

Integrated Risk Information System (IRIS)

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Agency Problem/Client Need: EPA Program and Regional Offices have the responsibility to assess and, if necessary, regulate the release of chemicals and other substances to air, water, and land and to remediate and restore contaminated sites. To support decisions about acceptable levels of substances in the environment, these programs need scientifically credible human health assessments, including toxicity values, which are supplied by the Integrated Risk Information System (IRIS) Program. International agencies and other Federal as well as State and local agencies use IRIS as a source of toxicity information to inform risk-based decision-making. The public, including academia, regulated industries, environmental organizations, and individuals, frequently use IRIS as a reference for chemical-specific toxicity and risk values.

Science Questions: How are chemicals selected for IRIS assessment? What is the process for developing an IRIS assessment? What types of data are required for an IRIS assessment, and how are these data used to qualitatively describe the chemical? How can data for a chemical be used to develop quantitative risk values associated with exposure to the chemical? How is the qualitative and quantitative information for a chemical assessment evaluated for scientific validity? Where can users find completed assessments and track the progress of ongoing assessments?

Approach: Nominations are solicited from EPA Program and Regional Offices and from the public. Chemicals are selected using priority-based criteria. Chemical-specific human health risk assessments are developed by teams of toxicologists, biologists, health scientists, epidemiologists, and statisticians. The available data are critically evaluated to generate a toxicological review of the chemical. Assessments are subjected to internal agency, interagency, and external reviews to ensure the presentation of transparent and defensible scientific information for a chemical. The status of assessments as they undergo development and review is shown in IRIS Track (<http://cfpub.epa.gov/iristrac/index.cfm>) and completed assessments are posted on the publicly accessible IRIS database (www.epa.gov/iris).

Results/Outcomes: The IRIS database contains over 500 chemical-specific IRIS Summaries, many with Toxicological Reviews (or similar) background documents. IRIS human health risk assessments represent EPA scientific positions on potential adverse health effects that may result from exposure to chemicals found in the environment. Assessments provide qualitative hazard information, cancer weight-of-evidence characterizations, and quantitative health information, including reference doses (RfDs) for noncancer health effects resulting from oral exposure, reference concentrations (RfCs) for noncancer health effects resulting from inhalation exposure, and cancer risk estimates.

Impacts: Toxicity values and cancer risk estimates provided in the IRIS human health risk assessments are not regulatory values. However, the values are used to support risk-based decision-making at the local, state, national, and international levels. EPA Regional Risk assessors combine IRIS toxicity values with scenario-specific exposure values to estimate risk. EPA Program (i.e., OPPTS, OSWER, OAR, OW) and Regional Offices rely on IRIS assessments to determine acceptable levels of toxic substances in the environment and to inform their program-specific risk assessments. Federal, state, and local governments and other authoritative scientific agencies frequently use IRIS as a resource in their own assessments.

Provisional Peer Reviewed Toxicity Value Documents (PPRTVs)

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Agency Problem/Client Need: EPA's Office of Solid Waste and Emergency Response (OSWER) is charged with the responsibility to assess, remediate and restore contaminated sites or properties, especially uncontrolled or abandoned hazardous wastes sites (i.e., Superfund sites). EPA is most concerned with threats to human health resulting from exposures or releases from toxic materials at these sites and has set a goal to control releases or clean up sites to levels at or below health-based levels for current land or groundwater use. In order to accomplish this, the Agency must have scientifically credible human health assessments or toxicity values. Provisional Peer Reviewed Toxicity Values (PPRTVs) satisfy a significant need for timely information, which may not be available from the Integrated Risk Information System (IRIS) Program because of the considerably longer development and review time periods required to complete IRIS documents.

Science Questions: How can we provide timely, high quality and scientifically defensible chemical toxicity values to support the cleanup of hazardous waste sites? What alternative methods and approaches are used to evaluate risks to humans when data are not sufficient to develop toxicity assessments? How is this information on toxicity used by the Agency to support decision-making?

