Asia-Pacific
Economic Cooperation

FINAL REPORT

REGULATORY COOPERATION – INTRODUCTORY LEVEL TRAINING ON RISK ASSESSMENT AND RISK MANAGEMENT TO PROVIDE TOOLS FOR THE DEVELOPMENT OF SOUND CHEMICAL REGULATIONS

APEC Committee on Trade and Investment
Chemical Dialogue/Regulators Forum

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REGULATORY COOPERATION – INTRODCTORY LEVEL TRAINING ON RISK ASSESSMENT AND RISK MANAGEMENT TO PROVIDE TOOLS FOR THE DEVELOPMENT OF SOUND CHEMICAL REGULATIONS

November 7-8, 2012
Chulabhorn Research Institute
Thailand

Project Overseer:
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S CTI O5 12 (CD) REGULATORY COOPERATION – INTRODUCTION LEVEL TRAINING ON RISK ASSESSMENT AND RISK MANAGEMENT TO PROVIDE TOOLS FOR THE DEVELOPMENT OF SOUND CHEMICAL REGULATIONS

TABLE OF CONTENTS

BASIC DATA

The project provided an introductory level training on risk assessment and risk management of chemicals to regulators in the APEC region. The goal was to increase the capacity on risk assessment and risk management of chemicals, so that regulatory approaches in the region are developed in a sound manner and, in the long term, facilitate the trade of chemicals among economies in the region.

The project consisted of a two day training workshop on risk assessment and risk management, where technical and scientific approaches and tools to conduct risk assessments were discussed, as well as how data analysis leads to risk management approaches. The workshop also provided a forum to exchange experiences by economies in the region that use these tools and approaches.

The two day training workshop on risk assessment and risk management took place at the Chulabhorn Research Institute in Bangkok, Thailand, on November 7 and 8, 2012. The agenda is included in Appendix I.

VENUE: CHULABHORN RESEARCH INSTITUTE

The Chulabhorn Research Institute was founded by Professor Dr. Her Royal Highness Princess Chulabhorn Mahidol, the youngest daughter of Their Majesties King Bhumibol Adulyadej and Queen Sirkit of Thailand, with the purpose of assisting in the development of Thailand by highlighting the role of science in social and economic development.

The Chulabhorn Research Institute is currently working to develop a distance learning tool for the assessment of risk from the use of chemicals to support capacity building efforts in developing countries. The aim of the distance learning tool is to develop capacity building materials on risk assessment of chemicals for Thailand and other Asia-Pacific countries under the Strategic Approach to International Chemicals Management (SAICM). During the APEC workshop, economies were introduced to the draft distance learning tool, and invited to participate in the efforts to finalize the development of the tool, as well as to use it in their capacity building activities.

The Chulabhorn Research Institute also has the ability to host technical trainings in their facilities. They developed the information for participants and provided all the logistical support for the meeting. Their facilities allow for hosting a lecture style workshop of about 40 participants and also have break out rooms for group discussion. A highlight of the workshop was the implementation of the paperless concept, thanks to the ability of the Chulabhorn Research Institute to provide internet access and make computers available to all participants all training materials were available on line. Through the dedicated website, participants were able to access the workshop materials during the training, as well as download the materials once they were back at their home offices.

Participants were welcomed to the workshop by Dr. Mathuros Ruchirawat, Vice-president for Research and Academic Affairs of the Chulabhorn Research Institute, who emphasized the need for improving capacity and cooperation among chemical regulators in the region, particularly in developing economies, in the area of risk assessment and risk management of chemicals. Appendix II contains the welcoming remarks by Dr. Ruchirawat. As the Vice-president for Research and Academic Affairs, Dr. Ruchirawat directs the research in nine laboratories in Chemistry and Biomedical Science, as well as planning and initiating integrated research programs; in addition, Dr. Ruchirawat is responsible for directing and implementing an innovative post-graduate educational program and short-term training programs in the areas that are of urgent need in Thailand and in developing countries in Asia-Pacific region. Dr. Ruchirawat has a B.Sc. in Life Sciences from the University of Liverpool, England, and a Ph.D. in Nutritional Biochemistry and Metabolism from the Massachusetts Institute of Technology, Cambridge, MA, U.S.

WHO HUMAN HEALTH RISK ASSESSMENT TOOLKIT

The WHO developed the human health risk assessment toolkit to provide users with guidance to identify acquire and use the information need to assess chemical hazards, exposures and the corresponding health risks in their given health risk assessment contexts at the local and/or national levels. The toolkit provides a roadmap for conducting a human health risk assessment, identifies information that must be gathered to complete an assessment, and provides links to international resources from which the user can obtain information and methods essential for conducting the human health risk assessment (http://www.who.int/ipcs/publications/methods/harmonization/toolkit.pdf).

The APEC workshop training was based on the WHO toolkit, as well as risk management tools identified by OECD and included in the IOMC toolbox for decision-making in chemicals management (http://www.who.int/iomc/toolbox/en/index.html). Finally, a module on risk communication was added to the workshop to address some of the interest identified by participants before the workshop.

STEERING COMMITTEE

As part of the project, a steering committee was convened to provide overall direction to the planning of the workshop. The steering committee held conference calls and commented on documents by email. The steering committee provided the overall concept for the workshop, an objective, tentative program, and identified the ideal profile for the participants. The materials developed by the steering committee then were finalized by the group of experts that delivered the workshop. The steering committee included representatives from Australia, Chinese Taipei, Malaysia, Mexico, New Zealand, the Philippines, Thailand, U.S., Viet Nam and WHO. Some of the experts also participated in the steering committee discussions. The roster of the steering committee is included in Appendix III.

EXPERTS

A group of experts was identified to deliver the workshop. Dr. David MacIntosh was the principal expert who adapted the WHO toolkit concepts to the workshop concept developed by the steering committee, and through consultations with the other experts/speakers, developed the final agenda and training materials. David L. MacIntosh, Sc.D., C.I.H, is Chief Science Officer at Environmental Health & Engineering, Inc. (EH&E) in Needham, Massachusetts. Dr. MacIntosh oversees the scientific aspects of projects conducted by scientists, industrial hygienists, and engineers who specialize in diagnosing and analyzing the complex relationships among sources, pathways, and receptors of environmental stressors that influence health in the built environment. His recent activity has focused on problematic building materials, ambient air quality, heavy metals, naturally occurring radioactive materials, persistent organic pollutants, and risk analysis training materials. Dr. MacIntosh is also an Adjunct Associate Professor of Environmental Health at the Harvard School of Public Health where he teaches a course on exposure assessment. Prior to joining EH&E, Dr. MacIntosh was a tenured faculty member at the University of Georgia. He earned a doctorate in Environmental Health from the Harvard School of Public Health and a M.S. and B.S. from Indiana University. Dr. MacIntosh is active in professional service through organizations such as the International Society for Exposure Science, the Centers for Disease Control and Prevention, and the World Health Organization.

