

NATIONAL ACADEMIES OF SCIENCE REVIEW OF

EPA 2003 Exposure and Human Health Reassessment of TCDD and Related Compounds

Analysis and Comments
by
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PREFACE:

The U.S. EPA's 2003 *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* is a comprehensive (and extremely massive - more than 3,500 pages in length) review of an extensive amount of scientific data on TCDD, other dioxins, and dioxin-like compounds collected over the last forty years. The 2003 Reassessment is scientific, highly technical and extremely difficult to understand, for not only scientists, but also for persons without scientific training or education. The Reassessment has been developed, reviewed and modified over a span of nearly 15 years. Due to the potential impact of the Reassessment on future dioxin emissions and hazardous waste remediation standards, the chemical industry has been extremely critical of the EPA's conclusions on the need to regulate dioxin exposure at very low levels in order to protect human health.

To assure that the conclusions of the Reassessment are scientifically valid, the National Academies of Science, upon request of the U.S. Congress, reviewed the Reassessment beginning in 2004 and issued its report in July, 2006. While the NAS report is not as massive as is the 2003 Reassessment, the report, nevertheless, is highly technical and many persons may have difficulty in understanding the report, its recommendations and conclusions. The NAS Review references specific sections of the Reassessment and both documents must be examined simultaneously for full comprehension.

ChemTelligence, Inc. has reviewed both the NAS report and the 2003 Reassessment in great detail. This analysis is a summary of the most important findings of the NAS Review Panel about the Reassessment, with special emphasis on findings of most interest to residents of the Midland and Saginaw areas. Hopefully, readers will find this analysis much easier to understand than either the NAS Review or the Reassessment. Comments, criticism and suggested revisions are most welcomed.

SUMMARY:

1. Except as noted below, the National Academy of Sciences (NAS) agreed with many of the methods and conclusions presented in the 2003 Reassessment. The NAS review panel did not identify any portions of the 2003 Reassessment that contained significant errors or were invalid based on errors in data or data assessment. The NAS review committee recommended that the 2003 Reassessment could be improved through improved justification and better communication of the scientific methods used to model dioxin exposure with human health effects. Improved communication as to the uncertainty of human health effects resulting from low-level exposure to TCDD, other dioxins and dioxin like compounds was specifically recommended.
2. The NAS review panel unanimously agree that TCDD should be classified as *likely to be carcinogenic to humans*. Some members of the panel felt that TCDD should be definitely classified as *carcinogenic to humans*. Since the review committee agreed that both classifications had the same public health implications about the need to reduce TCDD exposure to non-harmful levels, further discussion on the issue of toxicity classification was not warranted.
3. The NAS review panel concluded that the Toxic Equivalency Factor (TEF) method, including the calculation of a Toxic Equivalent Quotient (TEQ) for a mixture of dioxins, is a reasonable, scientifically justifiable, and widely accepted method to estimate the relative potency of TCDD, the other dioxins and dioxin like compounds on human and animal health. The Reassessment should be updated as TEF values are revised.
4. The Review Panel agreed that dioxin body burden levels are the most reasonable and pragmatic measurement currently available to characterize risk from dioxin exposure but recommended that additional discussion about the uncertainties associated with body burden levels is needed.
5. The NAS review committee recommended that the straight-line method used in the 2003 Reassessment to model low level dioxin exposure with human health effects should be compared to a non-linear calculation and that the results of both methods should be used to evaluate health risk.
6. The Review Panel indicated that the Reassessment did not establish a minimal effect level of dioxin exposure associated with non-cancer health effects and, as a result, dioxin risk characterization is incomplete.

NAS BACKGROUND :

The National Academy was established by Congress in 1863 to provide scientific assistance to all branches of the Federal Government. The National Academy was expanded in 1916 to include the National Research Council. The National Academy of Engineering was added in 1964 and, finally, the Institute of Medicine was added in 1970. The Institute of Medicine has been investigating the health effects of dioxin exposure being experienced by Vietnam War veterans since 1991. The first report on health effects observed in veterans was published in 1994; the most current update was published in 2004 and Federal funding for this research has been authorized until 2014.

The EPA Appropriations Bill of 2003 required the National Academies to review the EPA's 2003 Reassessment in the event that a White House interagency task force could not reach consensus on its review of the Reassessment. The Review Panel, under direction of the National Research Council, began its review in 2004 and published its findings in July, 2006. With one exception, the Review Panel consisted entirely of members of universities and medical schools in the United States that are recognized as experts in the various scientific disciplines required to review the 2003 Reassessment. The Review Panel did not contain any members associated with industry or any federal or state regulatory agency. The single member of the panel not affiliated with an academic organization is a member of the European Food Safety Authority, located in Parma Italy.

The mission and membership of the Review Committee has been acceptable to both the US chemical industry and the US regulatory agencies. The membership, scientific qualifications and objectivity of the Review Committee have not been challenged to date.

CHEMTELLIGENCE , INC. ANALYSIS :

The NAS review was intended to serve as a very detailed analysis of which sections of the 2003 Reassessment were acceptable as presented and which sections should be revised and improved. The following is a brief summary of the conclusions presented by the NAS Review Panel. The Section numbers and titles are those used in the NAS review.