Approach: PPRTVs are dose-response assessment documents that provide provisional reference doses and reference concentrations (subchronic and chronic), and cancer values (oral and inhalation unit risks) to support remediation decisions by Superfund site managers. PPRTVs are generally produced within 6 to 8 months, with chemicals selected according to priorities defined by the Superfund program. The process includes a literature search, review and evaluation of all relevant studies, determination of critical studies and critical effects, consideration of uncertainty factors, quantification of toxicity values under a well-defined Standard Operating Procedure, and internal and external peer review. Once established, PPRTVs are reviewed every 5 years. If appropriate, the values are updated according to new information or improvements in methods. When information is not sufficient to develop values, the information is summarized in the document. In some cases, it may be possible to develop a "screening" value. Screening values are provided only for prioritization and are not to be used as a basis for site cleanup.

Results/Outcomes: The current goal is to produce 50 new or renewed PPRTVs per year. They are used to support decisions on acceptable levels of human exposure, establish remediation strategies, and set cleanup goals that are appropriate for protecting human health while not overly conservative or costly. The Office of Superfund Remediation and Technology Innovation (OSRTI) has defined a three-tiered hierarchy of toxicity values for use by the Regions and States in conducting assessments: Tier I, IRIS values; Tier II, PPRTVs; and Tier III, other peer-reviewed values available, e.g., Agency for Toxic Substances and Disease Registry (ATSDR) minimal risk levels (MRLs). PPRTVs are available to all Superfund site managers via an Intranet Web site (http://hhpprtv.ornl.gov/pprtv_papers.shtml) or by request to NCEA's Superfund Technical Support Center.

Impacts: OSWER/OSRTI ranks PPRTVs among the most valuable and important EPA Office of Research and Development (ORD) products with regard to Superfund decisions and support to Agency cleanup goals and restoration of land to productive uses.

Incidence response assessment activities

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Agency Problem/Client Need: During national emergencies involving potential risks to human health from exposures to environmental contaminants, the National Center for Environmental Assessment (NCEA) has been asked to play a significant role in responding to the unfolding situation. Often the combination of contaminants, the routes and patterns of exposure, and other aspects of the emergency, are unique and require creative solutions. Human health risk and exposure assessments, both quantitative and qualitative, are often needed to scientifically address questions of risks to human health. These national emergencies have involved events related to municipal water supply contamination, community health impacts of exposures to environmental contaminants, and human health risks in the aftermath of a natural event or a man-induced calamity.

Science Questions: What are the human health assessment questions that need to be addressed to effectively respond to the event? What are the scientific disciplines needed on the NCEA response team to effectively address those human health risk assessment issues?

Approach: NCEA is called upon to mobilize scientific staff and managers to respond to the emergency event. Based on the nature and scope of the emergency, NCEA may coordinate with a specific EPA Program or Region or across Federal agencies. As part of these coordination teams, NCEA determines how best to respond, first, to the emergency situation by assessing imminent human health hazards. NCEA may also be requested to conduct an assessment of long-term human health impacts resulting from the emergency.

Results/Outcomes: In 1991, NCEA was asked to help in the aftermath of the first Gulf War by providing human health risk information from the Integrated Risk Information System (IRIS) data base to the Army's Environmental Hygiene Agency on the contaminants being released from the burning oil fields that could result in contamination of food and water supplies. Since that time, NCEA has been called upon to be part of the EPA response team for other significant high-profile health assessment activities. NCEA conducted assessments to estimate risks associated with the aftermath of the attacks on the New York World Trade Centers. In 2004 and 2005, NCEA assisted the Office of Water and Region 3 after high levels of lead (Pb) were detected in numerous samples of residential drinking water in Washington, DC. NCEA scientists evaluated the potential impacts on pediatric blood Pb levels of the elevated Pb in the tap water. In 2005, NCEA contributed to the environmental and human health impact assessment of the aftermath of Hurricanes Katrina and Rita on the Gulf Coast region. NCEA is currently assessing the risks associated with asbestos exposure to residents in Libby, MT. Operations from a former vermiculite mine and processing plant generated significant past (and current) exposures to a unique amphibole fiber, resulting in asbestos-related disease in the general population. This work is of national significance, as materials were processed in over 200 locations across the country, and vermiculite attic insulation is in countless homes in the United States and Canada.