Dr. Lynn Panganiban further developed the materials on hazard identification and presented the topic at the workshop. Dr. Panganiban is the Chair of the Department of Pharmacology and Toxicology at the University of the Philippines, College of Medicine. In addition, she is a consultant with the National Poison Management and Control Center of the Philippine General Hospital and a consultant with the Environmental and Occupational Health Office of the National Center for Disease Control. Dr. Panganiban is also a member of the Interagency Committee on Environmental Health of the Department of Health, the Pesticide Technical Advisory Committee of the Fertilizer and Pesticide Authority, and of the roster of experts on the

Globally Harmonized System (GHS) of UNITAR/ILO. Dr. Panganiban holds a Doctor of Medicine and a Bachelor of Science in Zoology from the University of the Philippines.

Similarly, Dr. Salmaan Hussain Inayat-Hussain further developed the materials on hazard characterization and presented the topic at the workshop. Dr. Inayat-Hussain is the Dean of the Faculty of Health Science of the Universiti Kebangsaan Malaysia, and is also a Professor of Toxicology at the Environmental Health Program. Dr. Inayat-Hussain has extensive experience in academia, as well as capacity building in the private and public sectors, having been a visiting research associate at the University of Colorado Health Science Center in the U.S., the Chief Executive Officer of Melaka Biotechnology Corporation in Malaysia, as consultant in the Regional Capacity Building Program for Health Risk Management of Persistent Organic Pollutants in South East Asia (a project funded by the World Bank), and as an adviser for the development of the WHO Human Health Risk Assessment toolkit. Dr. Inayat-Hussain received his Ph.D. in Biochemical Toxicology at the University of Leicester in UK and a B.Sc. in Pharmacology from the Universiti Kebangsaan Malaysia.

The third speaker was Dr. Mario Yarto, who further developed the materials on risk management and risk communication and conducted a discussion on those issues at the workshop. Dr. Yarto is currently an independent environmental consultant, working internationally with UNITAR on projects related to their Chemicals and Waste Programme, UNEP chemicals (SAICM Secretariat, Stockholm Convention Secretariat and Mercury Programme), and the Commission for Environmental Cooperation. Dr. Yarto's experience includes project coordination, technical assistance and training on POPs, PRTR design and implementation, SAICM implementation and the sound management of mercury waste. Dr. Yarto's experience also includes membership on policy, scientific and technical international working groups, such as the Persistent Organic Pollutants Review Committee, the chemicals Review Committee of the Rotterdam Convention and the OECD Working Group on Pesticides. Previously Dr. Yarto was the Director of Research on Chemicals and Ecotoxicological Risks at the National Institute of Ecology of the Ministry of Environment and Natural Resources in Mexico. Dr. Yarto holds a Ph.D. in Chemistry, with a specialization on Instrumentation and Analytical Science from the University of Manchester Institute of Science and Technology (UK), and a B.Sc. In Chemistry from the Instituto Tecnologico y de Estudios Superiores de Monterrey, Mexico.

Finally, the team of speakers also received support from Dr. Daam Settachan, at the Chulabhorn Research Institute, who was instrumental in providing the link between the logistic arrangements and the needs of the experts and participants, as well as provided support with the group discussions during the workshop. Dr. Settachan leads the laboratory of Environmental Toxicology and has been involved with the assessment of exposure to carcinogenic air pollutants in populations with increased susceptibility either due to life-styles, occupation, or through dietary sources; and also oversees the rodent inhalation and toxicity facility. Dr. Settachan is also a member of the faculty of the Environmental Toxicology program at the Chulabhorn Research Institute, and has been involved in the development of the distance learning tool on risk assessment based on the WHO Human Health Risk Assessment toolkit. Dr. Settachan holds a Ph.D. in Environmental Toxicology form Texas Tech University.

Appendix IV contains the list of experts.

PARTICIPANTS

The main audience for the workshop was chemical regulators in the region. The Steering Committee and the team of experts developed the following profile for the participants:

> *The organizers are seeking managers and supervisors with basic knowledge of toxicology, and fate and transport terminology, e.g. reference dose, daily intake, acute toxicity, chronic toxicity, pathways of exposure, etc. The goal is that the training may cover more advanced concepts on risk assessment and risk management, allowing regulators to discuss challenges they face during their daily work. Organizers are also seeking managers and supervisors that:*

• are responsible for developing or reviewing risk assessment documents related to industrial chemicals;

• have an ability to influence risk management decisions in their organizations and influence regulatory decisions of other organizations in the economy; and/or

• are responsible for communicating findings of risk assessments and risk management decisions to others in their institutions, across the government, to the regulated community or the general public.

Ideally, the participants will be able to apply the knowledge acquired during the training to their routine work, and share the knowledge with others.

While the main audience for the training is regulators in the region, please note that the training is also open to industry, academia and civil society groups interested in chemical regulations.

Participants were invited based on their previous participation at Regulator's Forum meetings, and the Chemical Dialogue also received an invitation. Funding was provided to two representatives from those economies eligible for funding that were nominated by the Chemical Dialogue or by a representative at the Regulator's Forum. In addition, the U.S. government provided travel support for two speakers and additional participants from Malaysia, Philippines, and Viet Nam.

The list of participants is included in Appendix V, the final numbers include: 42 participants (without including those representing the Chulabhorn Research Institute and the APEC Secretariat), 15 economies represented, representatives from industry from Thailand and the U.S., and the gender distribution of the group was 16 males and 26 females. The information provided to the participants is included in Appendix VI.

KEY OUTPUTS

TRAINING MATERIALS

The main output from the workshop are the training materials developed that allow for a quick review of basic risk assessment and risk management concepts, with two case studies to apply the concepts reviewed. As mentioned before, the materials are intended for an audience with some previous knowledge on toxicology concepts and needs a review of the concepts and how to apply them on regulatory activities related to chemicals management.

The training materials developed were divided in three main sections: an introduction (which included a general overview and a specific review of the concepts related to risk assessment and risk management), the risk characterization (which included hazard identification and characterizations, and exposure assessment), and risk management (which also included risk communication).

The following sections will provide a more detailed description of the materials. Copies of the training materials and reference materials used by the speakers are included in Appendix VII, the case studies used for group discussion are included in Appendix VIII. In addition, speakers provided reference materials to the participants, which are available at the paperless website but not included in this report due to the length of the documents.

INTRODUCTION

The introduction consists of two modules: the overview and concepts on risk management and risk assessment.

The purpose of the overview module is to provide a review of basic concepts. At the end of the review, the participants have an understanding of environmental health, the benefits of the chemical industry to the overall economy, as well as the potential significant harm and risk to health. Also, participants will be able to articulate that sound management of chemicals is essential to avoid significant risks to human health and ecosystems and corresponding costs to national economies. Finally, the module reviews other international efforts and explains how APEC contributes to building capacity in the region.

