

Research Area: Human and Ecological Effects

New questions about chemicals found in the environment and their possible role on health have been raised that have challenged scientists, doctors, and policy makers to clarify scientific uncertainties and to put these issues into perspective. Some believe that adverse effects from exposure to environmental chemicals may occur at virtually all doses and tissue levels, while others believe that there may be a finite level of exposure needed to cause effects.

When there are uncertainties in health information, regulators and the public often turn to surrogate information and use conservative models and default assumptions. Many assert that the application of the regulatory processes for cancer, i.e., the use of linear dose-response models to estimate the toxicity of non-cancer health endpoints [e.g., endocrine system changes] particularly in the low dose range, is appropriate whenever there is a lack of relevant scientific data. Alternative biological-based models can be used in policy making when sufficient, high quality data exist to refine the assumptions in the default models.

Historically, most regulatory activities concerning low level environmental exposures to chlorinated substances found in the environment have focused on the potential for such substances to cause cancer, because carcinogenicity has been thought to be generally the most sensitive adverse endpoint for humans. Based upon the linear low dose models and conservative assumptions, regulators often assume a specific risk of cancer at very low exposure levels. As a result of this regulatory paradigm, it is assumed that regulations and policies for carcinogenic effects are protective against other adverse effects.

In recent years, concern has turned to non-cancer effects. Wildlife effects have tended to focus on lethality and impacts on reproduction and development. Until recently, it was assumed that these effects were related to high-dose exposures. For example, reproductive and developmental effects related to DDT and other similar compounds were thought to result from relatively high exposures. However, some scientists and policy makers now believe that exposure to a wide variety of chemical agents found in the environment may pose a non-cancer threat to wildlife and to humans based on: [1] measured biochemical effects (which may not be

adverse) and certain effects that cannot be replicated on some target organs, and [2] theories concerning the interaction of substances with potentially sensitive biological systems (e.g., endocrine and immune) or potentially sensitive stages of development (e.g., developing fetuses).

A recent example of the focus on non-cancer effects concerns the endocrine disruption hypothesis. While it is biologically plausible that exogenous chemical agents can exert endocrine effects, such hypotheses and theories have not been adequately tested and evaluated, particularly as they relate to environmentally-relevant exposures and to potential effects in humans. In fact, an expert panel of the National Research Council concluded, "the extent of harm caused by exposure to these compounds [hormonally active agents] in concentrations that are common in the environment is debated."¹ Nevertheless, the endocrine disruption hypothesis has been evoked as support for the claim that low level chemical exposures may adversely effect the endocrine and other hormonally sensitive systems in humans and wildlife, resulting in behavioral and neurodevelopmental effects, thyroid disorders, diabetes, endometriosis,

reproductive disorders, developmental disorders, and perhaps other effects.

Since the first publication of this hypothesis, the federal government, industry, foundations, and activists have all sponsored research concerning various aspects of cancer and non-cancer effects mediated via a hormonal mechanism. Many questions remain. The National Research Council, in its 1999 report *Hormonally Active Agents in the Environment*, concluded that there are still many unanswered questions concerning the hypothesis on hormonally activated effects at low levels. For example, to date, essentially no effort has been directed at the critical issue of how data on the potential hormonal effects of any chemicals of concern might be used for risk assessment purposes.

Persistent chlorinated chemicals have tended to be the focus of intense scrutiny for subtle, non-cancer effects. Chlorine chemistry has received additional scrutiny because some chlorinated compounds are known to persist and bioaccumulate, thereby increasing the potential for increased environmental and human exposure over a lifetime. These chemicals have included TCDD and dioxin-like compounds, PCBs, hexachlorobenzene, chlorinated water disinfection byproducts (DBPs), and chlorinated pesticides.

Critical to future policy development for chlorine chemistry is a better understanding and interpretation of effects and potential risks associated with chronic exposure to chemicals found in the environment that are often present at concentrations well below their observable dose-response range in typical animal tests. For example, it will be important to determine if exposure, particularly during "critical windows" of sensitivity, to environmental concentrations of both persistent and short-lived chlorinated compounds, either directly or indirectly [via food or other routes] have the potential to

adversely affect the health of wildlife or humans. It will be important to determine the attributes of an adverse health impact on hormone-controlled processes, and how and when such effects should be measured. Similarly, it is important to understand whether the mere presence of a chemical in a tissue directly contributes to and is sufficient for an effect, especially an adverse effect.

