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United States Environmental Protection Agency | Office of Research and Development Washington, DC 20460 | October 15, 2004 Update

Information Sheet 1

Dioxin: Summary of the Dioxin Reassessment Science

Scientists from the Environmental Protection Agency (EPA), other federal agencies and the general scientific community have conducted a reassessment of dioxin exposure and human health effects since 1991. This information sheet summarizes the draft reassessment, which is entitled *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds.* A more in-depth discussion can be found in the companion piece, *Dioxin: Scientific Highlights from the NAS Review Draft of EPA's Dioxin Reassessment.*

The term "dioxin" refers to a group of chemical compounds that share certain similar chemical structures and mode-of-action biological characteristics. A total of 30 of these dioxin-like compounds exist and are members of three closely related families: the chlorinated dibenzo-*p*-dioxins (CDDs), chlorinated dibenzofurans (CDFs) and certain polychlorinated biphenyls (PCBs). The term dioxin is also used for the most well-studied and one of the most toxic dioxins, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). CDDs and CDFs are not created intentionally, but can be produced inadvertently in nature and by a number of human activities. Combustion, chlorine bleaching of pulp and paper, certain types of chemical manufacturing and processing, and other industrial processes all can create small quantities of dioxins. PCBs are no longer manufactured in the United States but formerly were widely used as coolants and lubricants in electrical equipment.

Combining Risks from Dioxins - the Toxic Equivalents Approach:

Dioxins are believed to cause toxic effects in similar ways; that is, they share a "common mechanism of toxicity." As a result, EPA and others use an approach that adds together the toxicity of individual dioxins in order to evaluate complex environmental mixtures to which people are exposed. Because dioxins differ in their toxic potential, the toxicity of each component in the mixture must be accounted for in estimating the overall toxicity. To do so, international teams of scientists have developed Toxic Equivalency Factors that compare the toxicity of different dioxins. Given these factors, the toxicity of a mixture can be expressed in terms of its Toxic Equivalents (TEQ), which is the amount of TCDD it would take to equal the combined toxic effect of all the dioxins found in that mixture. The use of the TEQ approach represents a key assumption upon which many of the conclusions in the reassessment are based.

Dioxin Toxicity:

The reassessment finds that, based on all available information, dioxins are potent animal toxicants with potential to produce a broad spectrum of adverse effects in humans. Dioxins can alter the fundamental growth and development of cells in ways that have the potential to lead to many kinds of impacts. These include, for example, adverse effects upon reproduction and development; suppression of the immune system; chloracne (a severe acne-like condition that sometimes persists for many years); and cancer. EPA characterizes the complex mixtures of dioxin to which people are exposed as a "likely human carcinogen." 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."

Dioxin Exposure:

The reassessment proposes that most dioxin enters ecological food webs by being deposited from the atmosphere, either directly following air emissions or indirectly by processes that return dioxins already in the environment to the atmosphere. Once they reach the environment, dioxins are highly persistent and can accumulate in the tissues of animals. EPA estimates that most dioxin exposure occurs through the diet, with over 95% of dioxin intake for a typical person coming through dietary intake of animal fats. Small amounts of exposure occur from breathing air containing trace amounts of dioxin on particles and in vapor form, from inadvertent ingestion of soil containing dioxin, and from absorption through the skin contacting air, soil, or water containing minute levels. These processes result in widespread, low-level exposure of the general population to dioxins.

Dioxin levels in the environment have declined significantly since the 1970s following EPA regulatory controls and industry actions. EPA's best estimates of emissions from sources that can be reasonably quantified, indicate that dioxin emissions in the United States decreased by about 75% between 1987 and 1995, primarily due to reductions in air emissions from municipal and medical waste incinerators, and substantial further declines continue to be documented. 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. Dietary intake of dioxin also appears to be declining.

Dioxin Effects in Human Populations

EPA estimates that the amount of dioxin found in the tissues of the general human population (which is known as the "body burden") closely approaches (within a factor of 10) the levels at which adverse effects might be expected to occur, based on studies of animals and highly exposed human populations. Despite the potential risks, currently there is no clear indication of increased disease in the general population attributable to dioxin-like compounds. This may be due to limitations of current data and scientific tools rather than indicating that dioxin exposure is not causing adverse effects. For cancer, EPA estimates that the risks for the general population based on dioxin exposure may exceed 1 in 1,000 increased chance of experiencing cancer related to dioxin exposure. Actual risks are unlikely to exceed this value and may be substantially less. This range for cancer risk indicates an about 10-fold higher chance than estimated in EPA's earlier (1994) draft of this reassessment.