The concepts on risk management and risk assessment module presents an overview of the training and the topics that will be covered during the training, through diagrams and a roadmap that will be revisited during the discussions to ensure that participants keep in mind the overall process of risk assessment, risk management and risk communication for the management of chemical hazards in the environment.

RISK CHARACTERIZATION

This section consisted of four modules: hazard identification, hazard characterization, exposure assessment and risk characterization.

The hazard identification module goal is to provide participants with an understanding of how to identify and describe the hazardous properties of a chemical substance and what resources are available from international organizations to further identify a chemical of interest. Participants should be able to understand that the goal of hazard identification is to determine the possible adverse effects of an agent or situation to which an organism, system or population could be exposed.

The hazard characterization module goal is to provide participants of an understanding of the metrics used to characterize the toxicity of a chemical for human health risk assessment and of the "dose-response" relationship. Similar to the previous module, the hazard characterization module also present resources from international organizations that area available to further characterize a chemical of interest.

The learning objectives of the exposure assessment module are to provide participants with an understanding of the purpose of exposure assessment for health risk assessment, the primary attributes of exposure, the routes and pathways by which people and other organisms can be exposed to hazardous substances, common metrics of exposure (concentration, intake rate, and dose), general approaches to how exposure is evaluated and their corresponding strengths and limitations, how knowledge of exposure can support a risk management process, and international resources that provide additional exposure information.

The last module of this section was the risk characterization module. The purpose of this module is to integrate the results of hazard identification, hazard characterization and exposure assessment into a risk characterization. In addition, the module provides participants with an understanding of the purpose of a risk characterization, common metrics used to describe risk and approaches for discussing uncertainties, assumptions, and scientific judgments.

CASE STUDY I. RISK ASSESSMENT – NONYLPHENOL

The risk characterization section of the training concluded with a case study on risk assessment of nonylphenol. The case study was conducted thorough smaller working groups during the workshop. The purpose of the case study was to apply the concepts of risk assessment through an example, practice the roadmap provided during the workshop and share experiences with other workshop participants.

RISK MANAGEMENT AND COMMUNICATION

The first module of this section on risk management provides participants with an understanding of the relationship of risk management with risk assessment, the objective of risk management, the socio-economic

factors and considerations that are involved in risk management, the role of cost-benefit analysis in risk management, types of tools available to risk managers, and consultations with stakeholders.

The second module on risk communication is intended to provide participants with an understanding of the importance and place for skills in risk communication, the principles of risk communication, key elements of effective risk communication, and resources available to gain a deeper understanding of risk communication.

CASE STUDY II. RISK MANAGEMENT AND RISK COMMUNICATION – PCB CONTAINING CAULK IN AN ELEMENTARY SCHOOL

At the end of the lecture, workshop participants worked on a second case study focusing on PCB containing caulk in an elementary school. The case study included an application of the risk assessment methodologies reviewed the previous day, and incorporation of risk management decisions and risk communication with school administrators, teachers, parents, students and the community at large.

SHARING EXPERIENCES BY ECONOMIES

Four economies and an industry representative were invited to do presentations of how they use risk assessment and risk management in their regulatory processes; and the rest of participants were invited to share their experiences on similar topics. The presentations included:

- Industry's perspective on the sound management of chemicals: elements for decision making by Marianne Heinrich of BP.

- Risk Assessment and Management in Chemical Industry in Viet Nam by Nguyen Xuan Sinh of the Ministry of Industry and Trade of Viet Nam.

- Chemical Risk Assessment and Management among Institutions of the Environment Sector by Maria Teresa Gomez Osorio and Leonor A. Cedillo of the Ministry of the Environment in Mexico and the National Institute of Ecology and Climate Change of Mexico (respectively).

- Risk Assessment and Risk Management: Applications and Practices in the Philippines by Perseveranda-Fe J. Otico of the Department of Environment and Natural Resources of the Philippines.

- U.S. TSCA New Chemicals Program by Ana Corado of the U.S. Environmental Protection Agency.

KEY OUTCOMES

FUTURE USE OF THE MATERIALS

The materials will be available to participants for their use at their home offices, and the project overseer will contact them six months after the workshop to assess how they have been using the materials. Also, the Chulabhorn Research Institute is keeping a copy of the materials and a videotape of the workshop for future use in their trainings. In addition, the materials will be available to other participants at the Regulator's Forum and the Chemical Dialogue.

Finally, the project overseer is reaching out to WHO and OECD to share the materials and case studies; as well as with other technical experts in the Asia-Pacific region. It is expected that the materials will be available through several networks in the region for future use.

SUGGESTIONS FOR FUTURE TRAININGS

Initial reactions by participants indicated their interest in similar trainings at the sub-regional level, making it easier for more participants from a specific economy to attend the workshop. In addition, there was an interest to further explore the links between risk assessment, risk management options and regulatory activities. It is worth noting that the Philippines included a detailed series of recommendations regarding future trainings in their presentation.

According to the evaluation received, participants indicated interest in longer workshops with more hands on training and including case studies dealing with specific regulatory activities underway at economies in the region.

OTHER AREAS OF POSSIBLE FUTURE COOPERATION AMONG ECONOMIES

During the presentations by the economies, feedback from the evaluations received, and several comments from participants at the workshop indicated interest in related topics, these include: chemical inventories and tracking of chemicals in commerce, outreach to small and medium size enterprises, implementation of PRTR and GHS systems, responding to oil spills, collaboration on a common research agenda. Participants were encouraged to consider the objectives of APEC and the Chemical Dialogue in particular, as well as the Regulator's Forum action plan, and to identify if there are specific proposals that could be put forward as formal projects sponsored by the Chemical Dialogue and the Committee on Trade and Investment.

In addition, participants were introduced to the distance learning tool developed by the Chulabhorn Research Institute and also invited to participate in its validation process and other trainings sponsored by the Institute.

OVERALL IMPACT AND LESSONS LEARNED

Participants found the workshop a useful review of methodologies. The discussions regarding the case studies and the examples from the economies were also useful to further understand the technical concepts, as well as the challenges economies face in their daily application of their regulatory systems.

Lessons learned from the workshop include:

1. The commitment from a group of CD members and Regulator's Forum members to serve in a steering committee to provide guidance to the workshop, to ensure the content is of interest to all participants.

2. Selection of a hosting institution with an excellent scientific reputation in the region and with the experience to deliver training. In addition, the Chulabhorn Research Institute provided great hosting accommodations and ensured that all participants had appropriate logistic support during the workshop.

3. The use of a paperless workshop allowed for flexible approach to the training materials while at the same time implementing "green" meeting practices.

4. A team of experts with excellent academic credentials and practical experience that could respond to the questions raised by the participants, as well as guide the discussion to drawn on the personal experience of the participants.

5. Administrative support from the APEC Secretariat was key to ensure that all the participants and experts could attend the meeting.

