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Workshop 6.1

Risk management options for endocrine disruptors in national and international programs*

James C. Lamb, IV[1], Herman B. W. M. Koëter[2], Richard Becker[3], Andreas Gies[4], Les Davies[5], Tohru Inoue[6], Abigail Jacobs[7], Gwynne Lyons[8], Mitsuo Matsumoto[9,‡], and Gary Timm[10]

[1]BBL Sciences, BBL, Inc., Reston, VA 20190, USA; [2]Organization for Economic Cooperation and Development, Paris, France; [3]American Chemical Council, USA [4]UBA, Germany; [5]Department of Health and Ageing, Australia; [6]NIHS, Japan; [7]U.S. Food and Drug Administration, USA; [8]World Wildlife Fund, UK; [9]Chemical Management Policy Division, Ministry of Economy, Trade and Industry, 1-3-1 Kasumigaseki, Chiyoda-ku, Tokyo 100-8901, Japan; [10]U.S. Environmental Protection Agency, USA

Abstract: This workshop was convened to address common issues and concerns associated with risk management of endocrine-disrupting chemicals (EDCs). The talks described the tools and policies for key Japanese, Australian, German, and U.S. regulatory agencies. The agencies participating in the workshop were responsible for the regulation of various substances including: chemicals, pesticides, environmental contamination, pharmaceuticals, and food additives. The panel also described the role of the Organization for Economic Cooperation and Development (OECD) in standardizing the tools and validation of testing and screening methods. The panel also included nongovernmental organizations presenting the views of the World Wildlife Fund, and the chemical industry from industrialized nations; each organization described its concerns and proposed approaches to risk management of EDCs. This summary highlights the most important areas of common points of view of government, industry, and environmentalists. We also try to identify issues upon which viewpoints diverge.

GOVERNMENT AGENCY VIEWPOINTS

The presentations in this workshop discussed governmental authority to regulate chemicals, pesticides, food additives, drugs, and contaminants in the air and water. Concerns were expressed for the potential risks to both wildlife and humans of exposure to endocrine active substances (EASs).

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‡Corresponding author

Japan

In his presentation on certain aspects of the Japanese government efforts, Dr. Inoue explained that little is known about the experimental evidence for human effects of EDCs [1]. Data gaps are most pertinent in exposure monitoring and understanding of the dose–response relationship. He explained that the relevance of the low-dose effects issue, if any, must be better understood. He noted that this may also lead to a better understanding of issues relating to additivity and synergism. He further informed the meeting attendees of the Japanese Intergovernmental Agencies cooperation on the EAS issue, and the extensive research efforts being undertaken by the Japanese government. He acknowledged that the evidence of human health effects for EASs is uncertain at this time, and that considering the biological plausibility of such effects, human data should be a major focus of future research.

In his talk and paper [2], Dr. Matsumoto gave a full overview of all Japanese government-sponsored research activities in the endocrine disruptor (ED) area. The Ministry of Economy, Trade and Industry (METI) facilitates trade activities, while the Ministry of Health, Labour, and Welfare (MHLW) promotes human health and worker safety. The Ministry of the Environment (MoE) is responsible for environmental protection, the Ministry of Agriculture, Forestry and Fisheries (MAFF) covers natural resources and food safety, and the Ministry of Education, Culture, Sports, Science and Technology (MEXT) promotes basic studies and research. Japan has formed an inter-ministry collaboration body that brings the efforts of these ministries to promote efficient use of resources and appropriate risk assessment and risk management.

Germany

Dr. Gies provided his view of the German and European perspective on EAS regulation. He explained in his talk and manuscript [3] the plans for the new European Directive for new and existing chemicals. Chemical production is growing faster than the population. He described evidence on imposex in snails and endocrine disruption in fish as evidence of adverse effects in wildlife from EDCs. Effects are reported worldwide and include population effects. In his opinion, environmental effects could be considered as early indicators of human effects. He reported to the meeting that there is a candidate list of more than 500 suspect EDs. He described changes in chemical regulation under the European Union's New Chemical Policy that shifts the burden of proof to the manufacturer. He called for intensified research, increased coordinated monitoring programs, facilitated flow of information, and promoted improvements to quantitative risk assessment, especially the use of wildlife data as a model for humans and vice versa.

Australia

Dr. Les Davies, of the Office of Chemical Safety, TGA Department of Health and Ageing, explained the current legislation in Australia [unpublished presentation] and focused on a few cases including the exposures of sheep to contaminated clover, resulting in infertility in sheep. Many of the issues that have concerned the Office of Chemical Safety have included contamination of veterinary feed, foods, and industrial chemicals. Australian chemical regulatory agencies support the improved screening and testing for potential EDCs. However, endocrine activity is one of many chemical or biological properties of concern, and other mechanisms can also be affected by excessive exposure. He mentioned that an extensive package of tests required for drugs, pesticides, new HPV chemicals, and food additives is unlikely to miss any ED effect. The Australian government is concerned about the protection of the environment and of public health as it is intimately related to the environment.

United States

The United States government's approach to regulating EASs was described for two regulatory agencies, the U.S. Environmental Protection Agency (USEPA) and the U.S. Food and Drug Administration (USFDA).

