

The WHO/UNEP/ILO International Programme on Chemical Safety (IPCS) Global Assessment of the State-of-the-Science of Endocrine Disrupting Chemicals (EDCs)

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Thank you, Mr. Takei. On behalf of my coauthor, Dr. Terri Damstra from the IPCS, who could not be here to make this presentation, I would like to express the honor to be able to come here and give the keynote address, and to talk about a project that has been ongoing for the last several years entitled "The Global Assessment for the State-of-the-Science of Endocrine Disrupting Chemicals." I think it is apropos that the first public presentation of the completed product be at this meeting sponsored by the Ministry of the Environment here in Japan.

Work on the project began about five years ago, when the International Forum on Chemical Safety made a recommendation that there should be approaches and means to coordinate and support the development of an international inventory of research and also the coordination of testing and assessment strategies around the world.

As a result of that recommendation for the International Organization for the Sound Management of Chemicals, OECD was given the lead for test method development and validation, and yesterday you heard a session on the progress that has been made there.

The IPCS, the International Program on Chemical Safety, was given the lead for the state-of-the-science assessment.

The actual charge to the IPCS was twofold.

The first was to create an inventory of research that was ongoing around the world. That was completed about two years ago and is available on the internet.

The other project, which was a lot more substantial in nature, was to create a review of the current state-of-the-science on endocrine disrupters. As a result of that effort, it was hoped that that would provide recommendations for research around the world, and also to promote international coordination around the world on research activities.

So, where are we at in this process? Almost exactly four years ago, a 14-member steering group of international experts was convened by the IPCS. They have liaisons from both the OECD, from UNEP, and from the Joint Research Center of the European Commission. We met seven times over the last four years, and developed an outline of the review, selected authors for writing various parts of it, reviewed the early drafts, and also harmonized the text and expanded where necessary to add additional information.

Over 25 scientific experts around the world were invited to participate in the process. And only one author that we asked to contribute actually said they could not afford the time to do so.

The document reviewed more than 1,500 scientific publications. A draft was completed in October 2001 and was sent out for external scientific peer review. There are about 30 scientists around the world now who have the document and who are making comments. Those comments are due back to the IPCS at the end of this month, and then there will be one final revision incorporating those comments.

It is expected that it will be published by the WHO in early 2002. It will also be available on the internet as soon as that happens.

This is the steering group who helped develop the document in one of its happier days as we finished reviewing the final draft at our 7th meeting in d'Orta, Italy in July 2001. I just want to point out a few members of the steering group. Terri Damstra, who is from the secretary of the IPCS is here, this is

Larry Reiter who was the chair of the group, he is from the U.S. Environmental Protection Agency, and I think most of you know Tohru Inoue, who was the delegate from Japan.

This is a list of the authors who participated in the process. I will not go through their names. Many of them have participated in one of the four international symposiums that you have had here. They are from around the world: Great Britain, Sweden, Canada, France, Japan, Germany, Mexico, Argentina, and the Netherlands. So it really does represent an international perspective on the issue.

The book is divided into eight chapters, and they are listed on the left here. Each one of these chapters had a member of the steering group, a coordinator who was responsible for working with the authors and bringing additional information to the text when the steering group noticed there were certain gaps in the information.

It begins with an executive summary. Chapter 2 is a background and introduction to the general issue. Chapter 3 discusses endocrinology and endocrine toxicology. Chapter 4 deals with effects in fish and wildlife. Chapter 5 deals with human health. Chapter 6 deals with exposure issues related to endocrine disrupters. Chapter 7 develops criteria for how we can begin to assemble the information that has been generated into actual cause and effect relationships. Finally, Chapter 8 has the general conclusion and research recommendations.

As the talk proceeds, I will walk you through each one of the chapters and give you a little bit more detail of what is contained in them.

Before that, let me give just a little bit of a background material. The document was intended to build on existing assessments; and it actually references 32 such reviews that have already been produced by various governments or organizations around the world.

It is limited to publicly available information on both human and wildlife effects. To the extent possible, it emphasized the attention to global concerns. And as I mentioned, it will be published as a peer-review document and hopefully will be a basis for fostering additional collaborations.

Importantly, there are a few things, which it is not: it is not a risk assessment document; it does not go into individual chemicals and identify NOELs and safety factors. It does not review screening and testing strategy because that subject is being covered by the OECD on a parallel track. Nor does it try to cover all potential endocrine targets, of which there are many in the body, but it does try to cover the principal ones, which have been implicated in the environmental causes of disruption of life.

The document has a definition — like we all probably do — for endocrine disrupters. The definition is important because when we go and start to then assess whether a chemical or a situation or an outcome is due to an endocrine disrupter, it is important that the conditions fulfill the definition, which is: “An exogenous substance or mixture that alters the function of the endocrine system and consequently causes adverse effects in an intact organism or its progeny or subpopulations.” The definition is very similar that developed by the European Union at the Weybridge meeting several years ago.