A follow up evaluation would allow for a better assessment of the impact after 6 months of the workshop.

During the evaluation process, the following recommendations were identified:

- Support for further capacity building activities sponsored by APEC.

- Additional coordination with participants and sharing materials in advance to better prepare participation at the workshop.

- Additional time for more interactions and discussions of activities underway at the economies in the region.

- Some participants indicated that they will be applying the concepts during the implementation of specific programs at their organization; also some of them indicated that they will be sharing the materials with others in their organization.

- More guidance is needed during project implementation to appropriately use the funds approved in the budget.

CONCLUSIONS AND NEXT STEPS

Participants expressed great appreciation for the workshop and interest in future use of the materials, as well as seeking opportunities for future collaboration among economies in the region, the expectation is that the support and interest will translate in additional topics for discussion at future Regulator's Forums, at the Chemical Dialogue or through future project proposals. Interest seem to be focused on sub-regional workshops using translation or other local languages, more discussions regarding cooperation on current regulatory activities, more in depth application of risk assessment methodologies to regulatory activities.

APPENDICES

APPENDIX I. AGENDA

7 November 2012 - 8 November 2012 - Bangkok

Regulatory cooperation - Introductory level training on risk assessment and risk management to provide tools for the development of sound chemical regulations

Objective

To provide introductory level training on risk assessment and risk management of chemicals to regulators in the region. The goal is to increase the capacity on risk assessment and risk management of chemicals, so that regulatory approaches in the region are developed in a sound manner and, in the long term, facilitate the safe trade of chemicals among economies in the region. Technical and scientific approaches and tools to conduct risk assessments will be discussed, as well as how data analysis leads to risk management approaches. The workshop will also provide a forum to exchange experiences by economies in the region that use these tools and approaches.

DAY ONE - November 7, 2012	
07.30 - 08.00	**Registration** *All participants pre-registered & materials distributed electronically in advance. Registration table to confirm participants at location, provide any necessary updates to materials, & other handouts that might be useful to guide the workshop.*
08.00 - 08.10	**Opening ceremony**
08.10 - 08.30	**Introduction** *Participants & trainers introduce themselves. Short explanation of logistics & overall program for two days of work. Short review of objectives of workshop.*
08.30 - 09.00	**Introductory overview** David MacIntosh (Environmental Health and Engineering, USA) *Introductory discussion of chemical industry, chemical production & use, health & environmental impacts, international agreements & approaches, & existing tools in risk assessment & risk management.*
09.00 - 09.30	**Concepts on risk assessment & risk management** David MacIntosh (Environmental Health and Engineering, USA) *Overview of Risk Management & role of Risk Assessment in the process: note components of risk management: risk evaluation, control points, risk monitoring, & risk communication [OECD toolkit]; Review risk assessment: environmental health paradigm & a roadmap [WHO toolkit].*
09.30 - 10.30	**Hazard Identification & characterization** Lynn Panganiban (University of Philippines) and Saalman Hussain Inayat Hussain (Universiti Kebangsaan Malaysia) *Chemical identity & hazardous properties; suggestions for international resources.*
10.30 - 10.45	**Coffee Break**

10.45 - 11.45	**Hazard identification & characterization (continued)** *Qualitative or quantitative description of inherent properties of chemicals having potential to cause adverse health or environmental effects. Main focus on training will be on identifying & discussing applicability of existing evaluations conducted at international level, with reference to national evaluations as needed. GHS, INCHEM & other sources of hazard characterization information will be introduced.*
11.45 - 12.30	**Exposure assessment** David MacIntosh (Environmental Health and Engineering, USA) *Exposure pathways, exposure factors & exposure routes, exposure vs dose, exposure metrics [WHO toolkit].*
12.30 - 13.30	**Lunch break**
13.30 - 14.15	**Exposure assessment (continued)** *Estimating exposures: validity & reliability; modeling or measurement approaches, including biomarkers of exposure.*
14.15 - 15.30	**Risk characterization** David MacIntosh (Environmental Health and Engineering, USA) *Comparison with guidance/guideline values & description of uncertainties [WHO toolkit].*
15.30 - 15.45	**Coffee break**
15.45 - 17.30	**Case study - risk assessment** led by David MacIntosh (Environmental Health and Engineering, USA) *Problem formulation, hazard assessment, exposure assessment, risk characterization (guided exercises & facilitated discussion).*
DAY TWO - November 8, 2012	
08.00 - 09.30	**Risk management and Risk Communication** Mario Yarto (Environmental Consultant, Mexico) *Problem definition, management options, costs & benefits, evaluation; socio-economic considerations [OECD toolkit].*
09.30 - 09.45	**Coffee break**
09.45 - 12.30	**Case study (continued)** led by David MacIntosh (Environmental Health and Engineering, USA) *Risk management & risk communication.*
12.30 - 13.30	**Lunch break**
13.30 - 15.15	**Examples of risk assessment & risk management in APEC region** *Countries & stakeholders present examples of how risk assessment & risk management concepts are applied in their regulatory processes. Presenters will be provided key messages & templates to ensure presentations reinforce topics covered during training & to avoid redundancy. Please note there will be time for about 3 presentations before the coffee break & 2 after the break, for a total of 5. Presentations anticipated at this time include:* • *Industry's perspective: Sound Management of Chemicals: Elements for Decision Making, by Marianne Heinrich (BP)* • *Risk Assessment and Management in Chemical Industry in Viet Nam, by Nguyen Xuan Sinh (Ministry of Industry and Trade of Viet Nam)* • *Chemical Risk Assessment and Management among Institutions of the Environment sector, by Maria Teresa Gomez Osorio and Leonor A. Cedillo (Ministry of Environment in Mexico)*

	• *Risk Assessment and Risk Management: Applications and Practices in the Philippines, by Perseveranda-Fe Otico (Environmental Management Bureau, Philippines)* • *TSCA New Chemicals Program, by Ana Corado (U.S. EPA)*
12.30 - 13.30	**Lunch break**
15.30 - 16.30	**Examples of risk assessment & risk management in APEC region (continued)**
16.30 - 16.45	**Final questions & answers, & comments on examples**
16.45 - 17.00	**Conclusion and final remarks** *Participants will be asked to participate in an evaluation of the workshop.*

Hosting and application development for CRI Paperless Office is provided by the Office of Computer Services, Chulabhorn Research Institute

APPENDIX II. WELCOME ADDRESS BY DR. MATHUROS RUCHIRAWAT

Dear distinguished experts and participants of the workshop entitled, “Regulatory cooperation - Introductory level training on risk assessment and risk management to provide tools for the development of sound chemical regulations”.

It gives me great pleasure to welcome you all today, on behalf of the team of organizers and sponsors, to the Chulabhorn Research Institute for the start of this very important workshop. This training workshop will consist of two days of training on risk assessment and risk management, where technical and scientific approaches, tools to conduct risk assessments, as well as how data analysis leads to risk management approaches, will be discussed.

