDR would likely require additional information to support the choice or removal of uncertainty factors as performed by WHO, SCF, and JECFA. In particular, the focus on accounting for residual toxicodynamic differences in cross-species scaling and interindividual variability in the general population to account for sensitive individuals, including children, would suggest larger uncertainty factors than have been proposed by these groups if EPA were to set an RfD.

The choice of any composite uncertainty factor greater than 10 applied to effect levels based on body burden in any of the analyses described above would result in TDIs or MRLs below current background intakes. The use of uncertainty factors in the range of 30 to 100 or more, as traditionally used by EPA, would result in values even further below some current background body burdens or intake levels than the values presented by other organizations. Given the range of choices for a POD, the range of potential composite uncertainty factors and the uninformative nature of an RfD below current background levels, the Agency has chosen to continue to focus on MOE analyses and to not establish an RfD for dioxin and related compounds.

Children's risk from exposure to dioxin and related compounds may be increased, but more data are needed to fully address this issue.

The issue of children's risk from exposure to dioxin-like compounds has been addressed in a number of sections throughout this reassessment. Data suggest a sensitivity of response in both humans and animals during the developmental period, both prenatal and postnatal. However, these data are limited. Because evaluation of the impacts of early exposures on both children's health and health later in life is important for a complete characterization of risk, collection of additional data should be a high priority in order to reduce uncertainties in future risk assessments.

Data from the Dutch cohort of children exposed to PCBs and dioxin-like compounds suggest subtle impacts on neurobehavioral outcomes, thyroid function, and immune system alterations from prenatal—and perhaps postnatal—exposure to 1980s background levels of dioxin and related compounds. Although these effects cannot be attributed solely to dioxin and related compounds, several associations suggest that these effects are, in fact, likely to be Ah-mediated. An investigation of background dioxin exposure and tooth development was done in

Finnish children as a result of studies of dental effects in dioxin-exposed rats, mice, and nonhuman primates and in PCB-exposed children. The Finnish investigators examined enamel hypomineralization of permanent first molars in 6- and 7-year-old children. The length of time that infants breast fed was not significantly associated with either mineralization changes or with TEQ levels in the breast milk. However, when the levels and length of breast feeding were combined in an overall score, a statistically significant association was observed.

In addition, effects have been seen in cases where significantly elevated exposure occurred. The incidents at Yusho and Yu-Cheng resulted in increased perinatal mortality and low birth weight in infants born to women who had been exposed. Rocker bottom heal was observed in Yusho infants, and functional abnormalities have been reported in Yu-Cheng children. The similarity of effects observed in human infants prenatally exposed to the complex mixture in Yusho and Yu-Cheng and those reported in adult monkeys exposed perinatally to only TCDD suggests that at least some of the effects on children are due to the TCDD-like congeners in the contaminated rice oil ingested by the mothers of these children. The similar responses include a clustering of effects in organs derived from the ectodermal germ layer, referred to as ectodermal dysplasia, including effects on the skin, nails, and Meibomian glands, and developmental and psychomotor delay during developmental and cognitive tests.

Some investigators believe that because all of the effects in the Yusho and Yu-Cheng cohorts do not correlate with TEQ, some of the effects are due exclusively to nondioxin-like PCBs or to a combination of all the congeners. In addition, on the basis of these data, the extent of the association between overt maternal toxicity and embryo/fetal toxicity in humans is still not clear. Further studies in the offspring as well as follow-up of the Seveso incident may shed further light on this issue. In addition to the chloracne and acute responses to TCDD exposure seen in Seveso children, elevated levels of serum GGT have been observed within a year after exposure in some of the more highly exposed Seveso children. Long-term pathologic consequences of elevated GGT have not been illustrated by excess mortality from liver disorders or cancer or in excess morbidity, but further follow-up is needed. It must be recognized that the absence of an effect thus far does not obviate the possibility that the enzyme levels increased concurrently with the exposure but declined after cessation. The apparently transient elevations in ALT levels among the Seveso children suggest that hepatic enzyme levels other than GGT may react in this manner to TCDD exposure. Recent studies in Seveso have also demonstrated an altered sex ratio in the second generation (Mocarelli et al., 2000).

Impacts on thyroid hormones provide an example of an effect of elevated postnatal exposure to dioxin and related compounds. Several studies of nursing infants suggest that

ingestion of breast milk that has a higher dioxin TEQ may alter thyroid function. Thyroid hormones play important roles in the developing nervous system of all vertebrate species, including humans. In the United States, all infants are tested for hypothyroidism shortly after birth. Results from the studies mentioned above suggest a possible shift in the population distribution of thyroid hormone levels, particularly T4, and point out the need for collection of longitudinal data to assess the potential for long-term effects associated with developmental exposures.

