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Information Sheet 2

Dioxin: *Scientific Highlights from Draft Reassessment (2000)*

Scientists from the Environmental Protection Agency (EPA), other federal agencies and the general scientific community have conducted a comprehensive reassessment of dioxin exposure and human health effects since 1991. See the discussion of the process in the companion document entitled, "Dioxin Reassessment Process: EPA is Moving Toward Completion of the Dioxin Reassessment." In the next few pages, the Agency summarizes the scientific highlights of the updated, draft reassessment of dioxin and related compounds, including the updated and revised "Dose Response" Chapter (Part II. Chapter 8), the new "Toxicity Equivalence (TEF)" Chapter (Part II. Chapter 9), and the updated, revised, and reformatted "Integrated Summary and Risk Characterization" (Part III).

Throughout this reassessment, concentrations of dioxin and related compounds are presented as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) equivalents (TEQs). One compound, TCDD is the best studied of this class of compounds and is the reference compound for assignment of toxicity equivalence factors (TEFs) for related congeners. The strengths and weaknesses as well as the uncertainties of the TEF/TEQ approach have been discussed in the report and, particularly, in a newly developed chapter (Part II. Chapter 9). Use of the TEQ approach is widely accepted in the international scientific community and is fundamental to the evaluation of this group of compounds which always exist in nature as complex mixtures of dioxins. The use of the TEQ approach represents a key assumption upon which many of the conclusions in this characterization hinge.

The reassessment finds that there is adequate evidence based on all available information, including studies in human populations as well as in laboratory animals and from ancillary experimental data, to suspect that humans may respond with a broad spectrum of effects from exposure to dioxin and related compounds. Research has highlighted certain prominent, biologically significant effects of TCDD. These biochemical, cellular, and organ-level endpoints have been shown to be affected by TCDD in experimental systems, but specific data on these endpoints do not generally exist for many of the other TCDD-like congeners. Despite this lack of congener specific data, there is reason to infer that these effects may occur for all dioxin-like compounds, as embodied in the concept of toxicity equivalence. A few of these effects have been observed under high exposure conditions in human populations; many others have not been investigated with well-designed human studies or in relevant populations. The mechanistic relationships of biochemical and cellular changes seen at very low levels of exposure in animals and humans to production of adverse effects generally detectible at higher levels remains uncertain and controversial. Based on the experience of the scientific community using animal models and evaluating a limited human data base, it is reasonable to infer that effects in the human population may span a wide range. These effects may range from changes in biology or biochemistry which may be judged by some to be adaptive (with little or no adverse impact), or which may arguably be considered by others to be adverse, at or near background levels of exposure to clearly adverse effects with increasing severity as exposure increases above background levels by orders of magnitude (10 to

100 times background). Enzyme induction, changes in levels of gene regulators or related receptors, and indicators of altered cellular function represent examples of biomarkers of exposure of unknown clinical significance which may or may not be early indicators of toxic response. Induction of activating/ metabolizing enzymes at or near background levels, for instance, may be adaptive or may be considered adverse since induction may lead to more rapid metabolism and elimination of potentially toxic compounds, or may lead to increases in reactive intermediates and may result in toxic effects. Demonstration of examples of both of these situations is available in the published animal literature. Other potentially adverse effects have been reported to be associated with exposure to dioxin and related compounds in human populations at or near average background population levels (within a factor of 10 of these levels). These include delay of developmental milestones, impacts on immune function, and, perhaps, increased incidence or susceptibility to disease, e.g., elevated incidence of adult onset diabetes. While potentially present in exposed populations, clearly adverse effects, including cancer, may not be detectable as increased incidence of disease until exposures exceed background by one or two orders of magnitude (10 or 100 times).

With regard to sensitivity, it is well known that individual species vary in their sensitivity to any particular dioxin effect. However, the evidence available to date indicates that humans may fall in the middle of the range of sensitivity for individual effects among animals rather than at either extreme. In other words, evaluation of the available data using comparable dose metrics suggests that humans, in general, are neither extremely sensitive nor insensitive to the individual effects of dioxin-like compounds as compared to other animals. Human data provide direct or indirect support for evaluation of likely effect levels for several of the endpoints discussed in the reassessment although the influence of variability among humans remains difficult to assess.