Impacts: NCEA contributes to assessing possible human health risk impacts after an environmental contamination event. NCEA develops problem-specific high-profile risk assessments and other human health risk impact analyses that combine the human health risk information provided by the IRIS and Provisional Peer Reviewed Toxicity Values (PPRTV) programs with exposure data to derive estimates of risk that respond to questions of immediate health risk and, if appropriate, long-term risk. The methods and models work developed in LTG 2 directly contribute to the development of assessments and other analyses that respond to these high-profile, incidence response activities.

IRIS Toxicological Review of Acrylonitrile – State of the Art Assessment

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Agency Problem/Client Need: Acrylonitrile (AN) is widely used in the production of acrylic fibers, acrylonitrile-styrene resins, nitrile rubbers, and as an intermediate in the production of other chemicals. The current assessment has been on the Integrated Risk Information System (IRIS) database since the early 1990s. Voluminous new data from epidemiological and animal studies have since become available. In addition, new methods and guidelines have been developed and utilized by the Agency. EPA Program Offices and Regions have been challenged with the question of whether the existing toxicity values for AN are still appropriate for use in quantifying risk associated with AN exposure.

Science Questions: What are the toxicity values for cancer (oral slope factor, inhalation unit risk) and noncancer (RfD, RfC) hazard assessment of AN, using new information and methodology? What is the mode of action (MOA) for the carcinogenicity of AN? Should linear or nonlinear approaches be used for quantification of cancer risk?

Approach: EPA is preparing an IRIS Toxicological Review of AN. The assessment is an update to the current assessment. This reassessment constitutes a major undertaking of the IRIS Program. State-of-the-art methods are used, including evaluation of cancer and noncancer epidemiological studies on AN; evaluation and modification of available physiologically based pharmacokinetic (PBPK) models for AN and its reactive metabolite, 2- cyanoethylene oxide, in rats and humans; evaluation of animal toxicity studies; benchmark dose modeling; statistical approach to derivation of the inhalation unit risk taking into account temporal changes in the exposure in extensive epidemiological data; evaluation of MOA for the carcinogenicity of AN (in accordance with the framework outlined in EPA's 2005 *Guidelines for Carcinogen Risk Assessment*); and quantitative adjustment for carcinogenic response to early-life exposure to AN. The approach has been presented to the scientific community at various conferences.

Results/Outcomes: A draft assessment has been developed for AN. New toxicity values (RfD, RfC, oral slope factor, inhalation unit risk) have been derived, using epidemiological and animal studies for comparison. The experimental evidence appears to be sufficient to support direct mutagenicity as a key MOA for carcinogenicity. Other MOAs, particularly oxidative DNA damage are plausible, but the evidence suggests they may not be key to the carcinogenicity of AN. A conclusion of direct mutagenicity would support use of linear extrapolation in cancer quantification. A chemical-specific, dose-response data-derived, age-dependent adjustment factor for early life exposure may also be warranted. After revising an existing rat PBPK model to incorporate a previously missing metabolic pathway (thereby impacting the extrapolated human model), the rat and human PBPK models were used to estimate reference dose and slope factors for noncancer and cancer endpoints, respectively. The draft assessment has been through the first round of Agency review and will be submitted to interagency review.

Impacts: This reassessment of AN is anticipated to provide a much-needed update to the current assessment. The toxicity values will be considered by EPA Program Offices and States for development of emission standards, drinking water standards, and cleanup levels.

Use of epidemiologic data in IRIS assessments

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Agency Problem/Client Need: EPA Program and Regional Offices are responsible for assessing and, if necessary, regulating the release of chemicals and other substances to air, water, and land and for remediating and restoring contaminated sites. To support decisions about acceptable levels of substances in the environment, these programs need scientifically credible human health assessments. The Integrated Risk Information System (IRIS) is charged by the Agency to provide a comprehensive summary of toxicity data for the purpose of making inferences about the risk to human health from exposure to chemicals of concern. The quantity and quality of epidemiologic studies of the effects of chemical exposures have grown over the past 20 years, and IRIS assessments increasingly rely on data from such studies for the characterization of risk of a variety of diseases, including cancer, that may arise from environmental exposures.