A large number of studies in animals, including studies of single congeners and exposures to complex mixtures, have addressed the question of effects of dioxin-like chemicals after in utero or lactational exposure. However, the vast majority of the data are derived from studies of 2,3,7,8-TCDD, single congeners (e.g., PCB 77), or commercial mixtures of PCBs. Exposure patterns have included single doses to the dams as well as dosing on multiple days during gestation beginning as early as the first day of gestation. These studies are discussed in detail in Part II, Chapter 5. The observed toxic effects include developmental toxicity, neurobehavioral and neurochemical alterations, endocrine effects, and developmental immunotoxicity. For instance, results of this body of work suggest that 2,3,7,8-TCDD clearly has the potential to produce alterations in male reproductive function (rats, mice, hamsters), male sexual behavior (rats), and female genitalia (rats, hamsters) after prenatal exposure. In addition, impacts on neuromotor and cognitive behavior as well as on development of the immune system have been indicated in a number of studies.

No epidemiological data and limited animal data are available to address the question of the potential impact of exposure to dioxin-like compounds on childhood cancers or on cancers of later life. The direct impacts of increased early postnatal exposure on the carcinogenic process may be small, noting the limited impact of nursing on total body burden (see the discussion of breast milk exposures and body burdens below), the assumption that cancer risk is a function of average lifetime body burden, and the possibility that, because dioxin is a potent cancer promoter rather than a direct initiator of the cancer process, exposures later in life might be more important than those received earlier. However, recent studies of Brown et al. (1998) suggest that prenatal exposure of rats to dioxin and related compounds may indirectly enhance their sensitivity as adults to chemical carcinogenesis from other chemical carcinogens. Further work is needed to evaluate this issue.

Fetuses, infants, and children are exposed to dioxins through several routes. The fetus is exposed in utero to levels of dioxin and related compounds that reflect the body burden of the mother. It is important to recognize that the greatest impact on the mother's body burden is from

of her lifetime exposure history rather than from the individual meals she eats during pregnancy. Good nutrition, including a diet with appropriate levels of fat, has consequences on dietary intake and consequent body burdens of dioxin and related compounds. Nursing infants represent special cases because for a limited portion of their lives they may have elevated exposures on a body-weight basis when compared with non-nursing infants and with adults (see discussion below).

In addition to breast milk exposures, intakes of CDD/CDFs and dioxin-like PCBs are more than three times higher for a young child than for an adult, on a body-weight basis. Table 4-7 in Section 4 of this document describes the variability in average intake values as a function of age using age-specific food consumption rates and average food concentrations, as was done for adult intake estimates. However, as with the nursing infants, the differences in body burden between children and adults are expected to be much less than the differences in daily intake. Assuming that body burden is the relevant dose metric for most if not all effects, there is some assurance that these short-term increased intake levels will have limited additional impact on risk as compared with overall lifetime exposure.

Background exposures to dioxin and related compounds need to be considered when evaluating both hazard and risk.

The term "background exposure" has been used throughout this reassessment to describe exposure of the general population to environmental media (food, air, soil, etc.) that have dioxin concentrations within the normal background range. Adult daily intakes of CDD/CDFs and dioxin-like PCBs are estimated to average 43 and 23 pg TEQ_{DFP}-WHO_{98}/day, respectively, for a total intake of 66 pg/day TEQ_{DFP}-WHO_{98}. On a body-weight basis, this corresponds to approximately 1 pg TEQ_{DFP}-WHO_{98}/kg-day. Daily intake is estimated by combining exposure media concentrations (food, soil, air) with contact rates (ingestion, inhalation). Table 4-6 summarizes the intake rates derived by this method. The intake estimate is supported by an extensive database on food consumption rates and food data. Pharmacokinetic modeling provides further support for the intake estimates. Current adult tissue levels reflect intakes from past exposure levels, which are thought to be higher than current levels.

CDD/CDF and dioxin-like PCB intakes for the general population may extend to levels at least three times higher than the mean. Variability in general population exposure is primarily a result of differences in the dietary choices that individuals make in terms of both quantity and types of food consumed. A diet that is disproportionately high in animal fats will result in an increased background exposure over the mean. Data on the variability of fat consumption

indicate that the 95th percentile is about twice the mean and the 99th percentile is approximately three times the mean. Additionally, a diet that substitutes meat sources that are low in dioxin (e.g., beef, pork, or poultry) with sources that are high in dioxin (e.g., freshwater fish) could result in elevated exposures.