The goal of this workshop is to increase the capacity on risk assessment and risk management of chemicals so that regulatory approaches in the region are developed in a sound manner and, in the long-term, facilitate the safe trade of chemicals among economies in the region. The workshop will also provide an opportunity for regulators to exchange experiences on how these tools and approaches are used by each economy in the region.

The Chulabhorn Research Institute, through the leadership and guidance of Her Royal Highness Princess Chulabhorn Mahidol, the youngest daughter of Their Majesties the King and Queen of Thailand, and President of the Institute, has been involved in capacity building activities in the areas of toxicology and risk assessment of chemicals for over 20 years, primarily in the Asia Pacific Region. The Institute has organized more than 50 training courses and workshops in the areas of toxicology and risk assessment with more than 3,000 participants from over 35 economies, to train a critical mass of people with the knowledge to carry out risk assessments in the region. In addition to training on-site here at the Institute, in-country training has also been organized in many economies in South Easy Asia, including Bhutan, Cambodia, Indonesia, Laos PDR, Malaysia, Myanmar and Viet Nam.

The Institute, through our WHO Collaborating Center for Capacity Building and Research in Environmental Health Science and Toxicology, has also been involved in collaborations with the World Health Organization, through their International Programme for Chemical Safety at their headquarters in Geneva, as well as their South East Asia regional office in New Delhi, in areas related to risk assessment and chemical safety.

Through a Quick Start Programme-funded project, the Institute, the WHO, and the Universities of Ottawa in Canada and Utrecht in the Netherlands, have been working for the past 2 years to develop an electronic distance learning tool in risk assessment and risk management, that will complement our on-site training activities and help us to reach a larger audience. This interactive tool will allow government officials who need a refresher course to go through training at their own pace and in their own free time, without the costs associated with traveling, as well as the disruptive time away from work. This distance learning tool is scheduled to be completed and unveiled early next year.

Through our annual international training course on “Environmental and Health Risk Assessment and Management of Toxic Chemicals” held here on-site at the Institute, as well as the interactive electronic distance learning tool, the Chulabhorn Research Institute will continue to train participants in the areas of toxicology, risk assessment and risk management, with the goal of training a critical mass of qualified personnel who can carry out risk assessments in the region. It is our belief that risk assessments will allow identification and prioritization of chemical safety and chemicals management issues that will lead to minimization of impacts on health and the environment from the use of chemicals in development.

I wish you all a very pleasant stay here in Bangkok, and hope that this workshop will be very informative and useful for you for your daily work.

If there is anything we can do to make your stay more enjoyable, please don’t hesitate to let one of our staff know. We also look forward to seeing you all at the welcome dinner this evening.

Thank you.

APPENDIX III. STEERING COMMITTEE

Title	Last name	First name	Organization	Position	Economy	Gender
Dr.	Gredley	Matthew	NICNAS, National Industrial Chemicals Notification and Assessment Scheme, Australian Government Department of Health and Ageing	Head, Reform Program	Australia	M
Dr.	Li	Jowitt	SAHTECH, Safety and Health Technology Center		Chinese Taipei	M
Mr.	Abdul Aziz	Nor Azam	Department Of Environment, Malaysia	Assistant Director	Malaysia	M
Ms.	Eng	Andrea	Environmental Protection Authority	General Manager	New Zealand	F
Ms.	Vilma	Morales	Directorate General of Environmental Quality, Ministry of Environment		Peru	F
Ms.	Mendoza	Emmanuelita	Environmental Management Bureau – DENR	Supervising, Environmental Management Specialist	Philippines	F
Ms.	Brabante	Angelita	Environmental Management Bureau – DENR	Chief, Chemical Management Section	Philippines	F
Ms.	Rivera	Ana	Environmental and Occupational Health Office Department of Health	Supervising Health Program Officer	Philippines	F
Ms.	Chareonsong	Pornpimon	Pollution Control Department	Senior Environmental Scientist	Thailand	F
Ms.	Heinrich	Marianne Urbauer	BP	Lead Product Regulatory Specialist	USA	F

Title	Last name	First name	Organization	Position	Economy	Gender
Mr.	Irwin	Mike	The Procter & Gamble Company	Principal Engineer, Product Safety & Regulatory Affairs	USA	M
Ms.	Nguyen	Thi Ha	Head of Conventions, Inter Cooperation Division	Viet Nam Chemicals Agency	Viet Nam	F
Dr.	Nguyen	Xuan Sinh	Director, Center of Chemical Database and Incident Response	Viet Nam Chemicals Agency	Viet Nam	M
Dr.	Gutschmidt	Kersten	Public Health and Environment, WHO		Technical expert	M
Dr.	Yarto	Mario	Independent consultant		Technical expert	M
Dr.	Panganiban	Lynn	University of Philippines, College of Medicine	Chair of Pharmacology and Toxicology	Technical expert	F

APPENDIX IV. LIST OF EXPERTS

Title	Last name	First name	Organization	Role	Gender
Dr.	MacIntosh	Daivd	Chief Science Officer, Environmental Health & Engineering	Technical contractor	M
Dr.	Ruchirawat	Khunying Mathuros	Chulabhorn Research Institute (CRI)	Logistics contractor and speaker	F
Dr.	Settachan	Daam	Chulabhorn Research Institute (CRI)	Overall logistics and technical support	M
Dr.	Gutschmidt	Kersten	Public Health and Environment, WHO	Technical support	M
Dr.	Yarto	Mario	Independent consultant	Speaker	M
Dr.	Panganiban	Lynn	University of Philippines, College of Medicine	Speaker	F
Dr.	Inayat-Hussain	Salmaan Hussain	Malaysia	Speaker	M

APPENDIX V. LIST OF PARTICIPANTS

Chile

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   Engineer
   Ministry of Environment
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2. Ingrid Henriquez Cortez
   Lawyer
   Ministry of Environment
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   ihenriquez@mma.gob.cl

China

3. Li Ningtao
   Deputy Director
   Technical Center for Safety of Industrial Products China
   lint@tjciq.gov.cn

4. Zhao Jie
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11. Ron Yang
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15. Thahirah Kamarulzaman
Principle Assistant Director Department
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Mexico

16. Mario Yarto
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17. Leonor Cedillo Becerill
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18. Maria Teresa Gomez Osorio
Secretariat of the Environment and
Natural Resources
Jefa de Departmento de Gestion para
Suelos Contaminados de la DGGIMAR
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Peru

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Ambientales y Sustancias Quimicas
Direccion General de Calidad Ambiental
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Philippines

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Thailand

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33. Chaveng Chao
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34. Mahabir Koder
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35. Mayuree Na Rangsilpa
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37. Ana Corado
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38. Donald L. Wilke
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40. Bui Thanh Huong
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42. Nguyen Xuan Sinh
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43. Vu Tat Dat
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Ministry of Natural Resource and Environment
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INFORMATION FOR PARTICIPANTS

(If you have any questions, please contact krittika@cri.or.th or vina@cri.or.th)

1. PURPOSE

This information document provides administrative, logistical and general information for the workshop on risk assessment and risk management for regulators and other stakeholders in the APEC region.