The scientific community has identified and described a series of common biological steps that are necessary for most if not all of the observed effects of dioxin and related compounds in vertebrates including humans. Binding of dioxin-like compounds to a cellular protein called the "Ah receptor" represents the first step in a series of events attributable to exposure to dioxin-like compounds including biochemical, cellular and tissue-level changes in normal biological processes. Binding to the Ah receptor appears to be necessary for all well-studied effects of dioxin but is not sufficient, in and of itself, to elicit these responses; further steps beyond receptor binding are required. The effects elicited by exposure to TCDD are shared by other chemicals which have a similar structure and Ah receptor binding characteristics. Consequently, it is reasonable to assume that the biological system responds to the cumulative exposure to other dioxin-like chemicals instead of exposure to any single dioxin-like compound. Based on our understanding of dioxin mode(s)-of-action to date, it is reasonable to conclude that interaction with the Ah receptor is necessary, that at comparable doses (e.g. similar body burdens) humans are likely to respond with many of the effects of dioxin demonstrable in laboratory animals, and that there is likely to be a variation among and within species and among tissues in individual species based on differential responses "down stream" from receptor binding.

Some of the effects of dioxin and related compounds such as enzyme induction, changes in hormone levels and indicators of altered cellular function have been observed in laboratory animals and humans at body burdens comparable to exposures at or near levels to which segments of the general population are exposed. Other effects are detectable only in highly exposed populations, and there may or may not be a likelihood of response in individuals experiencing lower levels of exposure. Adverse effects associated with temporary increases in dioxin blood levels based on short term high level exposures, such as those that might occur in an

industrial accident or in infrequent contact with highly contaminated environmental media, may be dependent on the impact of exposure on total body burden.

The exposure document (Part I) has been revised to reflect comments from the public and the Agency's Science Advisory Board (SAB). It presents an up-to-date (1999) and comprehensive emission inventory of dioxin and related compounds for the United States. A large variety of sources of dioxin have been identified, and characterized but others may exist. The available information suggests that the presence of dioxin-like compounds in the environment is primarily a result of formation of unintentional by-products of combustion or industrial practices and is likely to reflect changes in release over time. The principal identified sources of environmental release may be grouped into five types: Combustion and Incineration Sources; Metals Smelting, Refining and Processing; Chemical Manufacturing/Processing; Reservoir Sources; and Biological and Photochemical Processes. The Exposure Document provides "snapshots" of estimated emissions for the years 1987 and 1995. Because of the nature of the available data and the need to extrapolate national emission levels, confidence in these estimates varies. However, EPA's best estimates of releases of dioxin and related compounds (CDDs/CDFs) to air, water and land from reasonably quantifiable sources suggests an approximately 75% decrease between 1987 and 1995, due primarily to reductions in air emissions from municipal and medical waste incinerators. Regulations promulgated in 1995 for municipal waste combustors and 1997 for medical waste incinerators should result in a greater than 95% reduction in dioxin emissions from these two categories. Uncontrolled combustion such as burning of household waste is expected to become the largest quantified source of dioxin emissions to the environment. With the reduction in combustion and incineration sources, reservoir sources are likely to increase in importance.

Because dioxin-like chemicals are persistent and accumulate in biological tissues, particularly in animals, the major route of human exposure is through ingestion of foods containing minute quantities of dioxin-like compounds. This results in wide-spread exposure of the general population to dioxin-like compounds. It appears that daily intakes have come down since the 1970s and that, as of the mid-90s, adult daily intakes of dioxin and related compounds, including dioxin-like PCBs average 65 pg$TEQ_{DFP}WHO_{98}$/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. The estimated levels of dioxin and related compounds in the environment and contributing to daily intakes in the U.S. are based on additional data collected since 1995. Further data collection is underway in studies by EPA, FDA and USDA scientists. Current estimated U.S. levels are consistent with levels reported for Western Europe and Canada, and support a conclusion that increased dioxin exposures are associated with industrialization. The consistency of U.S. levels with those of other industrialized countries also provides additional reassurance that the U.S. estimates are reasonable in the face of the limited data on U.S. levels, recognizing that some differences among countries will reflect national and international control efforts.

The reassessment presents the hypothesis that the primary mechanism by which dioxin-like compounds enter ecological food chains and human diet is via atmospheric deposition. Dioxin and related compounds enter the atmosphere directly through air emissions and are widely spread in the environment as a result of a number of physical and biological processes, for example, through erosion and run-off, volatilization from land or water, or from re-suspension of particles. Deposition can occur directly on to soil or plant surfaces. At present, it is unclear whether atmospheric deposition represents primarily current contributions of dioxin and related compounds from all media, or past emissions that persist and recycle in the environment. Understanding the relationship between these two scenarios will be particularly important in understanding the relative contributions

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

The term "background" exposure has been used throughout this reassessment to describe exposure of the general population, which is not exposed to readily identifiable point sources of dioxin-like compounds. Data on human tissue levels suggest that body burden among industrialized nations are reasonably similar. Average background exposure led to body burdens in the late 1980s ranged from 30-80 pg TEQ/g lipid (this equates to 30-80 ppt), with a mid-point of approximately 55 pg TEQ/g lipid, when all dioxins, furans and dioxin-like PCBs are included. High-end estimates of body burden of individuals in the general population (approximately the top 1% of the general population) may be more than 3 times higher, based on evaluation of blood-level data and on consumption of fat as a surrogate for dioxin intake. The average CDD/CDF/PCB tissue level for the general adult U.S. population appears to be declining and the best estimate of current (late 1990s) average body burden levels is 25 ppt (TEQ_{DFP}-WHO_{98}, lipid basis).