Section 1 : Introduction and Summary

This section is a general review of dioxin contamination in the U.S., dioxin levels in the food supply and human exposure experience. Since the Review Panel was asked to only evaluate the 2003 Reassessment, the panel did not review any scientific studies or health effect data that been published after 2003 nor did the panel attempt to adjust the 2003 health assessment based on more current information, other than to note recent availability.

Section 2 : General Considerations of Uncertainty and Variability, Selection of Dose Metric and Dose-Response Modeling

1. The panel recommended that the 2003 Reassessment should be revised to better address the uncertainty and variability in estimating the risk of cancer associated with dioxin exposure, including information on the magnitude of the uncertainty. A portion of this uncertainty is the result of the variability of response demonstrated by human test subjects.

Section 3 : Toxic Equivalency Factors

1. Even though there is some uncertainty in the underlying data, the Toxic Equivalency Factor (TEF) method, including the calculated Toxic Equivalent Quotient (TEQ) is a reasonable, scientifically justifiable, and widely accepted method to estimate the relative toxic potency on human and animal health. The 2003 Reassessment should be reviewed and be revised, if necessary, to reflect revisions to the TEF factors made by the World Health Organization (WHO).

2. The TEF methodology, which was developed to assess the relative toxicity of a mixture of dioxins and dioxin-like compounds resulting from *dietary exposure*, may not be appropriate to assess the impact of internal TEQ concentrations in human and test animals. This issue was not well addressed in the 2003 Reassessment.

Section 4 : Exposure Assessment

In general, the Review Panel agreed with many of the methods and conclusions in this section of the Reassessment. A number of recommendations were made about the need to expand various dioxin databases and the need to clarify how measurements below the analytical Level of Detection (LOD) in environmental samples were incorporated into test results and conclusions.

Section 5 : Cancer

1. The Review Panel was unanimous in their conclusion that there is strong and convincing evidence that dioxin is *likely to be a human carcinogen*. The panel was not in agreement that dioxin is *carcinogenic to humans*. The panel concluded that the distinction between the two classifications is based more on semantics than on science. The panel recommended that the EPA could better spend its energies and resources in other areas rather than trying to clarify these distinctions any further.

2. The Review Panel concluded that there is adequate scientific basis to support the hypothesis that the relationship between dioxin dose and cancer risk is variable at very low dosages and not a straight-line relationship as assumed in the 2003 Reassessment. However, until the exact relation-

ship can be confirmed, the estimated cancer risk at a specific dioxin dose should be calculated based on both the straight-line assumption and the variable dose-response assumption.

Note: Although the Review Panel indicated that many human exposures in the U.S. occur at very low dosages, much higher daily dioxin intake levels are being experienced by residents in the Midland and Saginaw areas. Residents exposed to dioxin soil concentrations of 500 ppt-TEQ are estimated to have a daily dioxin intake level approximately 3.5 times that of the typical U.S. resident. Residents exposed to 2,000 ppt-TEQ are estimated to have dioxin intake levels nearly 12 times the average U.S. exposure. These dosages may be at a level for which dose-response data may be available thereby eliminating the need for modeling.

3. The EPA should offer an expanded discussion of the uncertainty associated with risk estimates based on human epidemiological data. The Review Panel recognized that uncertainty could result in an especially wide range of human risk estimates and that a narrowing of the range of estimates would need to be part of risk management, including the need to establish a conservative health protective estimate that would be based on an imperative to protect human health. Other risk criteria, such as the economic costs of risk mitigation, could result in a different range of risk estimates and cleanup criteria.

Section 6 : Non-cancer Health Effects

This section discusses in some detail the approach taken in the 2003 Reassessment on the non-cancer health effects associated with dioxin exposure. The panel noted that the EPA was cautious in stating the overall conclusions of non-cancer health risks and that the Reassessment acknowledged the uncertainty of suspected relationships. The Review Panel acknowledged the lack of human data in this portion of the Reassessment.

1. To characterize the risks of adverse health effects other than cancer, a dose called the Reference Dose must to be identified. The Reference Dose is the exposure level which no adverse effects from dioxin exposure, even among the most sensitive members of the population (children, women of childbearing age, fetuses, and nursing infants), are expected to occur. The 2003 Reassessment did not establish a Reference Dose for TCDD, the other dioxins, or the dioxin-like compounds. The panel recommended that the EPA estimate non-cancer Reference Doses so that dioxin risk management programs could be better implemented.

The Reassessment stated that setting a Reference Dose would have little value in Risk Management since current background dioxin intake levels are already above any potential Reference Dose, perhaps by a factor of 10 or more. The Review Panel believed that this problem is the result of EPA's conservative approach in estimating human response to dioxin exposure and the use of default uncertainty factors. The panel recommended that EPA needed to better justify the basis for its conservative approach.

The Review Panel believed that, although the dioxin exposure levels of a portion of the U.S. population exceed a Reference Dose, it still would have been helpful for EPA to define the nature and magnitude of the risks at different levels of intake, the groups of the population most at risk, and the major sources of exposure for any at risk groups.