Dr. Gary Timm of the USEPA ran through U.S. laws that deal with chemicals [unpublished presentation] and informed the meeting that risk management of EDCs as a unique category is not yet done in the United States. There are 12 major laws that apply to the regulation of chemicals in the United States. Some of these laws (e.g., Toxic Substances Control Act, Federal Insecticide Fungicide and Rodenticide Act, and Federal Food Drug and Cosmetic Act) focus on the manufacture, distribution, and use of substances or products. Other laws (e.g., Clean Air Act and Clean Water Act) limit or control emissions or releases into the environment, and some laws (e.g., Resource Conservation and Recovery Act) address the damage already caused by releases. Each law has unique criteria for determining acceptable risk, and for managing that risk.

Risk is the driving element in the U.S. legislation, and this does not leave much room for the precautionary principle. Risk concepts in the United States in some cases include the consideration of benefits in a risk-benefit balancing formula. Such a method is applied to the registration of pesticides under FIFRA or management of chemicals under TSCA. In other cases, risk is the only criterion, and reasonable certainty of no harm is the standard applied under most of the Federal Food Drug and Cosmetic Act (FFDCA). The USEPA has found that the current state of the science does not support a special consideration of the low-dose hypothesis in the risk assessment or risk management process. While encouraging further research, the risk management process takes no specific account of this controversial area.

The current issues related to drug research and approval in the United States were presented by Dr. Abigail Jacobs and are described in her manuscript [4]. For drugs, there is no standard nonclinical battery of tests. She noted that in vitro tests can be useful in understanding the mechanism of action, but that even for EASs, in vitro studies were not necessarily of predictive value. Dr. Jacobs discussed many of the technical issues, such as the choice of test tissue, choice of receptor, and details of the test system. If there are risk issues, they can be solved in various ways. For drugs, warnings and precautions may be sufficient risk management techniques, because of the voluntary and relatively controlled nature of the exposure. In conclusion, an endocrine signal is not considered equal to a risk, and each case is evaluated on its own merits. The risk–benefit assessment is the paramount consideration for the USFDA and drug evaluation.

ROLE OF THE ORGANIZATION FOR ECONOMIC COOPERATION AND DEVELOPMENT (OECD)

Dr. Koëter of the OECD gave an overview of the EDTA (Task Force on Endocrine Disrupters Testing and Assessment) work and explained in detail the recently accepted conceptual framework for testing and assessment, comprising five levels [5]:

1. sorting and prioritization
2. in vitro assays providing mechanistic data
3. in vivo assays about single endocrine mechanisms
4. in vivo assays providing data about multiple endocrine mechanisms
5. in vivo assays providing adverse effects data from endocrine and other mechanisms

He described several of the test methods being evaluated for potential value in assessing EDCs. He also presented a list of reference chemicals for estrogenic agonism and antagonism, androgenic agonism and antagonism, thyroid agonism and toxicity, and aromatase and 5 α-reductase inhibitors.

He further mentioned the "Share the Burden" program that would allow countries to use data and assessments developed by other countries. He explained that risk management is driven by risk assessment, science, economic factors, social factors, and cultural factors.

The OECD is managing several complicated and aggressive programs designed to improve and standardize testing and assessment methods. Many nationalities are participating actively in these exercises.

ENVIRONMENTALIST ORGANIZATION VIEWPOINT

Dr. Lyons of the World Wildlife Fund (WWF), in her presentation and paper [6], put emphasis on the European legislation. She argued that the precautionary principle should be applied to EDCs. In the current proposal, the decision-making process does not really apply to this principle. She made a plea for enforcement of the use of substitute chemicals for endocrine disruptors, when available. The availability of substitutes should be grounds to refuse authorization. She criticized the European Community (EC) by moving away from minimal risks to acceptable risks. She made the following conclusions:

- The existing regulatory policy does not protect adequately health and the environment.
- It is too onerous a burden for regulators to prove unacceptable risk.
- Only 12 persistent organic pollutants (POPs) and a few other chemicals have been phased out in most countries.
- There is a need for a new paradigm toward comparative risk assessment, in order to find safer alternatives to EDCs.

She also presented views on the European Union (EU) Authorization Process and presented reasons to change the current conditions of the process.

INDUSTRIAL VIEWPOINT

Dr. Rick Becker's presentation and paper [7] on behalf of the American Chemistry Council, the European Chemical Industry Council (CEFIC), and Japan Chemical Industry Association, emphasized that endocrine disruption should not be considered as an endpoint for classification and, in fact, as such not as an adverse effect but as a mechanism. He stressed that the relative potency of EDCs would be an important element to consider in risk assessment. He presented the view that the risk management process should be based upon risks and benefits, considering certain alternatives and societal concerns. The risk assessment process is based upon collecting data and reviewing and assessing hazard potential, then reviewing and assessing exposures. Risk assessment includes evaluating individual and population effects. He noted that work needed to be done to identify representative taxonomic groups for the environmental assessment.

Dr. Becker described a holistic process for looking at EASs and potential adverse effects. The guiding principles and efforts of the international chemical industry-sponsored Long-Range Research Initiative (LRI) were described. Dr. Becker also proposed a process for dealing with nonvalidated, new, and novel methods or data.

CONCLUSIONS

Though not unanimous on all points, this diverse workshop demonstrated areas of considerable agreement and focus. Divergent viewpoints have also been highlighted by the papers, presentations, and this review. No one should expect such complicated and important issues to be quickly or easily resolved. Significant political or cultural differences were evident by the various organizations, and the needs of

different regulatory systems. Research efforts have been extensive and successful in many areas. That research is being increasingly applied in the risk assessment and risk management processes.

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