Update: The U.S. EPA's Scientific Reassessment of the Risks of Exposure to Dioxin

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In April, 1991, the U.S. EPA initiated a scientific reassessment of the health risks of exposure to 2,3,7,8-TCDD (dioxin) and related compounds. The EPA has undertaken this task in response to new knowledge about the biological effects of dioxin. The reassessment addresses the latest scientific information relating to ecological effects, exposure to, and health risks from dioxin and related compounds. The approach has involved the broader scientific community in every part of the reassessment, from chapter writing to final peer review.

In May, 1993, EPA released an interim report on data and methods for the assessment of 2,3,7,8-TCDD risks to aquatic life and associated wildlife. This peer-reviewed document compiles and evaluates toxicity and exposure data from the current scientific literature for aquatic life and associated wildlife. It is the first step in a long-term program to reexamine data and methods relating to ecological risks from 2,3,7,8-TCDD and related chemicals. This report is a critical review; it is not a risk assessment, does not set policy for EPA, and does not establish water quality criteria. The interim report addresses data and TCDD exposure to, and bioaccumulation, in aquatic organisms; toxic effects on aquatic life and wildlife; and issues relating to risk characterization. Findings of the report include: 1) TCDD is typically associated with sediments, biota, and particulates in water and bioaccumulates in fish; 2) exposures occur through combinations of water, sediment, and dietary routes; 3) the most sensitive effects thus far reported for aquatic organisms involve the reproductive cycle of fish and associated mortality in early life stages; 4) plants, aquatic invertebrates, and amphibians appear substantially less sensitive to TCDD than fish; 5) reproductive endpoints are also the most sensitive known effects for mammalian and avian wildlife. Later this year, EPA will sponsor an expert panel workshop on the use of the data and methods in the

interim report for ecological risk assessment. Subsequently, EPA expects to prepare a companion report incorporating data and methods for assessment of complex mixtures that add to or alter the risk of 2,3,7,8-TCDD.

Laboratory research is also being conducted to examine the aquatic toxicity of TCDD and related chemicals. The TCDD aquatic toxicology research involves further definition of the range of interspecies sensitivity and investigation of the possibility that more sensitive effects than presently known may impact populations of aquatic organisms. A sensitive freshwater species, the brook trout (Salvelinus fontinalis), and a saltwater species, the mummichog (Fundulus heteroclitus), are presently being studied, through long-term dietary exposure to TCDD, for a wide variety of reproductive and biochemical effect endpoints. The TEFs of certain PCB congeners for trout early life stage mortality are similar to those observed in the trout in vivo model, but lower than the conservative values previously suggested. Studies of the additivity of individual congener toxic equivalencies for exposures to complex mixtures of TCDD and related chemicals and development of TCDD toxicity equivalence model-compatible bioaccumulation models are under development. At the present, EPA's aquatic ecological assessment research is focused on acquiring data to facilitate completion of a draft final report on methods and data for assessment of risks of TCDD to aquatic life and wildlife in June, 1995. If development of TEFs and complex mixture toxicity models proceeds as planned, a draft report on methods and data for assessment of risks of complex mixtures of polyhalogenated planar aromatic chemicals which exert toxic effects through an Ah receptor-mediated mode of action will be available for peer review in 1996. Each report in this series will provide information for risk assessors to use in addressing specific problems with varied ecological risk assessment needs. As in the interim TCDD report, risk characterization examples will be provided to illustrate how the data and models can be applied and what levels of uncertainty to expect.