In addition to general population exposure, some individuals or groups may also be exposed to dioxin-like compounds from discrete sources or local pathways, including occupational exposures, direct or indirect exposure of local populations to discrete sources, exposure of nursing infants from mother's milk, or exposures of subsistence or recreational fishers. Daily exposures to these individuals may be significantly higher than among the general population. However, the differences in average body burden are expected to be much less than the differences in daily intake, particularly if these elevated exposures are periodic or for short duration. In addition, while it is often difficult, the health benefits of dietary components must factor into assessment of overall risk.

As described above, subtle changes in biochemistry and physiology such as enzyme induction, altered cellular function, and other potentially adverse effects have been detected in dioxin-exposed populations in a limited number of available studies. These findings, coupled with knowledge derived from animal experiments, suggest the potential for adverse impacts on human metabolism, and developmental and/or reproductive biology, and, perhaps, other effects in the range of current human exposures. Given the assumption that TEQ intake values represent a valid comparison with TCDD exposure, some of these adverse impacts may be occurring at or within one order of magnitude of average background TEQ intake or body burden levels. As body burdens increase within and above this range, the probability of occurrence, as well as the spectrum of human noncancer response, most likely increases. Because of the basic biological level at which dioxin and related compounds act, and because of the potential diversity of "down-stream" responses to a dioxin body burden, it is not currently possible to state exactly how or at what levels individuals in the population will respond. It is clear, that as recent data have developed, the margin of exposure (M-O-E)[1] between body burdens associated with background levels of exposure and levels where effects are detectable in humans, in terms of body burden

[1] The likelihood that noncancer effects may occur in the human population at environmental exposure levels is often evaluated using a "margin of exposure" (MOE) approach. A MOE is calculated by dividing the human, or human-equivalent animal, lowest observed adverse effect levels (LOAEL) or no observed adverse effect level (NOAEL) with the human exposure level of interest. MOEs in range of 100 -1000 are generally considered adequate to rule out the likelihood of significant effects in humans based on sensitive animal responses. The average intake levels of dioxin-like compounds in terms of TEQs in humans described above would be well within a factor of 100 of levels representing LOAELs in laboratory animals exposed to TCDD or TCDD equivalents. For several of the effects noted in animals, a MOE of less than a factor of ten, based on intake levels or body burdens, is likely to exist.

TEQs, is considerably smaller than previously estimated and, in some cases, may be 1 or even less. For certain effects, including subtle behavioral impacts, a "no effect level" has yet to be established.

These facts and assumptions lead to the inference that some members of the general population or more highly exposed, special populations may be at risk for a number of adverse effects. These may include, for instance, developmental toxicity based on the inherent sensitivity of the developing organism to changes in cellular biochemistry and/or physiology, impaired reproductive capacity based on structural or functional impacts, less ability to withstand an immunological challenge and others. This inference that more highly exposed members of the population may be at risk for various noncancer effects is supported by observations in animals, by human information, and by other scientific observations.

The deduction that humans are likely to respond with noncancer effects from exposure to dioxin-like compounds is based on the fundamental level at which these compounds impact cellular regulation and the broad range of species which have proven to respond adversely. Since, for example, developmental toxicity following exposure to TCDD-like congeners occurs in fish, birds, and mammals, it is likely to occur at some level in humans. It is impossible to state exactly how or at what levels individuals in the population will respond with adverse impacts on development or reproductive function, but some subtle effects on development have been noted in infants at near background exposures. Fortunately, there have been few human cohorts identified with TCDD exposures exceeding the high end of the background exposure range. When these cohorts have been examined, few clinically significant effects were detected. The focus of most currently available epidemiologic studies on occupationally TCDD-exposed adult males makes evaluation of noncancer effects in the general population difficult. 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. Some have argued that to deduce that a spectrum of noncancer effects will occur in humans in the absence of better human data overstates the science; most scientists in the reassessment as authors and reviewers have indicated that such an inference is reasonable given the weight-of-the-evidence from available data. As presented, this logical conclusion represents a testable hypothesis that may be evaluated by further data collection as more sensitive methods for evaluating human responses to dioxin exposure become available.