2. BACKGROUND

The project seeks to provide introductory level training on risk assessment and risk management of chemicals to regulators in the APEC region. The goal is to increase the capacity on risk assessment and risk management of chemicals so that regulatory approaches in the region are developed in a sound manner and, in the long term, facilitate the trade of chemicals among economies in the region.

This project builds upon a previous workshop funded by APEC, Good Regulatory Practice, “Case Study Workshop on the Chemicals Sector - from Principles to Practice” (CTI 10/2009A), as well as current activities of the Chemical Dialogue that seek to promote regulatory best practices for chemicals management in the region. In addition, it is envisioned that this training will be based on existing risk assessment training developed by the WHO under the International Programme on Chemical Safety and the OECD Environment Directorate on chemicals, as well as efforts by the Chulabhorn Research Institute to develop an electronic distance learning tool (DLT) on risk assessment of chemicals.

The project is sponsored by the government of the United States of America, and co- sponsored by the National Industrial Chemicals Notification and Assessment Scheme of the Australian Government Department of Health and Ageing; Safety and Health Technology Center, Chinese Taipei; the Environmental Protection Authority of New Zealand; and the Environmental Ministry of Peru.

The project consists of a 2-day training workshop on risk assessment and risk management, where technical and scientific approaches and tools to conduct risk assessments will be discussed, as well as how data analysis leads to risk management approaches. The training workshop will also provide a forum to exchange experience by economies in the region that use these tools and approaches.

The project overseer is Ms. Ana Corado, Environmental Engineer, US Environmental Protection Agency, USA. The Thai coordinator is Dr. Mathuros Ruchirawat, Vice-president for Research and Academic Affairs, Chulabhorn Research Institute.

3. OBJECTIVES

The key objectives of the workshop are as follows:

(i) To provide regulators in the region with information on technical and scientific tools to conduct risk assessment and risk management of chemicals;
(ii) To increase the understanding of chemicals management regimes in the region by continuing exchanges and enhancing the understanding of regulatory practices in place or under development in the different economies in the region; and
(iii) To inform stakeholders of the existing tools and methodologies used in the risk assessment and risk management of chemicals, and how such technical analysis can inform the development of regulations.

4. PARTICIPANTS

The workshop is designed for regulators in the region, particularly those from developing economies, and those in charge of developing or implementing regulations of industrial chemicals. The project offers an equal opportunity for participation regardless of gender, and nominations of female regulators and participants across the APEC region is encouraged.

The organizers are seeking managers and supervisors with basic knowledge of toxicology, and fate and transport terminology, e.g. reference dose, daily intake, acute toxicity, chronic toxicity, pathways of exposure, etc. The goal is that the training may cover more advanced concepts on risk assessment and risk management, allowing regulators to discuss challenges they face during their daily work. Organizers are also seeking managers and supervisors that:

- are responsible for developing or reviewing risk assessment documents related to industrial chemicals;
- have an ability to influence risk management decisions in their organizations and influence regulatory decisions of other organizations in the economy; and/or
- are responsible for communicating findings of risk assessments and risk management decisions to others in their institutions, across the government, to the regulated community or the general public.

Ideally, the participants will be able to apply the knowledge acquired during the training to their routine work, and share the knowledge with others.

While the main audience for the training is regulators in the region, please note that the training is also open to industry, academia and civil society groups interested in chemical regulations.

5. MEETING DATES AND VENUE

The meeting is scheduled to take place at the Chulabhorn Research Institute, Bangkok, Thailand, on November 7-8, 2012.

6. PROGRAM AND LANGUAGE

A tentative programme is included (see attached). The workshop will be held in English.

7. SECRETARIAT

Ms. Krittika Polrat
Chulabhorn Research Institute
Office of Academic Affairs
Email: krittika@cri.or.th
Tel: (662) 574-0622 x3958

Ms. Vina Inpanbutr
Chulabhorn Research Institute
Office of Academic Affairs
Email: vina@cri.or.th
Tel: (662) 574-0622 x3930

8. NOMINATION

The project overseer requested nominations from regulators in all APEC economies. In addition, notifications were sent to Chemical Dialogue participants.

9. REGISTRATION

Those participants nominated by their economies and self-funded participants are invited to submit a completed pre-registration form (see attached). In addition, a

registration desk will be available on-site at the workshop venue (6th floor, Service Building, Chulabhorn Research Institute).

10.ENTRY FORMALITIES AND VISA REQUIREMENTS

All participants entering Thailand must be in possession of valid passports or travel documents endorsed and valid for Thailand.

Passport holders from 42 countries **DO NOT** require a visa when entering Thailand for tourism purposes if their stay in the Kingdom does not exceed 30 days. The 42 countries are as follows: Australia, Austria, Belgium, Brazil, Bahrain, Brunei Darussalam, Canada, Denmark, Finland, France, Germany, Greece, Hong Kong, Indonesia, Iceland, Ireland, Israel, Italy, Japan, Korea, Kuwait, Luxembourg, Malaysia, Monaco, Netherlands, New Zealand, Norway, Oman, Peru, Philippines, Portugal, Qatar, Singapore, Spain, South Africa, Sweden, Switzerland, Turkey, United Arab Emirates, U.K., U.S.A., and Viet Nam.