Draft documents have been prepared estimating exposure to dioxin-like compounds. The initial draft report was reviewed by an invited expert panel at a public meeting in September, 1992. Based on comments, the document has been revised and expanded and reissued for public comment in June, 1993. This exposure assessment examines properties, sources, occurrences, pharmacokinetics, and background exposures to PCDDs, PCDFs, and PCBs. Background exposure to PCDD/PCDF TEQs were estimated in the range of 100pg/day. The great majority of daily contact is via food ingestion. Background exposure levels can also be estimated on the basis of pharmacokinetic modeling applied to average concentrations found in human tissues. This modeling suggests similar exposure

levels as the diet-based estimates. Major US sources appear to be hospital waste incineration, metal smelting/refining, and industrial and residential wood burning. Diesel emissions may also be important, although the data are very limited and somewhat contradictory. Emission estimates appear to underpredict atmospheric deposition. Whether this is due to inaccuracies in the emission/deposition estimates, long range transport from outside the country, or unidentified sources remains to be determined. Procedures were also described for conducting exposure assessments to estimate potential dose, specifically over lifetime exposures. The approach entailed development of exposure scenarios. Uncertainties are also addressed, not only in the models but in the data. The exposure scenarios and models supported the earlier conclusion that ingestion of food is the most critical exposure source. Water ingestion and inhalation are generally minor exposure pathways. Data gaps and research needs are also identified.

Draft documents reviewing the latest information on health effects were prepared by outside scientific experts in conjunction with Agency scientists. Eight documents were peer reviewed by an expert panel at an open public meeting in September, 1992. These chapters covered: 1) pharmacokinetics; 2) mechanisms of action; 3) general toxicity; 4) immunotoxicity; 5) developmental and reproductive toxicity; 6) animal cancer; 7) epidemiology; and 8) dose/response models. These documents were critical reviews incorporating the most current information available. An additional expert panel was convened to review an updated draft of the epidemiology chapter (chapter 7) in June, 1993. Revisions of these documents which incorporate the comments received both from the expert panels and the public as well as additional information were made available for public comment in late summer, 1993. These documents reflect input from the expert panel that concluded that current body burdens of dioxin and related compounds (TEQ) are at or near the point where responses would be expected to occur. As the panel recommended, additional emphasis was placed on non-cancer endpoints, since effects on the immune system and developmental and reproductive effects appear to be occurring at extremely low levels. Dose/response models which describe relatively simple biochemical effects of dioxin have been developed and have been extended to describe more complex health endpoints.

Laboratory research is also being conducted to fill in data gaps related to the health effects of dioxin. Studies have been completed on dose/response relationships for receptor activation, enzyme induction, and immunotoxicity following both acute and subchronic exposure in mice. Similar studies following acute exposure have been conducted in rats. No evidence for low dose nonlinearity was

observed for sensitive biochemical responses. Mice appear to be much more sensitive to the immunotoxic effects of TCDD than do rats. However, exposure to TCDD compromises host defenses in both species.

Subchronic studies have been conducted in mice to examine the relative potency of dioxin-like compounds to that of 2,3,7,8-TCDD. Mice were exposed 5 days per week for 13 weeks to TCDD, TBDD, PCDD, 3 PCDFs, the 3 coplanar PCBs, 4 monoortho-coplanar PCBs, and azo- and azoxybenzene. Dose/response relationships for induction of CYP1A1 were compared in liver, lung, and skin, CYP1A2 in liver, and phosphorylation of cyclin-associated kinases in liver and skin. In addition, concentration of the compound in question were determined in liver, skin, adipose tissue, and blood. In general, the highly conservative TEF values which have been reported previously for the PCBs overpredict the biochemical responses examined in these studies. The levels of mRNA for CYP1A1 and 1A2 have also been examined in over 25 human livers. There is over a 10-fold variation in their levels in the general population and there is no correlation between the endpoints.

Characterization of the health risks from exposure to dioxin and related compounds involves exposure assessment, hazard identification, and dose/response analysis. The risk characterization based on all of the assessments and data collection activities described above will be presented along with all the supporting documents to EPA's external Science Advisory Board in the fall of 1993. Only following the recommendations of this committee, will the Agency review its current regulatory stance and determine whether different risk management decisions are necessitated by the incorporation of the newest and best science.