Children and Other Groups of Concern

Fetuses, infants, and children may be more sensitive to dioxin exposure because of their rapid growth and development. Data on risks to children are limited, however, and it is not known if the children in the general population are experiencing adverse effects from dioxin. Although breast milk appears to be a significant source of dioxin exposure for nursing infants, the overwhelming body of evidence supports the health benefits of breastfeeding despite the potential presence of dioxin. Other populations have experienced elevated exposures to dioxin as a result of food contamination incidents around the world, through the workplace or from industrial accidents, or from consumption of unusually high amounts of fish, meat, or dairy products containing elevated levels of dioxins. In some cases, such as U.S. Air Force personnel exposed to the herbicide Agent Orange contaminated with dioxin during the Vietnam War, dioxin exposure has been associated with adverse health effects.

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Information Sheet 3

Dioxin Reassessment Process: What is the Status of the Reassessment and How Was the Reassessment Developed?

The U.S. Environmental Protection Agency's (EPA or Agency) is continuing to work towards completion of its reassessment of dioxin exposure and human health effects entitled, *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* - - the dioxin reassessment. The purpose of this *information sheet* is to describe the process that EPA has used in developing the reassessment and to inform the public about the remaining steps needed to bring this complex scientific activity to a close.

STATUS: On October 15th , 2004, the EPA transmitted to the National Academy of Sciences (NAS) the NAS Review Draft of EPA's *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds*, in preparation for the first meeting of the NAS panel scheduled for November 22 and 23, 2004, in Washington, DC. For detailed information on the NAS's dioxin review activity, titled "Review of EPA's Assessment of the Health Implications of Exposure to Dioxins," please visit the NAS website at www.nas.edu. This will bring you to a description of the project, a list of the provisional panel, and information about the upcoming meeting.

BACKGROUND: In April 1991, EPA announced that it would conduct a scientific reassessment of the health risks of exposure to dioxin and dioxin-like compounds. EPA began this task in light of significant advances in our scientific understanding of mechanisms of dioxin toxicity, significant new studies of dioxin's carcinogenic potential in humans and increased evidence of other adverse health effects. EPA has worked to make each phase of the dioxin reassessment an open and participatory process. These efforts have included the involvement of outside scientists as principal authors of several chapters, frequent public meetings to report progress and take public comment, and publication of early drafts for public comment and peer review. Early in the reassessment process, EPA held public meetings (1991 and 1992) to inform the public of the Agency's plans and activities for the reassessment, to hear and receive public comments and reviews of the proposed plans, and to receive any current, scientifically relevant information. In 1992 and 1993, the Agency convened three peer-review workshops to review early drafts of the reassessment chapters. The Agency remains committed to an open and participatory process as it approaches the final reassessment.

STRUCTURE OF FINAL REASSESSMENT DOCUMENT: The final dioxin reassessment will consist of three parts. *Part I. Estimating Exposure to Dioxin-Like Compounds* will include three volumes that focus on sources, levels of dioxin-like compounds in environmental media, and human exposures. *Part II. Health Assessment for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* will consist of two volumes that include information on critical human health end points, mode of action, pharmacokinetics, dose-response, and TEFs. Part II will have nine chapters. *Part III. Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* will be a stand alone document. In this part, key findings pertinent to understanding the potential hazards and risks of dioxins are described and integrated, including a discussion of all important assumptions and uncertainties.

1994 PUBLIC REVIEW DRAFT AND 1995 SCIENCE ADVISORY BOARD REVIEW: In September 1994, EPA released the external review drafts of the health effects and exposure documents.

EPA took public comment on the drafts, followed by Science Advisory Board (SAB) review of the draft dioxin re assessment in May 1995. The SAB's report was received in Fall of that year. In its report to the Agency, the SAB responded favorably to most of the reassessment, but recommended revision of two key sections. The SAB recommended that Chapter 8: Dose-Response Modeling for TCDD and the Risk Characterization document, be revised. Further, it recommended development of an additional document that would focus on the toxic equivalency factors (TEFs) for dioxin and dioxin-like compounds. In addition to these substantive recommendations, the SAB suggested that the redrafting process include broader participation of outside scientists from both public and private sectors. They also requested that the two redrafted chapters and the new TEF chapter be submitted to independent external peer review, before being returned to the SAB for re-review. With respect to Chapters 1-7 of the health document and the full exposure reassessment document, the SAB accepted these sections. It suggested that they be updated to address public and SAB comments and to incorporate new scientific data, but stated that no further review of these sections by the SAB was needed.

POST-SAB REVISION PROCESS: After receipt of the SAB's 1995 report, the Agency worked with over 40 stakeholders from the private and public sectors, representing environmental, industry, academic, state, and other public interest and public health communities, on next steps and to gather input on possible approaches for conducting the revision process. The Agency has tried to keep these individuals apprised of reassessment activities at critical points in the revision process. These stakeholder groups have been important avenues of public input as the revised dioxin reassessment sections have been made available for public comment. The three draft sections recommended for revision and subsequent review by the SAB were:

Part II. Chapter 8: Dose-Response Modeling ➜ This chapter was revised using a writing team process. The writing team was composed of a dozen leading scientific experts in fields related to dioxin health effects and quantitative risk assessment. These experts came from a wide range of public and private organizations, as well as academia. The draft Chapter 8 underwent public comment and external peer review in March 1997. The writing team developed the draft final chapter based on the peer review and public comments and any relevant new scientific data, in January 2000.