A potential endocrine disrupter would be: “A chemical that possesses properties that might be expected to lead to endocrine disruption in an intact organism, but for which that evidence is not yet available.” That would include, for instance, studies from *in vitro* systems.

Now I will begin to talk in a more detail about what is in the chapters.

Chapter 2 contains the introduction and background. Basically, it provides the foundation and overview for the issues to come in later chapters. It talks about the endocrine system being responsible for homeostasis in the body and how because of its nature in the programming of physiological systems that the developing life stages tend to be very sensitive to exposures.

It talks about the fact that many of these systems have cross talk with one another, so what happens in the thyroid system may affect what happens in the adrenal system, which then may affect the gonadal

system. It talks about the fact that there are multiple sites through which endocrine disrupting chemicals may affect an individual or an organism.

It talks about the fact that there are multiple mechanisms involved and can be either receptor or non-receptor based. We have heard references throughout this meeting to some of these issues.

It notes that these chemicals may be man-made as well as natural, that there could be direct as well as indirect effects on the body, and that it is important to understand the whole process leading to disease when looking at the situation.

It recognizes that while we may know something about the interaction of events at the receptor system, we often times do not understand what those downstream events are; we are just left with a phenotype. Some of the toxicogenomics information that is coming out may help us understand those intermediary events.

Dose response relationships for endocrine disrupting chemicals, as you well know, may be complex, and we may need to view these in a special relationship. There are populations around the world, which show heterogeneity in response, and therefore, there must be some genetic or environmental factors involved with that, and we need to understand them.

A number of people have mentioned in this meeting the lack of exposure information, both from environmental monitoring, as well as for internal dose to the affected target organ, and that gets to be a very strong limitation in trying to evaluate where we are in terms of causality.

Chapter 3 deals with the endocrine system and an introduction to endocrine toxicology. It focuses on the hypothalamic-pituitary-gonadal axis, primarily in mammals, but it also covers various vertebrate classes, and it addresses some aspects related to the adrenal axis as well as the thyroid axis. Where appropriate, it also addresses endocrine targets in other species such as the invertebrates.

A large part of this chapter is devoted to looking at modes of action and phenotypic outcomes using the reproductive system as a primary target. It takes examples for the androgen receptor, the estrogen receptor, the Ah receptor as well as steroid biosynthesis, and presents an understanding about how those particular modes of action affect the development of the reproductive tracts.

It also addresses what we know about mechanisms for neurotoxicity, immunotoxicity, and carcinogenicity, but clearly the amount of information available for those health endpoints is less than for reproductive effects.

Finally, the Chapter 3 discusses certain aspects of scientific analysis, which are important for looking at how a chemical might be an endocrine disrupter. It emphasizes the need to look *in vivo*, that it is important to look at multiple levels of organization, from molecular to biochemical, from tissue level to whole organism, and that it is important (at least in some levels) to look at the direct effect of altered hormone action so you can understand how the endogenous hormones are being affected.

It is important to look at dose response relationships for these chemicals, and to consider what is the analogy to phenotype to pharmacological effects: if we have a known anti-thyroid agent, for instance, are we seeing a phenotype that is similar to that.

The issue of life stage sensitivity is well known to you all and is something oftentimes demonstrated in endocrine disrupting chemicals.

Another line of evidence can be provided by trying to restore an altered phenotype by pharmacological manipulation: if it is an anti-androgen, can you reverse that effect by treating it with an androgen? Finally, you may have supporting *in vitro* data that will help you with your assessment.

Turning to the chapters that deal with outcome. Chapter 4 specifically deals with fish and wildlife. It covers all taxonomic categories, from invertebrates through marine mammals, and focuses on what are the unique aspects in the life history of each one of the taxa. It contains discussions in terms of what is the

reproductive strategy that they employ, what trophic level are they located on, and aspects about the local environment that may make them more or less susceptible to an exposure.

It talks about effects on both the individual level, which may be studied in laboratory situations as well as population level effects, which have to be studied in ecosystems.

For each one of the taxa we provided case examples of endocrine disrupters. The chapter concludes with statements on the underlying uncertainties and data gaps for each one of the taxa.

Chapter 5 deals with human health concerns, and it is the largest chapter in the book – about 95 pages of text without references or figures. It covers both human and experimental studies, and has sub-issues dealing with reproductive and developmental effects, neurobehavioral effects, immunological effects, and cancer. Because of the amount of information covered, it is difficult to summarize the contents in this brief talk.

Chapter 6 deals with exposure issues. We made a strong effort to look for what are the available data sets around the world for both monitoring of environmental exposures as well as issues related to internal dose, and we recognized that there really is a paucity of long-term monitoring data. This is particularly true in developing countries and also as relates to children's health.