Science Questions: How can epidemiologic data contribute to the assessment of chemical hazards and the derivation of accurate toxicity values? Can epidemiologic data be used to ensure that the most susceptible among our population are protected from harm? What role can epidemiologic data play in understanding potential modes of action (MOAs)?

Approach: NCEA epidemiologists review comprehensive literature archives and all accessible data to identify any adverse effects associated with chemical exposures. The potential impact of various biases is examined within individual studies and across studies by assessment of the direction and estimated magnitude of selection bias, confounding, and misclassification of exposure and of disease outcomes. Special emphasis is placed on the identification of susceptible populations by examining available evidence pertaining to differential risks across demographic factors (e.g., lifestages, ethnicity, gender) or clinical conditions (e.g., diabetes, cardiovascular disease). Determinations of any adverse effects serve as a basis for deriving toxicity values for both cancer and noncancer endpoints. Human data are also used in establishing MOAs and quantifying parameters for biologically based dose response (BBDR) and physiologically based pharmacokinetic (PBPK) models.

Results/Outcomes: Examples of the use of epidemiologic data in assessments that are currently underway include their use in (1) hazard identification to provide insight into the type of cancer that would be relevant in humans (trichloroethylene); (2) dose-response assessment to develop cancer and noncancer reference values (asbestos); (3) comparison of reference values developed using human studies to those derived from animal studies (carbon tetrachloride, tetrachloroethylene); (4) providing support for potential MOAs (ethylene oxide); (5) aiding in the quantification of BBDR or PBPK modeling; and (6) identifying data gaps and facilitating the research needed to fill these gaps .

Impacts: Human data are preferred over other types of data to support human health hazard identification and dose-response assessment. The cited chemical examples demonstrate the use of epidemiology to answer questions on causality, species relevance, susceptibility, and MOA. Furthermore, quantitative analysis of epidemiologic datasets can be used to establish acceptable exposures for the prevention of both cancer and noncancer toxicity.

Linear and nonlinear approaches for human health risk assessment

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Agency Problem/Client Need: Human health risk assessments for the Integrated Risk Information System (IRIS) Program database are developed based upon the existing scientific literature for environmental pollutants. Frequently, the available literature for an environmental pollutant does not adequately characterize in vivo adverse responses for low-dose exposures. This necessitates the development of quantitative approaches to estimate the risk of exposure to a given pollutant at potentially relevant human exposure levels. These approaches are derived using the best available science and biologically plausible hypotheses.

Science Questions: How can mode of action (MOA) data inform the quantitative approach for low-dose extrapolation of risk? What additional information may impact the shape of the dose response curve at low doses? What are the human health implications of using nonlinear approaches for cancer endpoints?

Approach: The EPA's *Guidelines for Carcinogen Risk Assessment* essentially provide that linear low-dose extrapolation should be used in the following cases: (1) for agents that are DNA-reactive and have direct mutagenic activity, (2) whenever high background exposure to the agent or other compounds that operate through a common MOA exists; and (3) as a default for agents that have an unknown MOA. Nonlinear low-dose extrapolation is used for agents that do not demonstrate mutagenic activity and have sufficient data to conclude that the MOA is not linear, but have inadequate data to develop a biologically based dose-response model. The choice between linear and nonlinear methods for low-dose extrapolation relies heavily on the scientific evaluation of the weight of evidence for an MOA and whether an MOA is supported by the existing data. As indicated in the guidelines, there is no checklist to assist in determining whether sufficient scientific evidence exists to identify an MOA. This decision is performed for each individual IRIS assessment and is best represented by presenting a scientifically diverse group of environmental pollutants to exemplify the qualitative and quantitative decisions that are supported by the available scientific literature.

Results/Outcomes: Cancer assessments at different stages of development under the IRIS Program illustrate the factors that are considered in selecting an approach for low-dose extrapolation. The proposed qualitative decisions and how those decisions impact the quantitative approaches for ethylene oxide, tetrachloroethylene, carbon tetrachloride, and inorganic arsenic are presented here to characterize the current application of the *Guidelines for Carcinogen Risk Assessment*.