2. The following is a brief summary of the Review Panels conclusions on the non-cancer effects of dioxin exposure to humans.

A. Immunotoxicity (adverse effects to human immune system)

(1) In the light of a large database showing that dioxins and dioxin-like compounds are immunotoxic in laboratory animals, together with sparse human data, the 2003 Reassessment was prudent in judging TCDD, the other dioxins, and the dioxin-like compounds to be *potential human immunotoxicants*.

Note: Based on the importance of the immune system in protecting the human body from disease, illness and the effects of aging, potential adverse impact on the human immune system may be one of the most significant and far-reaching consequences resulting from dioxin exposure.

B. Other Non-cancer Health Effects

(1) The Reassessment extensively documents the known reproductive, developmental and ectodermal (the outermost of the three primary germ layers of an embryo) consequences of dioxin exposure in a variety of laboratory test animals and describes other non-cancer consequences, including hepatic (liver), thyroid and cardiovascular effects.

While the collected data is suggestive that humans experience non-cancer effects similar to the effects observed in a wide range of laboratory animals, observed response in humans is inconsistent and the body of evidence is not yet compelling.

One of the difficulties in assessing the effects of dioxin exposure to human fetuses, infants and young children is the lack of information on dioxin body burden levels in this sensitive population. In addition, there is substantial difficulty in assessing health effect that may be subtle and within the range of normal clinical observation. It is also possible that some of the health effects associated with very early life stage exposure might not become apparent for a significant number of years after dioxin exposure.

Note : Testing of infants and young children to determine dioxin body burden levels is an extremely sensitive topic and is one which public health agencies, for the most part, have chosen to avoid. With the financial support of The Dow Chemical Company, the University of Michigan School of Public has been conducting a study to determine dioxin blood serum levels of persons living within the floodplain of the

Tittabawassee River. The study specifically excluded children below the age of 18 years. The reason given for the exclusion is the health concerns associated with drawing large amounts of blood (a maximum of 80 milliliters (less than 3 oz.) from very young test subjects. However, smaller amounts of blood would have been needed if the study protocol had not required duplicate samples and retained samples. In addition, smaller amounts of blood would have been required if higher dioxin detection limits had been acceptable.

There is almost no scientific information on the health effects of a specific dioxin blood serum levels in infants and young children. In the event that high levels of dioxins were found in these test subjects, neither the University of Michigan nor the Michigan Department of Community Health would have been able to address the fears of concerned parents.

(2) The 2003 Reassessment adequately summarizes the uniformly agreed upon and well documented association between dioxin exposure and the development of chloracne.

Section 7 : Review of Risk Characterization

Risk characterization is the final step in risk assessment. It is meant to assemble all of the relevant scientific information on dioxin toxicity and exposure into a comprehensive and quantitative (numerical) understanding of potential health risks to all potentially exposed persons, including the most sensitive populations.

The Review Panel considered the Risk Characterization section of the 2003 Reassessment to be the most important section but, in many ways, the weakest and least scientifically rigorous in its support of the decisions taken.

The Review Panel agreed that the use of dioxin body burden levels as a measurement of health risk is the most reasonable and pragmatic approach at the present time. However, the EPA should better address the uncertainties of using dioxin body burdens to develop risk estimates. It remains to be determined whether the current TEFs, which were developed to assess the toxic potency of a dioxin mixture ingested by an organism, are appropriate for determining TEQ levels in the human body.

1. The Review Panel was of the opinion that the 2003 Reassessment was incorrect in only using a straight-line extrapolation for carcinogenicity and that the EPA did not adequately support the use of such a model, to the exclusion of all other models. The panel recommended that the EPA revise the 2003 Reassessment to include both a straight-line and a non-linear model for carcinogenicity and a comparison of the results from each model.

The Review Panel acknowledged that quantitative evidence of either a straight-line relationship or a nonlinear relationship will never be available since the point from which carcinogenicity must be extrapolated is at the bottom of the available dose-response data. However, the lack of data is not

sufficient justification for assuming that there is only a straight-line relationship.

2. The panel noted that the Reassessment highlighted the greater susceptibility of in-utero, perinatal and neonatal life stages to dioxin exposure. However, EPA did not clarify the additional data that would be needed before a non-cancer Reference Dose could be established or before definitive advice could be given on the adverse effects detected in animal studies after in-utero exposure. The Reassessment commented on the greater exposure of nursing infants and children from dioxins in the environment but concluded that, because the risk characterization is based on dioxin body burden levels, overall lifetime dioxin exposure will have a greater impact than will short term dioxin intake.

3. The Review Panel agreed with the Reassessment on breast-feeding but indicated that the EPA's treatment was superficial in many points. EPA noted that while a nursing infant, whose mother was exposed to background levels of dioxins, would ingest 87 times the adult daily intake over the first year of nursing, that a corresponding increase in body burden would not be experienced due to the rapid increase in body weight of the infant and more rapid elimination. The Reassessment did not fully support its position with well-founded evidence and made no attempt to compare dioxin intake by infants with the doses producing adverse effects in relevant animal studies (that is, those evaluating in-utero exposure with subsequent developmental effects in early life).