DIOXIN AFTER EPA'S REASSESSMENT: SCIENCE AND POLICY

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Introduction

Scientists from the Environmental Protection Agency (EPA), other Federal agencies and the general scientific community have been involved in a comprehensive reassessment of dioxin exposure and human health effects since 1991. The final dioxin reassessment will consist of three parts. *Part 1: Estimating Exposure to Dioxin-Like Compounds* will include four volumes that focus on sources, levels of dioxin-like compounds in environmental media, pathways and levels of human exposures and guidance on exposure assessment procedures. *Part 2: Human Health Assessment Document 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 3: 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 summary and characterization, 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. Final peer review comments are being addressed and it is expected that the completed reassessment will be available before the end of the year. Using this emerging scientific understanding, EPA is in the process of reviewing its dioxin control efforts to determine if, collectively, they adequately address dioxin risks, and to determine if redirected or additional action is needed. Research needs identified in the reassessment are also being considered.

Discussion

Findings of the Reassessment

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (dioxin) is highly toxic to many animal species producing a variety of cancer and noncancer 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 supporting 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 (Ah) receptor. This common mode of action is supported by consistency in effects evident from data from multiple congeners. 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. The data 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. In addressing receptor-mediated responses resulting from complex mixtures of dioxin-like congeners, this assessment has provided a strong scientific support for reliance on integrated measures of dose, such as average body burden, as being more appropriate default dose metrics than daily intake. The Agency recognizes, however, that the final choice of an appropriate dose metric may depend on the endpoint under evaluation.

Dioxin and related compounds have been shown in multiple animal species to be carcinogenic, developmental, reproductive, immunological and endocrinological hazards, among others. There is no reason to expect, in general, that humans would not be similarly affected at some dose, and indeed there is a growing body of human data supporting this assumption. Based upon the animal data, current margins of exposure are low for both cancer and several non-cancer endpoints. The human database supporting this finding is less certain and less robust, but fully consistent with the finding of low margins of exposure.

For cancer outcomes, the epidemiological evidence provides consistent findings of statistically significant elevations and 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, associated with dioxin exposure. Given this substantial, yet still not definitive, epidemiological data; the positive cancer bioassays at multiple sites and in all animal species tested; and mechanistic considerations common to animals and humans for dioxin carcinogenicity, EPA characterizes complex mixtures of dioxin-like compounds as highly potent, "likely" carcinogens. The best studied congener, TCDD, has been proposed by the Agency to be characterized as "carcinogenic to humans," but this remains controversial. Using a simple linear approach, the calculated body burdens of TCDD and dioxin-like substances leading to an estimated one percent increase (ED_{01}) in the lifetime risk of cancer all fall within a 10-fold range when comparing the occupational studies, and are approximately the same as those calculated based on the animal bioassay data. For comparison, current background body burdens in the United States of approximately 5 ngTEQ/kgBW fall close to this range. Using these same studies and a linear model for the slope calculation, EPA estimates an upper bound on the lifetime risk of all cancers combined of 1×10^{-3} risk/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 must be coupled with a recognition that a small percentage of people may be both more susceptible and consume three times the average level of animal fat per day (the principal exposure pathway for dioxins in the general population). This estimate of cancer dose-response, when compared with mean exposure to dioxin-like compounds to the general population , leads to an estimate of the upper bound on general population lifetime risk for all cancers which might exceed 1 in 1,000. Most other dose-response modeling approaches would suggest lower estimates of upper bound risk. Therefore, "true" risks are not likely to exceed the reassessments'upper bound estimate, are likely to be less than the upper bound and for some individuals may even be zero.

For noncancer effects of many environmental chemicals, EPA calculates an RfD/RfC value which 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. The current estimated average intake of dioxins to the U.S. population (~1 pgTEQ/kg/day) is more than 10 times greater than RfD/RfC intake values that could be established given the data reviewed in this assessment. Since, under these circumstances such values are considered by the Agency to be uninformative for assessing the significance of incremental espousers, EPA has proposed not to establish a RfD/RfC at this time. Instead, EPA has chosen rather to characterize the margins-of-exposure (MOE) for noncancer endpoints in order to better inform risk management decisions. MOE is the ratio of the human body burden to the body burden associated with an effect level in the comparison species (ED_{01} or low effect level), animal or human. For the most sensitive endpoints identified, MOE's range from, for example, less than one for enzyme induction in mice, through 2.6 - 15 for enzyme induction in rats, <3 for developmental effects, and 5 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. Children's risks from dioxin and related compounds may be greater than for adults for some effects, but more data are needed to fully address this issue before informed conclusions can be made.

Overall, releases of dioxins to the environment from sources that have been characterized have decreased significantly over the last decade and further decreases are expected. Many sources are still poorly characterized, and an environmental reservoir of dioxins from both man-made and natural sources has been recognized as a potentially significant contributor to human exposure. Human body burdens have also declined, but the quantitative relationship between specific sources, contemporary or reservoirs, and human exposure remains poorly defined.