The challenge, both from an exposure and toxicological perspective, is to be able to interpret and place in perspective the results of studies on potential hormonally active agents, including chemical pollutants. In March 2001, the Centers for Disease Control [CDC] released its *National Report on Human Exposure to Environmental Chemicals*, which attests to the critical importance of this issue. In this report, the CDC identified measurable levels of 27 chemicals (some of which contain chlorine) and stated that it planned to expand the list of chemicals analyzed in future studies of human exposure to 100 chemicals. As noted by Dr. James Pirkle, deputy director of the CDC Environmental Health Laboratory, "Just because it's measured in a person doesn't mean that it causes a disease."² In conjunction with anticipated expansion of this program, which is likely to include more chlorinated compounds, a future challenge will be to develop supporting toxicological data that will assure the public that Dr. Pirkle's statement is correct. This will be particularly important as it pertains to development of data concerning the relevance, if any, of the presence of chlorinated chemicals in various subpopulations.

Questions have also been raised concerning other effects associated with environmental releases of chlorinated substances. Recently, some scientists have speculated about short-lived chlorinated compounds that contribute to ozone depletion in the stratosphere or ozone formation in the troposphere. It is

expected that policy attention will focus increasingly on levels of short-lived chemicals found [or hypothesized to be] in the environment, including some chlorinated compounds. Undoubtedly, further research conducted in these areas can help shape health and public policy regarding chlorine chemistry. However, it is imperative that the policy-critical questions be better defined to guide researchers. Once clarified, improved data are needed to determine if there are potential effects on environmental and atmospheric air quality from chlorinated compounds. These data are needed to improve the inputs for modeling and risk assessment.

Policymakers and scientists are likely to focus on biomarkers of exposure or early effects included in epidemiological studies of populations exposed to chemicals found in the environment (at levels which may be declining), including TCDD and dioxin-like compounds, water disinfection byproducts, or short-lived chlorinated compounds. Of particular importance is the consideration of background concentrations of these compounds in the tissues of humans and wildlife and a determination of whether these environmental concentrations are biologically important or relevant. Use of biomarkers will improve both the sensitivity and specificity of epidemiological studies, but will also require that markers be rigorously established and validated in laboratory studies and reflect the consequences of low dose exposures of interest. The interpretation of such data will present a challenge from both a toxicological and epidemiological perspective. This will be particularly important with respect to the development of guidelines and methods to account for the multiple confounding factors that typically must be considered in

epidemiological studies. Of particular importance is the consideration of background concentrations of these compounds in the tissues of humans and wildlife and a determination of whether these concentrations are biologically important or relevant.

Within the public health decision process, it is imperative that more certainty is built into the decision process. This means identifying and conducting research on those policy-critical data that add information to the body of scientific literature and that clarify the health implications from chemicals found in the environment.

Finally, it is important to note that rapidly emerging growth in genomics and proteomics (i.e., toxicogenomics) is certain to substantially influence the field of toxicology in the coming years. This will permit the rapid testing of chemicals for toxicity while reducing the number of animals required for testing, as well as improving scientists' ability to determine the sequence of events at a truly molecular level. However, at present, numerous questions surround this technology, not the least of which involves whether gene changes at low doses represents the first indication of a toxic response. In addition, it is unknown how results of microarray testing might eventually apply to risk assessment of chemicals. Consequently, while toxicogenomics undoubtedly represents the future of toxicology, at the present time, RFHEE will critically monitor progress in this evolving field to determine when it might prove useful in answering key questions about chlorine chemistry in the future.

RESEARCH THEMES:

RFHEE intends to partner with others, including governmental agencies and other organizations, to examine and understand the potential health impacts for key chlorinated

compounds, which might include TCDD and dioxin-like compounds, other PBTs, water disinfection byproducts, and other key non PBT chlorinated compounds. RFHEE is particularly interested in supporting projects that:

1. Contribute to determining whether exposures to key chlorinated compounds found in the environment impact reproductive, developmental, immune, thyroid, and/or neurological functions in humans and/or wildlife.
2. Contribute to the understanding of the mechanism of action for key chlorinated compounds, including: TCDD and dioxin-like compounds, PBTs, water disinfection by-products, and short-lived chlorinated compounds.
3. Contribute to the development of relevant data to clarify the biological pathway for health endpoints of concern.
4. Contribute to clarifying whether chlorinated compounds in the atmosphere play a role in adversely impacting health.

CANDIDATE PROJECTS:

SEE SEPARATE LIST

¹ NRC, *Hormonally Active Agents in the Environment*, p1., 1999.

² CDC, *National Report on Human Exposure to Environmental Chemicals, Frequently Asked Questions*, March 21, 2001.