Evidence of widespread background exposure can also be seen by examining data on human tissue. These data indicate that the average CDD/CDF tissue level for the general adult U.S. population appears to be declining. A pharmacokinetic modeling evaluation of this declining trend suggests that the CDD/CDF tissue level will drop below 10 ppt TEQ_{DF}-WHO_{98}, lipid basis, by 2030 (Lorber, 2002). The best estimate of current (mid to late 1990s) levels is 25 ppt (TEQ_{DFP}-WHO_{98}, lipid basis). The tissue samples collected in North America in the late 1980s and early 1990s showed an average TEQ_{DFP}-WHO_{98} level of about 55 pg/g lipid. This finding is supported by a number of studies, all conducted in North America, that measured dioxin levels in adipose tissue, blood, and human milk. However, the number of people in most of these studies is relatively small, and the participants were not statistically selected in ways that ensured their representativeness of the general U.S. adult population. One study, the 1987 National Human Adipose Tissue Survey (NHATS), involved more than 800 individuals and provided broad geographic coverage, but it did not address coplanar PCBs. Similar tissue levels of these compounds were measured in Europe and Japan during similar time periods.

Because dioxin levels in the environment have been declining since the 1970s, it is reasonable to expect that levels in food, human intake, and, ultimately, human tissue have also declined over this period. The changes in tissue levels are likely to lag the decline seen in environmental levels, and the changes in tissue levels cannot be assumed to occur proportionally with declines in environmental levels. CDC (2000) summarized levels of CDDs, CDFs, and PCBs in human blood collected between 1995 and 1997. The individuals sampled were all U.S. residents who had no known exposures to dioxin other than normal background. The blood was collected in six different locations from 316 individuals ranging in age from 20 to 70 years. All TEQ calculations were made assuming that nondetects were equal to half the detection limit. Although these samples were not collected in a manner that can be considered statistically representative of the national population and they lack wide geographic coverage, they are judged to provide a better indication of current tissue levels in the United States than the earlier data (see Table 4-5).

PCBs 105, 118, and 156 are missing from the blood data for the comparison populations reported by CDC (2000). These congeners account for 62% of the total PCB TEQ estimated in the early 1990s. Assuming that the missing congeners from the CDC study data contribute the

same proportion to the total PCB TEQ as in earlier data, they would increase the estimate of current body burdens by another 3.3 pg TEQ/g lipid, for a total PCB TEQ of 5.3 pg/g lipid and a total TEQ_{DFP}-WHO_{98} of 25.4 pg/g lipid.

As noted, characterizing national background levels of dioxins in tissues is uncertain because the current data cannot be considered statistically representative of the general population. The task is also complicated by the fact that tissue levels are a function of both age and birth year. Because intake levels have varied over time, the accumulation of dioxins in a person who turned 50 in 1990 is different from that in a person who turned 50 in 2000. Future surveys should help to characterize national levels of CDD/CDF/PCBs during the last years of the 20th century and into the 21st century. The National Health and Nutrition Examination Survey (NHANES) conducted in 1999-2000 included measurements of dioxin blood levels in 1921 individuals, aged 12 and higher, from numerous locations around the country (CDC, 2003). Unfortunately, not enough blood serum was available per individual to be able to quantify the dioxin concentrations at low background levels, so the majority of measurements were nondetects. An effort is currently underway to pool remaining NHANES 1999-2000 samples and reanalyze them. This will allow for an estimate of average background body burdens of dioxin-like compounds representative of the turn of the century, and in future years should provide a picture of dioxin levels in the general U.S. population.

As described above, current intake levels from food sources are estimated in this reassessment to be approximately 1 pg TEQ/kg body weight/day. Certain segments of the population may be exposed to additional increments of exposure by being in proximity to point sources or because of dietary practices. These types of exposure are described below.

Evaluating the exposure of "special" populations and developmental stages is critical to risk characterization.

As discussed above, background exposures to dioxin-like compounds may extend to levels at least three times higher than the mean. This upper range is assumed to result from the normal variability of diet and human behaviors. Exposures from local elevated sources or unique diets would be added to this background variability. Elevated exposures may occur in small segments of the population, such as individuals living near discrete local sources or subsistence or recreational fishers. Nursing infants represent a special case. For a limited portion of their lives, they may have elevated exposures on a body-weight basis when compared to non-nursing infants and to adults. This exposure will be discussed in a separate section.

Dioxin contamination incidents involving the commercial food supply have occurred in the United States and other countries. For example, in the United States, contaminated ball clay was used as an anticaking agent in soybean meal, resulting in elevated dioxin levels in some poultry and catfish. This incident involved only a small fraction of national poultry production and the practice has since been eliminated. Elevated dioxin levels have also been observed in a few beef and dairy animals, where the contamination was associated with contact with pentachlorophenol-treated wood. This type of elevated exposure was not detected in the national beef survey; consequently, its occurrence is likely to be low, although it has not been determined.