Where we could, we focused our attention on those chemicals and situations, which were highlighted for effects in Chapters 4 and 5. It gives a discussion on the methodologies needed to do exposure assessment for endocrine disrupting chemicals, for instance, the fact that the timing of exposure is an important issue and how that tends to complicate interpretations of exposure.

It discusses what are some of the sources and pathways through which these chemicals may move through the environment, and then has a few case studies, primarily with persistent organic pollutants and how environmental monitoring has proceeded.

Chapter 7 deals with the development of criteria for endocrine disrupting chemicals, and was a rather late addition to the volume when we realized that it was not sufficient to just leave the document with Chapters 4, 5 and 6, which are a straight state-of-the-science reviews. Instead, we felt it was important to assemble and integrate that information into a bit more of a scientific assessment, so we tried to develop criteria for which we could actually do that. The criteria recognize that there are multiple lines of evidence that are dealt with in terms of endocrine disrupting chemicals: some may come from laboratory studies, some may come from epidemiology studies, and some may come from studies in wildlife. It is important to integrate all this information together.

Although the chapter coordinators made efforts to harmonize the text between chapters, the fact that we had multiple authors tended to indicate that the different levels of organs or endpoints or outcomes were addressed in different detail throughout the document, so Chapter 7 was also an attempt to even out the interpretation and give something in a more standardized format.

The criteria allowed us to focus on what were the underlying biological alterations between an exposure and an adverse outcome, so we really could begin to look at cause and effect relationships. They also allowed us to make a determination about the overall coherence of the evidence, and the strength of the evidence, that a particular situation was or was not likely to lead to an alteration in the endocrine system.

Through this rigorous process and you can also identify where research would actually help you identify cause and effect relationships better.

So what does a causal framework look like? First of all, this is adopted loosely from the "Hill Criteria" that were published in 1964. It begins with the statement of a hypothesis, both for the outcome of concern — that is the health outcome or the wildlife effect that you are looking at — and the stressor (or chemical) that you believe is involved in the action.

It, then, goes through a five-step process to look for the evaluation of scientific evidence, addressing aspects of temporality, the strength of the association, the consistency of the observations in the literature, the biological plausibility, and the evidence of recovery. Finally, then, it concludes with an overall strength of evidence interpretation, first for the outcome stress relationship: was there an association there, and then if that association can be based on endocrine disrupting mode of action.

The strength of evidence evaluation was a consensus opinion of the steering committee and is subject to new information as it becomes available as well as to other people's interpretation of the information.

This is a little bit more detail about what the criteria are.

In terms of temporality, there is the outcome of concern: is it preceded by the appearance of a stressor in the environment.

In terms of strength of the association, we looked at the incidence rate that was observed, what other known risk factors existed that could be attributable to that exposure, and the shape of the dose response curve, or how strong was the effect.

In terms of consistency of observation, we looked to see whether there were similar or dissimilar conclusions were reached by different investigators, were they the same in some geographical areas, were they going across species, and was there a dose-response pattern available.

Biological plausibility related to the definition of endocrine disrupter, really deals with whether we understand the mode of action in the organism.

The last aspect of the criteria dealt with recovery, or the tendency for the adverse outcome to lessen in severity or incidence when the exposure is reduced from the environment.

What I will quickly try to do is give you two examples of how we applied these to case studies. One concerns wildlife: we heard this morning a talk about tributyl tin and the induction of imposex in gastropods, and also I will give you one example from human health, which is the impaired neurobehavioral development related to the endocrine disruption mediated by exposure to PCBs. For both of those you can see there is a statement of the effect as well as the hypothesized mechanism.

In the actual chapter, these will be aligned in a table, and the strength of the evidence was indicated by a star system: with four stars being the strongest evidence, which we felt could be available and one star an indication that the evidence was relatively weak.

For imposex from TBT, the strength of the evidence is fairly strong across all elements of the assessment with the only question about the biological plausibility because it is not exactly clear what is the actual mechanism of action. Because of the talk this morning I will not go into detail on each one of these aspects.

In terms of neural development and PCBs, the strength of the evidence is a little bit weaker. For temporality, the evidence was pretty strong. Strength of the association was weaker, primarily because of the differences in effects that have been seen between several high dose exposures in certain populations here in Asia vs. the environmental levels, which we have been studied in populations in the U.S. and Europe.

Consistency of the findings was judged to be moderate, based upon the fact that there is not total consistency between the types of outcomes that have been found, particularly for the lower ranges of exposures. Biological plausibility was judged fairly good based upon mechanistic support from experimental animal models. There was no relevant data to judge recovery.