Impacts: Quantifying the risk of adverse health effects at low-dose exposures to environmental pollutants represents an evolving process that is heavily influenced by a better understanding of current and emerging science. Comparison and full characterization of the uncertainty in the process of low-dose extrapolation will help ensure informed decisions regarding risk of exposure to environmental pollutants.

**Assessment of early-life exposures and application
of age-dependent adjustment factors (ADAFs) to chemical carcinogens
with a mutagenic mode of action**

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Agency Problem/Client Need: Infants and young children may be more susceptible than adults to the carcinogenic effects of environmental chemicals. *The Guidelines for Carcinogenic Risk Assessment* and, in particular, the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* recommend that if a chemical induces tumors via a mutagenic mode of action (MOA), then for certain specified age groups adjustments should be made to the cancer potency value. EPA Program Offices and Regions, therefore, need health assessments that identify mutagenic modes of carcinogenic action, allowing the risk assessor to account for potential susceptibilities during early lifestages.

Science Questions: What evidence is needed to support a determination that a carcinogen is acting by a mutagenic MOA? How does one determine the adequacy of data on early-life exposure, if available, to derive chemical-specific cancer potency values? If a chemical is determined to be carcinogenic by a mutagenic MOA but specific early-life data are not available, how should age-dependent adjustment factors for early-life exposures be applied with the appropriate exposure information in the risk characterization step of risk assessment?

Approach: EPA's Office of Research and Development (ORD) has taken a lead role in the implementation of the *Cancer Guidelines and Supplemental Guidance*. Ongoing health assessments under development by the Integrated Risk Information System (IRIS) Program include an evaluation of the mutagenicity and carcinogenicity data to determine if a mutagenic MOA is operative based on the weight of evidence. In accordance with the Supplemental Guidance, if chemical-specific data are available to derive an adjusted cancer potency value, specific early-life potency values are derived. If the chemical is found to be carcinogenic by a mutagenic MOA, but chemical-specific dose-response data for early lifestages are not available, age-dependent adjustment factors (ADAFs) for early-life exposures are applied with the appropriate exposure information in the risk characterization step of risk assessment.

Results and Outcomes: When appropriate, the application of ADAFs is being recommended. ORD scientists are participating in the development of a framework for the determination of a mutagenic MOA. Case examples are illustrative of this approach. An Evaluation of the Mutagenicity of Coke Oven Emissions was developed under the lead of ORD staff at the request of EPA's Office of Air Quality Planning and Standards (OAQPS) to evaluate whether coke oven emissions act through a mutagenic MOA. The information in the analysis was used for rule-making purposes in the Residual Risk Analysis of Coke Oven Emissions conducted by OAQPS. In addition, a number of IRIS health assessments that are under development or currently undergoing peer review contain evaluations for a mutagenic MOA and indicate recommendations for the application of ADAFs. These include assessments for the carcinogenicity of ethylene oxide and acrylonitrile.

Impacts: The application of ADAFs should provide an added level of health protectiveness for early-life susceptibility to carcinogens that act by a mutagenic MOA. The participation of ORD on workgroups and the development of IRIS health assessments that address this issue are key to ensuring that sound science is applied across the Agency.

Physiologically-based pharmacokinetic (PBPK) model applications in IRIS

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Agency Problem/Client Need: EPA Program Offices and Regions are charged with determining acceptable levels of toxic substances in the environment as well as developing risk assessments that provide scientific support to their decisions. Database incompleteness often prompts the need for extrapolations across species, routes, or durations of exposure to derive toxicity values.

Science Question: Physiologically based pharmacokinetic (PBPK) models provide a quantitative representation of a chemical's toxicokinetics in humans or relevant test animals and can be used to estimate an internal dose from a variety of exposure regimens. How are PBPK models used in lieu of default adjustment factors or to bridge data gaps in the derivation of Integrated Risk Information System (IRIS) reference values?