These incidents may have led to small increases in dioxin exposure to the general population; however, it is unlikely that they have led to disproportionate exposures to populations living near where they occurred because, in the United States, meat and dairy products are highly distributed on a national scale. If contamination events were to occur in foods that are predominantly distributed on a local or regional scale, then such events could lead to higher exposure among local populations.

Elevated exposures associated with the workplace or with industrial accidents have also been documented. U.S. workers in certain segments of the chemical industry had elevated levels of TCDD exposure, with some tissue measurements in the thousands of parts per trillion TCDD. There is no clear evidence that elevated exposures are currently occurring among U.S. workers. Documented examples of past exposures for other groups include certain Air Force personnel exposed to Agent Orange during the Vietnam War and individuals exposed as a result of industrial accidents in Europe and Asia.

The discussion in Section 4.5 identified the general population distribution of exposure as extending up to roughly three times the mean. Most people will have exposures within this range even if they have unusual diets in terms of meat and dairy products because most people eat food from multiple sources, which tends to average out the contamination levels, and meat and dairy products have similar dioxin levels, so substitution of one type of meat for another should not have a great impact on total exposure. Clearly elevated exposures are possible in unusual situations where an individual consumes high quantities of meat or dairy products that have significantly increased dioxin levels. Elevated exposures resulting from fish consumption can occur in different situations because concentrations in freshwater fish are significantly greater than in meat and dairy products. Therefore, people who consume large quantities of freshwater fish at background contamination levels may have intakes elevated above the general population distribution.

Consumption of fish, meat, or dairy products containing elevated levels of dioxins and dioxin-like PCBs can lead to elevated exposures in comparison to the general population. Most people eat some fish from multiple sources, both fresh and salt water. If individuals obtain their fish from areas where the concentration of dioxin-like chemicals is elevated, they may constitute a highly exposed subpopulation. Although this scenario seems reasonable, very little supporting data could be found for such a highly exposed subpopulation in the United States. One study that measured dioxin-like compounds in blood of sports fishers in the Great Lakes area showed elevations over mean background but within the range of normal variability.

Another study that measured 90 PCB congeners—of which 7 were dioxin-like mono-ortho PCBs (although PCB 126 was not measured)—in Lake Michigan "sport-fish eaters" showed a significant elevation in these PCBs versus a control group (little or no sport fish consumption). Significantly elevated concentrations of dioxins, furans, and coplanar PCBs were measured in Great Lakes fish by the Ontario Ministry of the Environment, although this study was conducted in known or suspected hot spots for the purpose of setting consumption advisories. It is not known to what extent individuals would be consuming fish at the high concentrations measured. Elevated CDD/CDF levels in human blood have been measured in Baltic fishermen. Similarly, elevated levels of coplanar PCBs have been measured in the blood of fishers on the north shore of the Gulf of the St. Lawrence River who consume large amounts of seafood.

High exposures to dioxin-like chemicals as a result of consuming meat and dairy products would most likely occur in situations where individuals consume large quantities of these foods and the level of these compounds is elevated. Most people eat meat and dairy products from multiple sources, and even if large quantities are consumed, unusually high exposures are not likely. Individuals who raise their own livestock for basic subsistence have the potential for higher exposures if local levels of dioxin-like compounds are high. One study in the United States showed elevated levels in chicken eggs near a contaminated soil site. European studies at several sites have shown elevated CDD/CDF levels in milk and other animal products near combustion sources.

In summary, in addition to general population exposure, some individuals or groups of individuals may also be exposed to dioxin-like compounds from local discrete sources or pathways within their environment. Examples of these "special" exposures include contamination incidents, occupational exposures, direct or indirect exposure to local populations from discrete sources, or exposures to subsistence or recreational fishers.

Breast-feeding infants have higher intakes of dioxin and related compounds for a short but developmentally important part of their lives; however, the benefits of breast feeding are widely recognized to outweigh the risks.

Three studies have compared dioxins in infants who were breast fed with those who were formula fed, and all have shown elevations in the concentrations of dioxins in infants being breast fed. Formula-fed infants had lipid-based concentrations < 5 ppt TEQ_{DF}-WHO_{98}, whereas breast-fed infants had average lipid-based concentrations > 20 ppt TEQ_{DF}-WHO_{98}. A similar disparity is seen in more limited data on dioxin-like PCBs.