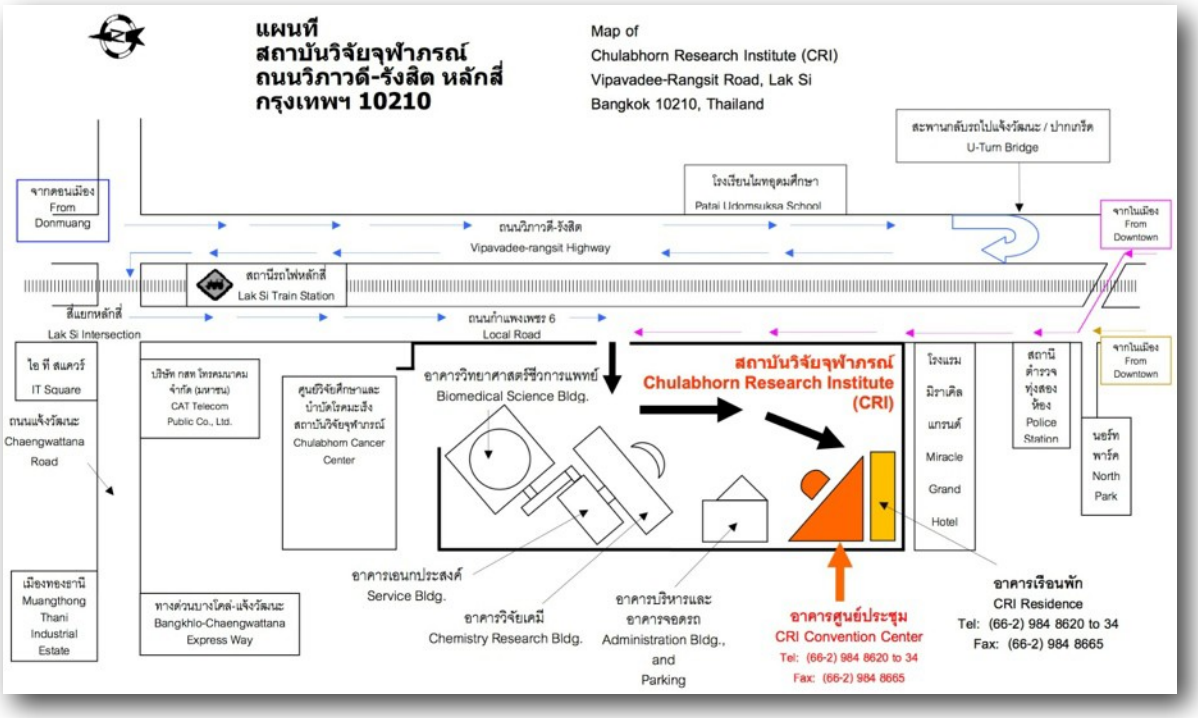
It is recommended, however, that enquiries regarding visa and entry regulations should be made to the Royal Thai Embassy or Consulate nearest to you before your departure.

11.DOCUMENTATION

The training will be conducted in a paperless system, meaning that all documents will be shared through a web-based system. Participants are requested to bring their own laptops or other mobile device with wireless capability for accessing and reading the documents. Wifi service will be made available and all participants will be provided with access codes.

12.ACCOMMODATION

Accommodation for participants to this workshop is reserved at 2 locations in walking distance of the venue (please see CRI campus map below):



(1) The Miracle Grand Convention Hotel

The Miracle Grand Convention Hotel is located next door to the Chulabhorn Research Institute. Please visit their official website at http://www.miraclegrandhotel.com for more information. Please be aware that the rates available for workshop participants (specified below) are special discount rates:

- “Superior” room - single occupancy (2,100* THB per room per night)
- “Superior” room - double occupancy (2,400* THB per room per night)
- “Deluxe” room - single or double occupancy (3,200* THB per room per night)

*All rates inclusive of breakfast.

(2) CRI Residence

The CRI Residence is located behind the CRI Convention Center on the campus of the Chulabhorn Research Institute. It includes 70 hotel rooms (standard, deluxe and suites), 10 apartment units for long-term stay, a swimming pool, and fitness center. The room rates are as follows:

- hotel unit - single occupancy (1,200** THB per room per night)
- hotel unit - double occupancy (1,500** THB per room per night)
- 1-bedroom apartment unit (1,500** THB per room per night)

**These rates do not include breakfast, which is an extra 150 THB per person per day.

Kindly complete and submit the Accommodation Reservation & Travel Itinerary Report form (attached) to indicate your preference. CRI will provide your details to the hotel or CRI Residence. Please note that due to limited availability, the hotel and apartment units at the CRI Residence are on a first-come-first-served basis, with priority given to funded participants.

13.MEALS

During the workshop, buffet lunches will be arranged for participants in the area in front of the room where the workshop is held (6th floor, Service Building). Kindly specify any special dietary requirements you may have in the pre-registration form so that any necessary arrangements can be made prior to your arrival. Payment for the buffet lunches will be collected on November 7th at the registration desk.

For participants who stay at the Miracle Grand Convention Hotel, breakfast is included in the room rates. For participants who stay at the CRI Residence, breakfast is an extra 150 THB per person per day. Dinner can be had at any one of the many restaurants available at the Miracle Grand Convention Hotel at reasonable prices, or at one of the local restaurants nearby. Kindly request further information regarding restaurants nearby from the local staff.

A reception hosted by the Chulabhorn Research Institute will be held on the evening of November 7th at the Chulabhorn Convention Center.

14.TRANSPORTATION

CRI will provide transportation to and from the airport for all participants on the day of arrival and departure. Kindly provide details about your finalized travel itinerary on the attached Accommodation Reservation & Travel Itinerary Report form at least two weeks before the workshop. The Miracle Grand Convention Hotel and CRI Residence are located within walking distance of the workshop venue.

The national airport of Thailand is Suvarnabhumi Airport. For more information kindly visit their official website at http://www.suvarnabhumiairport.com/index_en.php.

The best way to check for flight options to Suvarnabhumi Airport from your respective country is to check with your preferred airline or travel agency. The national airline of Thailand is Thai Airways International. For more information, kindly visit their official website at http://www.thaiairways.co.th/thailand/en/home.htm.

There, from the Timetable tab, you can select your city of origin, and preferred departure and return dates to see a list of scheduled dates and times for available flights from your city of origin to Bangkok (websites for other airlines may be slightly different). For example, for a flight from Los Angeles sometime around November 6th, flight TG693 leaves LAX airport on November 3rd (1 PM), 4th (12 noon) and 6th (12 noon) with stop over in Seoul, Republic of Korea. Flights from within the region, e.g. from Manila, will mostly be direct flights, and there will usually be more options in terms of flight departure times.

15.EXPENSES AND ALLOWANCE

APEC funding is being offered for 2 participants from the 10 travel-eligible economies with round trip economy class airfare and per diem according to the APEC guidelines. The 10 travel-eligible economies are Chile, Indonesia, Malaysia, Mexico, Papua New Guinea, the Philippines, Peru, Russia, Thailand and Viet Nam. If an economy wishes to send more than 2 participants, the expenses for the additional participants will be borne by that economy. The US government is also offering additional funding to some eligible economies.

Other participants from APEC economies are welcome to send participants on self-funded basis.

Participants from travel-eligible economies who wish to seek APEC funding for their travel expenses (airfare + per diem) should submit their best airfare quotation and detailed travel itinerary from a travel agent (clearly indicating the airfare, taxes, currency, flight duration of each sector, travel class, arrival and departure dates and times, etc.) to the APEC Secretariat directly, requesting attention to Ms. Mary Tan, for approval. Please quote the project number (CTI 05/2012T) in the correspondence to the APEC Secretariat.

Travel expenses, per diem and accommodation expenses will be provided on a reimbursement basis. If approved participants should require an advance payment, they must make such a request to the APEC Secretariat on an individual basis **10**

working days (by 17 October 2012) before travel commences. **Requests reaching the Secretariat after this deadline will not be accepted and processed**. The request should be made along with the requirements mentioned above.

All the details regarding the approval of the airfare (for participants from the 10 travel-eligible economies and the speakers) and the per diem for speakers **must be coordinated directly with the APEC Secretariat**.