These two case examples can be summarized as follows: for imposex related to TBT, the strength of the hypothesis is strong and there is strong evidence that it is related to an EDC mechanism. For the impact of PCBs on neurobehavioral development in humans, the strength of the evidence for the effect

was moderate, as was the strength of the evidence that an endocrine disrupting mechanism was involved in the effect.

I might add that the assessment for PCBs about the endocrine mechanism does not diminish the fact or the impact of that outcome in human populations; it is just the result of applying the definition of an endocrine disrupter to that outcome that you are concerned with.

These are the other examples that we applied from the human health to the causal criteria. We did not do it for every single possible outcome, but we tried to take ones that had better examples developed in the text. We did it for endometriosis and PCB exposure, we did it for impaired immune function from PCBs, we did it for breast cancer and DDE, as you just heard, as well as for sperm quality related to unspecified exposure to estrogenic or anti-androgenic chemicals.

For wildlife, and we developed at least one case from each one of the taxa and we sampled situations from different areas of the globe. Thus, we have invertebrates, marine mammals, birds from the Great Lakes, and reptiles from Lake Apopka, and fish from the Great Lakes, the U.S., the UK, and Canada.

Chapter 8, the final chapter, contains the higher order general conclusions and research recommendations. The first general conclusion is that certain environmental chemicals can and have interfered with hormonal processes; however, a causal role for these chemicals in inducing human health effects is generally unverified.

On the other hand, there is sufficient evidence to conclude that adverse effects of endocrine mediated chemicals, or endocrine mediated modes of action have occurred in some wildlife species.

Lastly, there are data gaps concerning the effects of low levels of exposure of EDCs in populations, exposures during some early life stages, and epidemiological cause and effect relationships that need to be filled in so that we can understand better the actual consequences of exposure of populations to endocrine disrupting chemicals.

Several research gaps must be closed. The first is that we need to do a better job of understanding the underlying endocrine mediated effects caused by these chemicals. This will encompass knowing more about the basic endocrinology of a number of species and how those processes can be disturbed by chemicals.

As to methodologies, we are particularly in the need of sensitive biomarkers that can be used to study populations around the world and which can help shed light on what might be the responses in a low dose region.

In terms of monitoring, there needs to be strengthened international collaboration in order to improve the way we evaluate the environment. We may want to settle on certain sentinel species and do a coordinated assessment of them, and we also need to do a better job of comparing human health status around the world. You saw the controversies relating to hypospadias and cryptorchidism in the talk just about an hour ago.

We would all benefit by having databases developed that could put this information together. We could understand what are the global trends to both exposures and outcomes, and we could have good quality data while we debate these scientific issues.

We need to have better techniques for identifying endocrine disrupters, both for the persistent organic pollutants, the subject of the opening talk of this conference, as well as the non-persistent ones, such as the atrazine work on frogs that you heard this morning.

We need to do a better job at identifying endocrine disrupters and at looking for where are the hotspots in the world so that we can begin to focus on looking at both exposures and effects, and to identify what are some of the more sensitive subpopulations following exposure.

Lastly, we need to put endocrine disruption in the context of the overall health of the humans and the environment as we heard about in previous discussion today.

I conclude with the website. It is housed at the Joint Research Center, which is part of the European Commissions laboratories in Ispra, Italy. At this website you can read the notes for all of the seven steering group meetings. As soon as the document is ready it will be put on a PDF format and posted on this site. It will be published, we hope, in early spring of 2002.

I thank you for your attention.

Q&A

Takei: Thank you, Dr. Kavlock. We have some time for one or two questions or comments.

Takei: Thank you. Any comments or questions? All right, let's move on. Thank you, Dr. Kavlock.

Q: Could you expand on the perceived inconsistencies in the PCB data? Because as far as I know, all of the studies at lower levels are consistent, at least in terms of finding of facts although some of the details may differ. Starting with the Michigan study, but then even the lower levels — the Dutch and the German, I saw that Gerhard was on the panel — and now the Oswego study, these are all positive studies.

It is not even one of those cases where there are some studies positive and some studies negative, although there may not be absolute consistency within studies on some of the tests, for example, the German study was negative with respect to the early memory of infants.

So which is it? Is it that everything is not absolutely consistent, or is there something that I have missed?

Kavlock: No, you are right, it was dealing with the consistency of the findings between the studies: some reported motor deficits, some reported sensory deficits. They were all positive in some aspect of neurobehavioral development.

Q: I guess I find that disturbing that that is the conclusion of the committee. Because that is the same thing that went on with respect to lead for many years, where there were really well designed, good prospective studies ongoing, and certain people would say, "Well, this study found an effect on the Bayley PDI but not the Bayley MDI, therefore, it is inconsistent, therefore, there is no evidence that lead produces adverse effects in kids." I would sure be disappointed if we were headed down that same road with respect to PCBs.

Kavlock: I will take your point back to the steering committee.

Q: Thank you.