The dose to the infant varies as a function of infant body weight, the concentration of dioxins in the mother's milk, and the trend of dioxins in the mother's milk to decline over time. Using typical values for these parameters, dioxin intakes at birth were estimated to equal 242 pg TEQ_{DFP}-WHO_{98}/kg/day, which would drop to 18 pg TEQ_{DFP}-WHO_{98}/kg/day after 12 months. The average infant dose over a year was calculated to be 87 pg TEQ_{DFP}-WHO_{98}/kg/day. Although this dose exceeds the currently estimated adult dose of 1 pg TEQ_{DFP}-WHO_{98}/kg/day, the effect on infant body burdens is expected to be less dramatic, that is, infant body burdens will not exceed adult body burdens by 87 times. This is due to the rapidly expanding infant body weight and lipid volume, the decrease in concentration of dioxins in the mother's milk over time, and more rapid elimination in infants.

A pharmacokinetic exercise comparing 6-month, 1-year, and 2-year nursing scenarios with formula feeding showed peak infant lipid concentrations of 44 ppt TEQ_{DFP}-WHO_{98} at 9 weeks of age, compared with peak lipid concentrations of less than 10 ppt for the formula-fed infants and average adult lipid concentrations of 25 ppt TEQ_{DFP}-WHO_{98}. The dioxin concentrations in breast-fed and formula-fed children were predicted to merge at about 10 years of age, at a lipid concentration of about 13 ppt TEQ_{DFP}-WHO_{98}. Breast feeding for 1 year was predicted to result in a lifetime accumulated exposure about 13% higher as compared to formula feeding only.

The American Academy of Pediatrics (1997) has made a compelling argument for the diverse advantages of breast feeding for infants, mother, families, and society. These include health, nutritional, immunologic, developmental, psychological, social, economic, and environmental benefits. Breast milk is the point of comparison for all infant food, and the breast-fed infant is the reference for evaluation of all alternative feeding methods. In addition, increasing the rates of breast-feeding initiation is a national health objective and one of the goals of the United States Government's Healthy People 2010. WHO (1988) maintained that the

evidence did not support an alteration of its recommendations that promote and support breast feeding. A more recent consultation in 1998 (WHO, 2000) reiterated these conclusions.

Although it is important that the recommendations of these groups continue to be reevaluated in light of emerging scientific information, the Agency does not believe that the findings contained in this reassessment provide a scientific basis for initiating such a reevaluation. This conclusion is based on the fact that stronger data have been presented that body burden, not intake, is the best dose metric; that many of the noncancer effects, particularly those seen in children, are more strongly associated with prenatal exposure and the mother's body burden than with postnatal exposures and breast milk levels; and that dioxin-like compounds are strong promoters of carcinogenicity, a mode of action that depends on late-stage impacts rather than on early-stage impacts on the carcinogenic process.

Many dioxin sources have been identified and emissions to the environment are being reduced.

Current emissions of CDDs/CDFs/PCBs to the United States environment result principally from anthropogenic activities. Evidence for this finding includes matches in time of the rise of environmental levels with the rise in general industrial activity (see discussion in Section 4.1), lack of any identified large natural sources, and observations of higher CDD/CDF/PCB body burdens in industrialized versus less industrialized countries (see discussion on human tissue levels in Section 4.4).

The principal identified sources of environmental releases are (1) combustion and incineration sources; (2) chemical manufacturing/processing sources; (3) industrial/municipal processes; (4) biological and photochemical processes; and (5) reservoir sources. Development of national estimates of annual environmental releases to air, water, and land is complicated by the fact that only a few facilities in most industrial sectors have been evaluated for CDD/CDF emissions. Thus, an extrapolation is needed to estimate national emissions. The extrapolation method involves deriving an estimate of emissions per unit of activity (i.e., an emission factor) at the tested facilities and multiplying this by the total activity level in the untested facilities.

In order to convey the level of uncertainty in both the measure of activity and the emission factor, EPA developed a qualitative confidence rating scheme. The confidence rating scheme, presented in Section 4, Table 4-1, uses qualitative criteria to assign a high, medium, or low confidence rating to the emission factor and activity level for those source categories for which emission estimates can be reliably quantified. The dioxin reassessment has produced an inventory of source releases for the United States (Table 4-2). The inventory is limited to

sources whose releases can be reliably quantified (i.e., those with confidence ratings of A, B, or C, as defined in Table 4-1). The inventory presents the environmental releases in terms of two reference years: 1987 and 1995. For both of these periods, emissions from combustion and incineration sources dominated total releases. EPA's best estimates of releases of CDD/CDFs to air, water, and land from reasonably quantifiable sources were approximately 3300 g (7 pounds) TEQ_{DF}-WHO_{98} in 1995 and 14,000 g (31 pounds) TEQ_{DF}-WHO_{98} in 1987. The decrease in estimated releases of CDD/CDFs between 1987 and 1995 (approximately 76%) was due primarily to reductions in air emissions from municipal and medical waste incinerators.