With regard to carcinogenicity, EPA characterizes the complex mixtures of dioxin to which people are exposed as a "likely human carcinogen."[2] This is based on the fact that individual components of this mixture could be characterized as " human carcinogens" or "likely human carcinogens" under EPA's draft cancer risk assessment guidelines (1996, 1999). In particular, TCDD, the most toxic of the dioxins, can be identified as a "human carcinogen" under the Agency's draft guidelines, based on the weight of the animal and human evidence, and the other dioxins as "likely human carcinogens." The epidemiological data alone are not yet deemed sufficient to characterize the cancer hazard of TCDD as being a "human carcinogen." However, combining consistent, suggestive evidence from epidemiology studies with the unequivocal evidence in animal studies and inferences drawn from mechanistic data supports the characterization of complex mixtures of dioxin and related compounds as "likely" cancer hazards. The confidence in this statement for specific environmental

[2] "Human carcinogen" and "likely" to present a cancer hazard to humans are descriptors which are consistent with the latest draft revised EPA Guidelines on Carcinogen Risk Assessment (1996, 1999). They are roughly equivalent to the terms "known" and "probable" human carcinogen which were contained in earlier (1986) EPA guidelines.

mixtures increases with the level of available congener-specific information. It is important to distinguish this statement of cancer hazard from the evaluation of cancer risk. While major uncertainties remain, efforts of this reassessment to bring more data into the evaluation of cancer potency have resulted in an estimate of 1×10^{-3} per pgTEQ/kgBW/day. This slope factor and resulting risk specific dose estimate represents a plausible upper bound on risk based on evaluation of human and animal data within the range of observation and at a minimally detectable response level (ED_{01}). These values are approximately 10 times higher than previous estimates (1985, 1994) which were based on fewer data. Considering the slope factors and current intake levels, upper bound (>95%-ile) risks for the general population may exceed 10^{-3} (1 in 1,000). "True" risks are not likely to exceed this value, are likely to be less, and may even be zero for some members of the population. The extent of cancer risk will depend on such parameters as route and level of exposure, overall body burden, dose to target tissues, individual sensitivity and hormonal status. This estimate of upper bound risk for the general population has increased from the risk described at background exposure levels based on EPA's earlier (1994) draft of this reassessment (10^{-4}-10^{-3}).

The current evidence suggests that both receptor binding and most early biochemical events such as enzyme induction are likely to demonstrate low-dose linearity. The mechanistic relationship of these early events to the complex process of carcinogenesis remains to be established. If these findings imply low-dose linearity in biologically-based cancer models under development, then the probability of cancer risk will be linearly related to exposure to TCDD at low doses. Until the mechanistic relationship between early cellular responses and the parameters in biologically based cancer models is better understood, the shape of the dose-response curve for cancer below the range of observation can only be inferred with uncertainty. Associations between exposure to dioxin and certain types of cancer have been noted in occupational cohorts with average body burdens of TCDD approximately 1-3 orders of magnitude (10 to 1,000 times) higher than average TCDD body burdens in the general population. In terms of total TEQ, the average body burden in these occupational cohorts level is within 1-2 orders of magnitude (10-100 times) of average background body burdens in the general population. Thus, there is no need for large scale low dose extrapolations to estimate upper bounds on general population cancer risk or to evaluate the impact of incremental exposures above background. Nonetheless, the relationship of apparent increases in cancer mortality in these populations to calculations of general population risk remains uncertain.

In summary, based on all of the data reviewed in this reassessment and scientific inference, a picture emerges of TCDD and related compounds as potent toxicants in animals with the potential to produce a spectrum of effects. Some of these effects may be occurring in humans at very low levels and some may be resulting in adverse impacts on human health. The potency and fundamental level at which these compounds act on biological systems appears to be analogous to several well studied hormones. Dioxin and related compounds have the ability to alter the pattern of growth and differentiation of a number of cellular targets by initiating a cascade of biochemical and biological events with the potential for a spectrum of responses in animals and humans. Despite this potential, and given the limited body of epidemiological evidence associating dioxin exposure with increases in various effects, there is currently no clear indication of increased disease in the general population attributable to dioxin-like compounds. The lack of a clear indication of disease in the general population should not be considered strong evidence for no effect of exposure to dioxin-like compounds. Rather, lack of a clear indication of disease is more likely a result of the inability of our current data and scientific tools to directly relate effects to dioxin exposure and related compounds at these levels of human exposure. Several factors suggest a need to further evaluate the impact of these chemicals on humans at or near current background levels. These are: the weight of the evidence on exposure and effects; an apparently low margin-of-exposure for noncancer effects; and potential for significant risks to some portion of the general population and

additivity to background processes related to carcinogenicity in the case of incremental exposures above background.

EPA CONTACT:

Linda C. Tuxen, NCEA, ORD (8601D), Washington, DC 20460
E-Mail:*tuxen.linda@epa.gov*
Tel: 202-564-3332; FAX: 202-565-0090