Approach: Adequately developed, tested, and evaluated PBPK models are being used to improve the scientific support and availability of IRIS reference values by replacing default adjustment factors for interspecies or intraspecies toxicokinetic differences that would impact the response to a given dose. PBPK models also provide a means to extrapolate an observed dose-response relationship from one route or duration of exposure to another when data are limited.

Results/Outcomes: Examples of the use of PBPK models in IRIS assessments are provided for two chemicals, acrylonitrile (AN) and 1,1,1-trichloroethane (1,1,1-TCA). EPA evaluated an AN PBPK model that was originally developed for rats (Kedderis et al., 1996) and then further elaborated to describe the dosimetry of AN and its metabolite 2-cyanoethylene oxide (CEO) in humans (Sweeney et al., 2003). The model results for two internal dose metrics (AN-AUC and CEO-AUC in blood) were used in the derivation of the reference dose (RfD), the oral cancer slope factor, and the inhalation unit risk to account for differences in AN toxicokinetics between humans and the test animals. In the 1,1,1-TCA assessment, a PBPK model was used to replace the interspecies default uncertainty factor in the derivation of the chronic reference concentration (RfC), and to extrapolate between exposure durations in the derivation of a less-than-lifetime RfC. The 1,1,1-TCA model was also used to extrapolate between routes in the derivation of an RfD for comparison to an RfD based on subchronic oral data.

Impacts: In contrast to the default approach, an adequately developed and tested PBPK model incorporates what is known about a chemical's toxicokinetics and mode of action into the derivation of a more scientifically sound and supportable toxicity value. In the absence of dose-response data for a given route or duration of exposure, the respective toxicity value may only be adequately derived with the use of a PBPK model. PBPK models also provide a conceptual and hypothesis testing framework that helps to direct future research towards obtaining the most needed data.

Benchmark dose modeling and its application in EPA chemical assessments

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Agency Problem/Client Need: Prior to the development of EPA's benchmark dose software (BMDS) and accompanying guidance, most EPA dose-response assessments were based on either no-observed-adverse-effect (NOAEL) or lowest-observed-adverse-effect (LOAEL) levels. The EPA now routinely uses the benchmark dose (BMD) approach for both cancer and noncancer assessments to generate points of departure (PODs) from which toxicity values are derived. The BMD approach provides several advantages over the NOAEL (and LOAEL) approach including being less dependent upon the doses used in the study and penalizing poor study design by generating lower PODs for studies of poor quality (e.g., those with small sample size).

Science Questions: When should the BMD approach be used versus another approach such as the NOAEL approach? What benchmark response (BMR) should be chosen as the basis for a BMD? How should BMD values be extrapolated across exposure durations?

Approach: BMD modeling is currently the preferred approach for EPA dose-response assessments. EPA Office of Research and Development (ORD) laboratories and centers have worked together to develop and update BMDS and associated guidance, Web sites, and training to assist risk assessors both inside and outside the Agency in evaluating and interpreting dose-response data. Experimental data for each critical cancer and noncancer endpoint are examined to determine whether these data will support BMD modeling. For those datasets that are amenable to BMD modeling, PODs are generated through use of one of the multiple dose-response models provided in BMDS. These PODs are then used in the calculation of cancer and noncancer toxicity values. To support BMD modeling across (and outside) EPA, NCEA offers readily accessible and up-to-date training and guidance on the use of BMDS and BMD methods.

Results/Outcomes: Hands-on and online BMD training courses developed by EPA have been taken by hundreds of EPA and non-EPA risk assessors. BMD methods have been increasingly used in Agency dose-response assessments to develop PODs whenever datasets are amenable to such an approach. Examples of the application of BMD methods in the Integrated Risk Information System (IRIS) Program to the evaluation of dichotomous (1,2-dibromoethane), continuous (toluene), and nested dichotomous (methyl ethyl ketone) data are presented.

Impacts: The routine use of the BMD approach yields dose-response assessments that better reflect both the strengths and weaknesses of the underlying data and, thus, produces a more scientifically defensible assessment that encourages additional research when uncertainties are large. Currently, EPA's BMDS and accompanying guidance are being used by thousands of EPA and non-EPA risk assessors throughout the world. BMDS has an ever-expanding universe of users, which EPA serves by offering a variety of different training materials and methods. BMDS continues to evolve to keep abreast of the current state-of-the-science in the application of BMD methods.