Although this inventory is one of the most comprehensive and well-documented in the world, it is likely to underestimate total releases because a number of known sources lacked sufficient data to be included in the inventory and the possibility remains that truly unknown sources exist.

Further reductions in environmental releases since the inventory for 1995 can be anticipated as a result of EPA regulations for waste combustion sources and pulp and paper facilities. EPA's regulatory programs estimate that, under full compliance with these regulations, an additional 1800 g I-TEQ reduction in CDD/CDF emissions should occur. With these anticipated emission reductions, uncontrolled burning of household waste would become the largest quantifiable source. Although the full magnitude of reservoir releases remains uncertain, their relative contribution to total annual releases be can reasonably anticipated to increase as contemporary formation sources continue to decrease.

No significant release of newly formed dioxin-like PCBs is occurring in the United States. Unlike CDD/CDFs, PCBs were intentionally manufactured in the United States in large quantities from 1929 until production was banned in 1977. Although it has been demonstrated that small quantities of coplanar PCBs can be produced during waste combustion, no strong evidence exists that the dioxin-like PCBs make a significant contribution to TEQ releases during combustion. The occurrences of dioxin-like PCBs in the U.S. environment most likely reflect past releases associated with PCB production, use, and disposal. Further support for this finding is based on observations of reductions since the 1980s in PCBs in Great Lakes sediment and in other areas.

As described in Section 4.1, combustion appears to be the most significant process of CDD/CDF formation today. Important factors that can affect the rate of dioxin formation include overall combustion efficiency, post-combustion flue gas temperatures and residence times, and the availability of surface catalytic sites to support dioxin synthesis. Although chlorine is an essential component for the formation of CDDs/CDFs in combustion systems, the empirical

evidence indicates that, for commercial-scale incinerators, chlorine levels in feed are not the dominant controlling factor for rates of CDD/CDF stack emissions. The conclusion that chlorine in feed is not a strong determinant of dioxin emissions applies to the overall population of commercial scale combustors. For any individual commercial-scale combustor, circumstances may exist in which changes in chlorine content of feed could affect dioxin emissions. For uncontrolled combustion, such as open burning of household waste, chlorine content of wastes may play a more significant role than commercial-scale combustors in levels of dioxin emissions.

Dioxins are widely distributed in the environment at low concentrations, primarily as a result of air transport and deposition.

The dioxin-like compounds are essentially insoluble in water, they are generally classified as semivolatile, and they tend to bioaccumulate in animals. Once introduced into the environment, they are widely distributed in the environment as a result of a number of physical and biological processes. There is some evidence that these compounds can degrade in the environment, but in general they are considered very persistent and relatively immobile in soils and sediments.

The dioxin-like compounds are transported through the atmosphere as vapors or attached to airborne particulates and they can be deposited on soils, plants, or other surfaces (by wet or dry deposition).

They enter water bodies primarily via direct deposition from the atmosphere or by surface runoff and erosion. From soils, these compounds can reenter the atmosphere as resuspended soil particles or as vapors. In water, they can be resuspended into the water column from sediments, volatilized out of the surface waters into the atmosphere, or buried in deeper sediments. Immobile sediments appear to serve as permanent sinks for the dioxin-like compounds. Anthropogenic materials (such as pentachlorophenol), although not always considered an environmental compartment, may also contain these compounds, and they have the potential to be released from these materials into the broader environment.

The two primary pathways by which dioxin-like compounds enter the ecological food chains and human diet are air to plant to animal and water/sediment to fish. Vegetation receives these compounds via atmospheric deposition in the vapor and particle phases. The compounds are retained on plant surfaces and bioaccumulated in the fatty tissues of animals that feed on these plants. In the aquatic food chain, dioxins enter water systems via direct discharge or deposition and runoff from watersheds. Fish accumulate these compounds through direct contact

with water, suspended particles, and bottom sediments and through the consumption of aquatic organisms.

Although these two pathways are thought to normally dominate contribution to the commercial food supply, others can also be important. Animal feed contamination episodes have led to elevations of dioxins in poultry in the United States, in milk in Germany, and in meat/dairy products in Belgium. Gaining a quantitative understanding of how dioxin moves in the environment will be particularly important in understanding the relative contributions of individual point sources to the food chain and assessing the effectiveness of control strategies to reduce human exposure. Although the emissions inventory shows the relative contribution of various sources to total emissions, it is unlikely that these sources make the same relative contributions to human exposure.