Part II. Chapter 9: TEFs for Dioxin and Related Compounds ➜ This new document was developed as a result of a recommendation from the SAB to gather in one place the discussion and scientific information on the complex issue and use of TEFs for dioxin and dioxin-like compounds. The draft was developed by an internal writing team with assistance from international experts.

Part III. Integrated Summary and Risk Characterization ➜ This section also followed the writing team process. A preliminary revised draft was developed by a writing group made up of scientists from a wide range of public and private organizations, as well as academia, and was reviewed by the stakeholders. This preliminary draft was used as the framework for an extensively revised document developed by a small internal EPA writing group.

OTHER MAJOR MILESTONES:

External Peer Review Meeting - On July 25 and 26, 2000, a two-day external peer review workshop was conducted in Washington, DC. This peer review meeting was for the purpose of reviewing the draft *TEF chapter* and draft *Part III. Integrated Summary and Risk Characterization.* The Agency used a private contractor to plan and conduct the meeting and to identify and secure the services of independent expert scientists as peer reviewers. The public was invited to attend the peer review meeting as observers and a limited amount of time was made available for comments by the observers. General view was that addition of the TEF chapter was beneficial and added to the strength of the reassessment and that the

characterization document was much improved over the previous draft. Major points of discussion were the following key dioxin science issues: the characterization of cancer risk, how to extrapolate between animals and humans, quantitative estimates of cancer risk, noncancer effects seen close to background exposures, and children's risk. The Agency used the peer review report, the public comments made at the meeting, and the public comments submitted as a result of the public comment period announced in the Federal Register on June 12, 2000, to revise the two documents in preparation for review by the SAB.

SAB Dioxin Reassessment Review Subcommittee Meeting - On November 1 and 2, 2000, the SAB's Dioxin Reassessment Review Subcommittee (DRRS) met to review the draft *"Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds."* The focus of the review was on three draft documents: *Part II. Chapter 8: Dose-Response Modeling; Part II. Chapter 9: TEFs for Dioxin and Related Compounds;* and *Part III. Integrated Summary and Risk Characterization*. There was considerable discussion on several significant science issues related to dioxin and Subcommittee consensus was not reached on some of them. Nevertheless, at the conclusion of the meeting, the review panel stated that they were confident that the Agency could address their review comments and that they did not need to see the document again. The Subcommittee further encouraged the Agency to expeditiously complete the dioxin reassessment. The two day meeting included over 40 public comments. The draft DRRS review report was submitted to the SAB's Executive Committee for review and approval in Spring 2001.

SAB Executive Committee Review Meeting - After a public meeting on May 15, 2001, the SAB's Executive Committee endorsed a review report of the draft dioxin reassessment contingent upon changes to address some of the differing scientific opinions raised in the review report. On May 31, 2001, the SAB forwarded its final review report to the Administrator. Upon receipt of the DRRS report, the Agency, after careful review and analysis of the SAB comments, began revision of the draft reassessment to address both SAB and public comments. EPA completed revision of the draft reassessment in response to SAB and public comments.

Dioxin IWG Review Process - On January 17, 2003, the revised draft dioxin reassessment was transmitted by EPA to the Interagency Working Group on Dioxin (Dioxin IWG). The Dioxin IWG is made up of federal agencies that address health, food, and the environment. These agencies are working together to ensure a coordinated federal approach to dioxin related issues. These activities include research on dioxin exposure and effects, and coordinated efforts to measure dioxin levels in the environment and food and to reduce dioxin risks. The Dioxin IWG, under the auspices of the National Science and Technology Council, provides the overall mechanism for coordinating these activities.

Because EPA is committed to ensuring that the dioxin reassessment has a strong scientific foundation, the Agency requested input from the IWG regarding the need and benefit of further review of the draft reassessment. The IWG recommended that the draft reassessment should be reviewed by the NAS.

NAS Review - The NAS project titled "Review of EPA's Assessment of the Health Implications of Exposure to Dioxins," began in June 2004. Information on the NAS dioxin review can be found on the NAS website at www.nas.edu. On September 9, 2004, the NAS posted in *Current Projects*, their review of EPA's draft dioxin reassessment, including a description of the project scope. The draft assessment will be reviewed by an expert panel convened under the auspices of the NAS Board on Environmental Studies and Toxicology (BEST). On September 10, 2004, the NAS has made available the names of the Provisional Committee, and opened a 20-day comment period for input on the provisional panel members.

That comment period closed on September 30, 2004. The first meeting of the NAS dioxin review panel is scheduled for November 22 and 23, 2004, at the National Academy of Sciences Building, 2100 C St. NW, Washington, DC. The review by the NAS is expected to take approximately 18 months.

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Information Sheet 2

Dioxin: Scientific Highlights from the NAS Review Draft of EPA's Dioxin Reassessment

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 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 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

[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.

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 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

[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.

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.

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