Characterizing uncertainty in IRIS assessments

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Agency Problem/Client Need: EPA Program Offices and Regions are charged with determining if levels of toxic substances in the environment are acceptable, and to take actions to reduce exposures if needed. Risk managers at the federal, state and local levels, and the public, can benefit from an improved understanding of uncertainty in the scientific data and methods used to assess hazard and dose-response. By understanding uncertainty in risk assessment, risk assessors and managers are better able to make decisions, set priorities, and allocate resources most effectively. There is a need to improve the characterization of uncertainty in risk assessments to better inform risk managers and the public about environmental health risks.

Science Questions: How can consideration of plausible alternative studies, endpoints, physiologically based pharmacokinetic (PBPK) models, and dose-response models be more effectively weighed in an assessment? How can their impacts on the assessment be presented more transparently? What aspects of these considerations can contribute to a quantitative analysis of uncertainty? How does data availability affect the measures of uncertainty that can be provided?

Approach: Following existing guidance, available studies for a toxic substance are considered for developing toxicity values following a weight-of-evidence framework, evaluating data quality, strength and thoroughness of evidence, relative biological significance of adverse outcomes observed, and consistency between studies. Scientific conclusions are identified separately from default assumptions and policy determinations. For assessments with a broad database, studies are judged for their potential as equally plausible alternatives or as studies supporting the stronger studies. Next, toxicity values developed for all adequate studies are arrayed graphically to facilitate comparison of data gaps. Where there is some basis for assuming that specific values or ranges of values can fill some of these data gaps, the assessment considers the impacts of alternate values.

Results/Outcomes: One assessment under development, tetrachloroethylene, has a broad database that supported the development of multiple reference values and multiple cancer risk values. The resulting reference values were not equally plausible alternatives, given the variety of available studies (e.g., varying batteries of measurements taken, different exposure ranges). The availability and use of human data for the reference values decreases uncertainty in the recommended values, although some uncertainty remains in characterizing the applicability of the reference values to the general population. The cancer risk values were derived from consistently designed rodent bioassays, leading to a set of relatively equally plausible alternatives, as compared with the noncancer database. These data permitted some characterization of statistical uncertainty in the risk estimates attributable to variability in the experiments. However, sufficient unquantifiable uncertainty remains that does not permit a quantitative uncertainty analysis to be applied to the current tetrachloroethylene toxicity database.

Impacts: This effort has improved EPA's approach to risk assessment through increased transparency, clarifying the assessment approaches used and promoting the use of good science to inform decisions.

Concentration x Time Response Relationships

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Agency Problem/Client Need: Reference values for less-than-lifetime durations are key in determining allowable short-term exposures during emergency response (Acute Exposure Guideline Levels [AEGs] for the Office of Prevention, Pesticides, and Toxic Substances [OPPTS] and Provisional Advisory Levels [PALs] for the National Homeland Security Research Center [NHSRC]), during cleanups (Superfund and Homeland Security Programs) and in regulatory programs (Residual Risk Program within the Office of Air Quality Planning and Standards [OAQPS]). Extrapolation from experimental observations to health effect reference values at another duration is often necessary.

Science Questions: What is the best method for duration extrapolation? What are the preferred approaches to extrapolation?

Approach: Traditionally, duration extrapolation has been performed using Haber's rule where the product of the concentration multiplied by the duration results in a constant ($C \times T = k$). The approach proposed by ten Berge et al. (1986), using the formula $C^n \times T = k$, has been adopted recently as more appropriate in defining this relationship. Categorical regression (CatReg) analysis can also be used to extend this approach to the evaluation of the $C^n \times T$ relationship at a given response severity when the endpoints can be categorized into ordered severity levels. The National Center for Environmental Assessment (NCEA) has developed methods for assessing health risks from acute and short-term inhalation exposures and applied them in assessments for hexachlorocyclopentadiene (HCCPD), acrolein, ethylene oxide (EtO), hydrogen sulfide (H₂S), and phosgene. These assessments explore several issues including the relevance of lethality to less severe endpoints (e.g., irritation, neurotoxicity), duration extrapolation for data-limited chemicals, and application of CatReg analysis. General issues discussed include dosimetry, estimating a time to recovery following an acute exposure, and toxicokinetic/toxicodynamic considerations when validating extrapolations from observed data.