It is quite possible that the major contributors of dioxin to food may not be those sources that represent the largest fractions of total emissions in the United States (see discussion in Section 4.4 indicating that the diet is the dominant exposure pathway for humans). The geographic locations of sources relative to the areas from which much of the beef, pork, milk, and fish are produced should be considered. Most of the agricultural areas that produce dietary animal fats are not located near or directly downwind of the major sources of dioxin and related compounds.

The contribution of reservoir sources to human exposure is likely to be significant. Several factors support this finding. First, human exposure to the dioxin-like PCBs is thought to be derived almost completely from reservoir sources. Because approximately one-third of general population TEQ intake is due to PCBs, then at least one-third of the calculated overall risk from dioxin-like compounds comes from reservoir sources. Second, CDD/CDF releases from soil via soil erosion and runoff to waterways appear to be greater than releases to water from the primary sources included in the inventory. CDD/CDFs in waterways can bioaccumulate in fish, leading to human exposure via consumption of fish. This suggests that a significant portion of the CDD/CDF TEQ exposure could be due to releases from the soil reservoir. Finally, soil reservoirs could have vapor and particulate releases that deposit on plants and enter the terrestrial food chain. However, the magnitude of this contribution is unknown. Collectively, these three factors suggest that reservoirs are a significant source of current background TEQ exposure, perhaps contributing half or more of the total.

Environmental levels, emissions, and human exposures have declined during recent decades.

The most compelling supportive evidence of a general decline in environmental levels for CDD/CDF/PCBs comes from dated sediment core studies. CDD/CDF/PCB concentrations in sediments began to increase around the 1930s and continued to increase until about 1970. Decreases began in 1970 and have continued to the time of the most recent sediment samples (about 1990). Sediment studies in lakes located in several European countries have shown similar trends.

It is reasonable to assume that sediment core trends are driven by a similar trend in emissions to the environment. The period of increase generally matches the time when a variety of industrial activities began rising, and the period of decline appears to correspond with growth in pollution abatement. Decreases in dioxin emissions will presumably have resulted from many of these abatement efforts, which included elimination of most open burning, particulate controls on combustors, phase-out of leaded gas, and bans on PCBs, 2,4,5-T, hexachlorophene and restrictions on the use of pentachlorophenol. Also, the national source inventory of this assessment documented a significant decline in emissions from the late 1980s to the mid-1990s.

Evidence of declines in human exposure can be inferred from the overall declines in environmental levels and emissions, and it is directly supported by limited data on concentrations in food and human tissues (see Sections 4.3 and 4.4). Because of the lag between environmental levels and body burdens, it is anticipated that further declines in tissue concentrations should occur as individuals with higher body burdens from past exposure age out of the population. A pharmacokinetic modeling exercise suggested that levels of TEQ_{DF}-WHO_{98} in the U.S. population should decline from levels of about 20 ppt lipid-basis measured in the mid-1990s CDC study to below 10 ppt lipid-basis by 2030. This analysis includes CDD/CDFs only, not PCBs. Dioxin-like PCBs currently make up approximately 20% of the current total TEQ body burden but may increase in percentage as CDD/CDFs decline. This modeling result is based on the assumption that current CDD/CDF intakes remain the same into the 21st century.

Risk Characterization Summary Statement

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD; "dioxin") is highly toxic to many animal species, producing a variety of noncancer and cancer effects. Other 2,3,7,8-substituted polychlorinated dibenzo-*p*-dioxins and dibenzofurans and coplanar polychlorinated biphenyls (PCBs) exhibit similar effects, albeit at different doses and with different degrees of confidence in the database.

The similarities in toxicity between species and across different dioxin congeners stem from a common mode of action via initial binding to the aryl hydrocarbon (AhR) receptor. This common mode of action is supported by the consistency in effects evident from multiple congener databases, although uncertainty remains due to data gaps for some congeners. The databases supportive of dioxin-like toxicity, both cancer and noncancer, are strongest for those congeners that are the major contributors to the risk to human populations. This has led to an international scientific consensus that it is prudent science policy to use the concept of toxic equivalency factors (TEFs) to sum the contributions of individual PCDD, PCDF, and coplanar PCB congeners with dioxin-like activity.

In addressing receptor-mediated responses resulting from complex mixtures of dioxin-like congeners, this assessment has provided a basis for the use of integrated measures of dose such as lifetime average body burden as more appropriate default metrics than average lifetime daily intake. Although average body burden over a lifetime appears to be the most useful dose metric for chronic effects, average body burden during the window of sensitivity may be the most appropriate metric for developmental effects. The Agency recognizes, therefore, that the final choice of the appropriate metric may depend on the endpoint under evaluation.