Implications for Regulatory Activities

Senior USEPA officials have been meeting for a number of years to ensure that the Agency's dioxin programs function in a coordinated manner consistent with the emerging science of the Dioxin Reassessment. With the reassessment effort nearing completion, the Agency is actively identifying and developing options for a USEPA cross-media dioxin strategy.

With the release of the draft reassessment in September of 1994, EPA formally announced its intent to release a draft, cross-media dioxin strategy, once the dioxin reassessment was completed. Once the draft strategy is released for public review, EPA will convene a series of public meetings around the country as part of a formal public comment processes. In recent years, EPA also announced its creation of the Persistent Bio-accumulating Toxics Initiative (PBTI). Dioxins are among the chemicals included within the PBTI. The PBTI calls for action plans to be developed for each of the PBTI chemicals. For dioxins, the preexisting work on developing a cross media dioxin strategy and the new commitment for a dioxin action plan, have been combined into a single integrated activity. A dioxin strategy is also called for under the terms of the pending international Persistent Organic Pollutants (POPs) treaty.

The intended purpose of the USEPA cross media dioxin strategy is to review EPA's existing dioxin activities and, where appropriate, to modify, expand or redirect them to insure that they are responsive to the scientific findings of the reassessment. Current thinking is focusing on a strategy which selectively expands current programs with a primary goal of reducing human exposure; i.e., targeting actions based on potential to reduce exposure. In considering an exposure reduction goal as the strategic focus of the cross media dioxin program, EPA is considering emission reduction priorities for smaller sources based primarily upon the potential for actions to result in meaningful exposure reduction. EPA will continue to place emphases on completion of dioxin regulations currently under development such as bio-solids, cement kiln dust, zinc dust, incorporating the science of the reassessment into the evaluation of risk management options. In addition, EPA will intensively track implementation of existing source standards for air and water and will review certain criteria and guidelines with an eye towards any necessary revisions. Current policy relating to the significance of incremental exposures will also be revisited in light of ubiquitous background levels.

This cross media dioxin strategy will also afford the Agency the opportunity to expand and coordinate outreach activities among federal partners and with the regions and states. It will also aid in the implementation of commitments under the international Persistent Organic Pollutants (POPs) treaty, the North American Regional Action Plan (NARAP), and several binational agreements.

Research Needs

EPA will, in the future, be called upon to reassess the human health and ecological impacts of exposure to dioxins (polychlorinated, polybrominated, and mixed bromo/chloro dioxins, furans, biphenyls, and naphthalenes) based on a rapidly expanding scientific knowledge base. In order to improve future assessments, the Agency will need to conduct, or support, research that fills in critical gaps and leads to a better understanding of the sources and potential adverse effects of dioxin exposure on humans, wildlife, and large ecological systems. 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. National, state, local, and international interests in dioxins are high; the NARAP and the POPs treaty will ensure that research on dioxin is an EPA priority for some time to come. The National Academy of Sciences has begun a 24-month study for the United Staes Department of Agriculture (USDA) and the Food and Drug Administration (FDA) regarding dioxin as a food contaminant and USDA and FDA are stepping up their data collection efforts and will look to EPA to collaborate, as in the past, on these important efforts.

The Reassessment identifies many areas where research is needed to reduce uncertainties in human health effects and exposure. This human health related research can be categorized into general areas: molecular biology and physiological role of the Ah receptor, dose metrics for different responses, interactions between dioxin-like PHAHs and short-lived AhR agonists/antagonists as wellas with non-dioxin compounds, uncertainties in the TEF methodology, mechanistic studies on the non-cancer and cancer effects of dioxins, and development of quantitative models to estimate both cancer and non-cancer health risks. The central exposure research need is to improve our understanding of what sources contribute most to human exposure. The understanding of this

relationship is critical for establishing exposure/risk based risk management priorities. The Reassessment identifies development of dioxin-specific regional air dispersion/deposition modeling as the key analytical tool for linking sources and exposure. Development of this tool also requires further work to better characterize dioxin emissions and air monitoring to calibrate the model. Risk management/reduction research needs include prevention techniques, treatment technologies and residuals management

The SAB dioxin reassessment review report (5/31/01) recommends that EPA "develop and implement a research strategy that is focused on the most critical information gaps that currently limit the quantitative evaluation of the risks of dioxin and related compounds." Following finalization of the dioxin reassessment, EPA intends to develop a Research Needs Document. It will include discussions of future information needs that will be tied to the Cross-Media Strategy and future needs of the EPA program offices. The needs document will include the knowledge and data gaps identified in the final dioxin reassessment, developed with input from across ORD and Agency, and subjected to public and external peer review and comment.

Summary and Conclusions

The USEPA's long term reassessment of dioxin a nd related compounds is drawing to a close. This summary of the science and characterization of sources, exposure, and potential health effects of dioxins will have significant implications for the review of current and future risk management activities at the USEPA and elsewhere. A comprehensive cross-media strategy for responding to these implications is underway and will be the subject of public review and comment in the near future. In addition, the Agency is committed to develop a research needs document to use in informing priorities for additional research related to dioxin sources, exposure, health effects and risk management.

(This abstract does not reflect USEPA policy.)