Results/Outcomes: The appropriate approach is most often dependent on the available data and requires toxicological judgment as to which data are most biologically relevant. Additionally, for certain endpoints in the acute time frame, concentration, not $C \times T$, is more determinant of toxicity (e.g., irritation from low-level exposure). The HCCPD database supported derivations of values for 1 and 8 h from 4-h observations. In the assessment of acrolein, available human data indicated there was no increase in effects with durations up to 1 h. The value derived for 1 h was used for all exposures up to 4 h. In the assessment of EtO, data were adequate to derive a value of n based on lethality using the models developed by ten Berge and to develop reference values using Benchmark Dose (BMD) analysis of neurotoxicity in rats for durations of 1 to 24 h and of developmental effects for durations up to 30 days. The assessment for H₂S used CatReg analyses for determining the point of departure (POD) and for duration extrapolation. In the assessment of phosgene, a hybrid approach using both BMD and CatReg analyses informed determination of a POD and the duration extrapolation.

Impacts: In performing the five exposure-response assessments, useful approaches have been demonstrated to perform duration extrapolations in acute and short-term assessments. The resulting exposure-response methods (see LTG 2, Poster 10) provide EPA Programs with the ability to develop health effect reference values for all relevant exposure durations.

HHRA Program Assessment Products: Outreach, Use and Impact

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Agency Problem/Client Need: Tasks confronting EPA Program and Regional Offices as well as State and local regulatory authorities, include assessing and making decisions on acceptable levels of risk from pollutants in order to protect human health. This task involves a large number of pollutants over a wide range of concentrations in air, water and soil. To accomplish this charge, these organizations depend on accessible toxicological information and products, including health effect values that are reliable and reflective of the current state-of-the-science.

Science Questions: How do assessment products from the HHRA Program contribute to regulatory and other environmental decisions? How does the HHRA Program promote dissemination of relevant information and collaborate to improve product quality?

Approach: NCEA's Technical Centers responsible for the creation and distribution of HHRA assessment products in collaboration with EPA's Program and Region liaisons, were surveyed about the outreach, use and impact of NCEA assessment products. Their use in regulatory decision-making, scientific consultation, and technical assistance was evaluated using sampled results from Superfund and air pollution management programs as examples of the success of our program. Additional indicators for outreach and use were the number of pages downloaded plus the number of requests or "hits" from our internet sites.

Results/Outcomes: Results show an extensive and increasing use of our scientific advice and products by clients internal and external to EPA, both nationally and world-wide. Examples include hotline requests for products and assistance, participation of NCEA scientists in regulatory workgroups, and internet access rates and retrievals from key NCEA internet sites. NCEA's assessment products are extensively used for regulatory decisions made to protect human health throughout EPA's Program and Regional Offices. Regulatory applications analyzed included samplings of beginning-stage baseline risk assessments and end-stage Records of Decision (RODs) from the Superfund Program, and the National Air Toxics Assessment (NATA) from the Office of Air and Radiation (OAR). NCEA also supports the Office of Water and the Office of Prevention, Pesticides and Toxic Substances.

Impact: That NCEA assessment products provide critical information for important environmental decisions and subsequent action is clear for every indicator examined. For example, OAR's NATA, which uses values produced by the HHRA Program to identify air pollutants estimated to pose the greatest risks, is being directly applied to set the regulatory agenda for the entire US. NATA also provides tools to help State, local and tribal governments understand risks in their specific areas. Also, the number of toxicity values provided by the HHRA Program in final reports on Superfund sites (RODs), demonstrates the utility of the HHRA Program in supporting development of remediation strategies. The usage rate of NCEA's toxicity values has been designated as a measure of performance for the HHRA PART (Program Assessment Rating Tool) evaluation by OMB, further illustrating their usefulness and value to EPA programs.