Dioxin and related compounds have been shown to be developmental, reproductive, immunological, endocrinological, and cancer hazards, among others in multiple animal species. There is no reason to expect, in general, that humans would not be similarly affected at some dose, and indeed, a growing body of data supports this assumption. On the basis of the animal data, current margins of exposure are lower than generally considered acceptable, especially for more highly exposed human populations. The human database supporting this concern for potential effects near background body burdens is less certain. Occupational and industrial accident cohorts exposed at higher levels show correlations with exposure for cancer and a number of noncancer effects consistent with those seen in the animal studies.

For cancer outcomes, the epidemiological evidence provides consistent findings of statistically significant elevations, with dose-response trends for all cancers combined and lung cancer risk in occupational cohorts along with evidence of possible additional tissue-specific cancer rate elevations. Given this substantial yet still not definitive epidemiological data, the positive cancer bioassays at multiple sites and in all animal species tested, in vitro studies, and the mechanistic considerations common to animals and humans for dioxin carcinogenicity, EPA characterizes 2,3,7,8-tetrachlorodibenzo-*p*-dioxin as "carcinogenic to humans." On the basis of similarities of response in multiple positive animal bioassays for non-TCDD congeners and mixtures, mode of action studies, and consistent with the concept of toxic equivalency, complex mixtures of dioxin and related compounds are considered highly potent "likely" carcinogens.

The calculated body burdens of dioxin and dioxin-like substances leading to an estimated 1% increase (ED_{01}) in the lifetime risk of cancer in the three occupational studies with the best exposure information fall within a 10-fold range, and those calculated from the animal bioassay data fall in the middle of this range. The ED_{01} for all cancers combined from the three occupational cohorts range from 6 to 62 ngTCDD/kg body weight (excluding the NIOSH power model calculation), depending on the study and the model used. By comparison, current background body burdens in the United States are approximately 5 ngTEQ/kg body weight, suggesting little margin of exposure (MOE) at today's body burden levels.

From these same occupational and animal cancer studies, EPA estimates an upper bound on the lifetime risk of all cancers combined of 1×10^{-3} per pgTEQ/kg/day. This cancer slope factor is based on a statistical estimate of risks from occupational exposures—principally to healthy, adult, male workers—and it must be coupled with a recognition that a small number of people may be both more susceptible and consume up to three times the average level of fat per day (the principal exposure pathway for dioxins in the general population). Conversely, this risk estimate is based on assumptions that the extra cancer risk seen in the occupational cohorts is attributable to dioxin and not other chemical agents present; that the appropriate metric for cancer risk is lifetime average body burden and not a measure of peak exposure, which would tend to mitigate risks at low exposures; and that the dose-response model curve continues below the range of statistically significant data and does not then exhibit some nonlinearity. Using the best available estimates of cancer risks, the upper bound on general population lifetime risk for all cancers might be on the order of 1 in 1000 or more. Upper-bound risk estimates allow the calculation of the high end of the probability of cancer risk in the population. This means that there is greater than a 95% chance that cancer risks will be less than the upper bound, and it could be as low as zero in some individuals.

For noncancer effects, EPA generally calculates an RfD/RfC value that represents an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. RfD/RfCs are generally calculated by estimating a point of departure dose just below the lower end of the range of observed adverse effects, and dividing this by uncertainty factors to account for extrapolation issues and database deficits. Applying these standard procedures to the data reviewed in this assessment would result in an RfD/RfC below the current estimated average dose to the U.S. population (~1 pgTEQ/kg/day), and would, therefore, be uninformative for a safety assessment.

EPA has chosen instead to characterize the MOEs for noncancer endpoints in order to better inform risk management decisions. The MOE is the ratio of the effect level in the

comparison species (ED_{01} or low effect level; animal or human) to the human body burden. For the most sensitive endpoints identified, MOEs range from, for example, less than 1 for enzyme induction in mice and rats, < 4 for developmental effects, and 4 for endometriosis in non-human primates. In evaluating MOEs, consideration should be given to uncertainties in distinguishing between adaptive biochemical changes and adverse effects, both on an individual level and as these changes impact whole populations. The risks from dioxin and related compounds may be greater for children than for adults, but more data are needed to fully address this issue.

Releases of dioxins to the environment from characterized sources have decreased significantly over the last decade and are expected to continue to decrease. Other sources are still poorly characterized, and an environmental reservoir of dioxins from both man-made and natural sources has been recognized. Human body burdens have also declined and are anticipated to be further reduced as additional, recently implemented, dioxin emission controls impact environmental and food levels and, ultimately, human exposure, although the relationship with reservoir sources remains uncertain.