16.SIGNINGS OF UNDERTAKINGS

Once the APEC Secretariat has approved travel fares and itineraries, they will send the participants a travel undertaking for their signature. The undertaking is a contract between the participants and the APEC Secretariat, in which the participants agree to perform the Terms of Reference and the APEC Secretariat commits to reimbursing the participants for the travel expenses. **The travel undertaking must be completed at least 8 working days before travel commences. The APEC Secretariat will not reimburse travel costs which are not supported by the signed undertaking.** The undertaking will be based on the quotation of the most direct and economic return trip (including airfare and airport taxes, if any) to attend the workshop.

17.DRESS CODE

The dress code for the workshop is formal unless otherwise announced.

18.EVALUATION

Participants are required to complete and return a questionnaire form at the end of the workshop. This questionnaire will be distributed at the workshop. In the evaluation form, each participant is encouraged to discuss the benefits of the workshop and to make requests for future projects concerning the subject.

19.GENERAL INFORMATION ABOUT THAILAND

(a) General information

Thailand is situated in Southeast Asia, with a population of about 65 million, approximately 7 million of whom live in Bangkok, the capital city. The official language is Thai, although English is also spoken and understood. Thailand is a constitutional monarchy, with the King as the Head of State, and an elected

Prime Minister authorized to be Head of the Government. The current Prime Minister is Yingluck Shinawatra. The economy of Thailand is reliant on exports, which account for 60% of the approximately US $200 billion GDP. The main exports are rice, rubber, textiles, automobiles, computers and other electronic appliances, and jewelry. The majority (95%) of Thais are Buddhist.

(b) Voltage, electrical plug/outlet information

Electrical outlets in Thailand are charged to 220V at 50 cycles per second, which is compatible with appliances from the U.K. but not those from the U.S. and many other nations. While most computer cables have adaptors for voltage, visitors from the U.S. and those not on the 220/50V system will have to bring adapters to run most other appliances. Outlets in Thailand generally feature flat, two-pronged plugs, though some feature holes for round plug ends. Few outlets feature three holes (grounded outlets), so it is often necessary to have a three to two prong adapter for using notebook computers in Thailand.

(c) Weather

The weather in Thailand is generally hot and humid. The weather can be divided into 3 seasons: the hot, rainy, and cool seasons. November is considered the very early part of the cool season for Thailand, with the rainy season peaking in September and ending around October. The average temperatures in Bangkok in November are approximately 23^{o}C (low) and 32^{o}C (high).

(d) Local currency & foreign exchange rate

The local currency is the Thai Baht (THB). The exchange rate is 30.09* THB to 1 US dollar (USD). [* As of 29 August 2012]

(e) Useful phone information

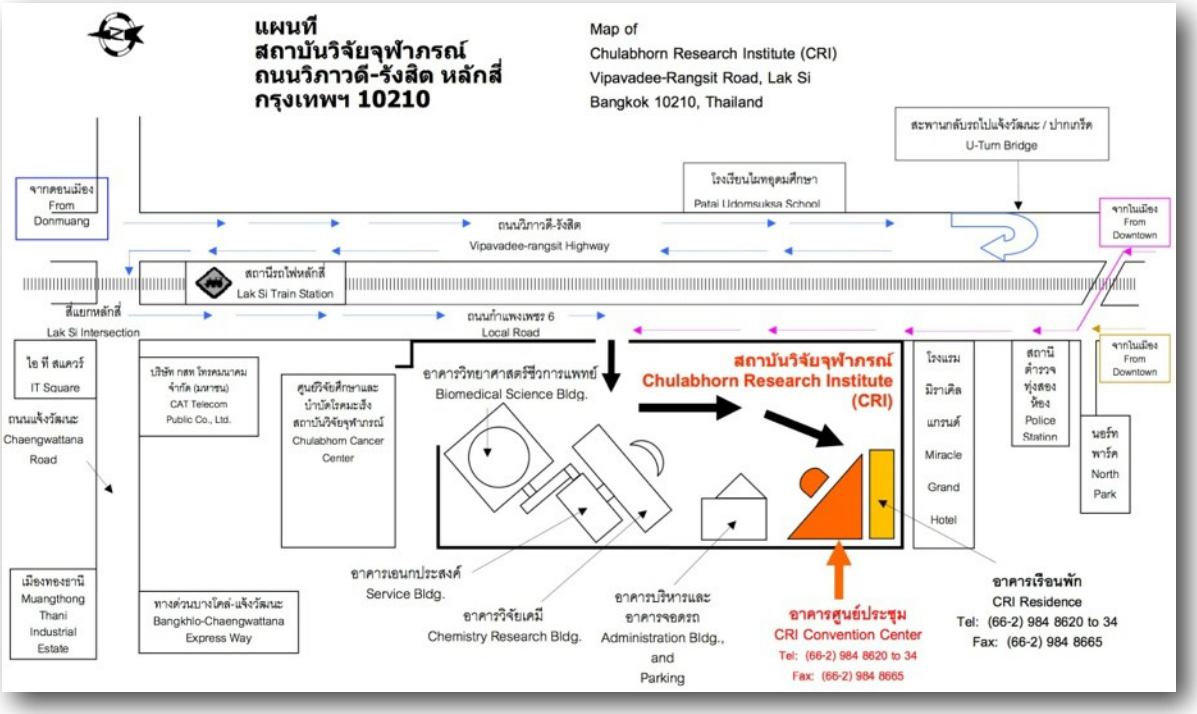
The country code for Thailand is 66 and the city code for Bangkok is 2. Calling from Thailand on a public phone is easy, with a phone card available at most convenience stores, e.g. “7-11”. Emergency numbers are often three or four digit numbers, including for the Thai Tourist Police, which is 1155. Mobile phones in Thailand use the GSM system, and pre-paid SIM cards can be purchased for the major carriers (AIS, DTAC and TRUE).

General Information for Confirmed Participants

1. Map

Please see the map below for guidance on how to get from the hotel to the venue for the workshop. For those participants staying at the CRI Residence there will be a van to pick you up in front of the residence for drop off at the front of the Chemistry Research Building (at 7.10 AM, 7.20 AM and 7.30 AM on November 7th). For those staying at the Miracle Grand hotel, there will be a van leaving from the hotel at 7.15 AM for drop off at the front of the Chemistry Research Building at the Chulabhorn Research Center.

The workshop will be held in room #607, which is located on the 6th floor of the Service Building (behind the Chemistry Research Building). Participants should enter the Chulabhorn Research Institute Chemistry Research Building, take the elevator to the 6th floor, and follow the signs to room #607 (take a left out of the elevator, take another left at the first corner, and then walk straight to the end of the corridor). The registration desk will be in front of room #607.



2. Address and phone numbers of the Miracle Grand Convention hotel (in English and Thai):

The Miracle Grand Convention Hotel
99 Kamphaeng Phet 6 Road,
Talad-Bangkhen, Laksi,
Bangkok 10210, Thailand
Tel : (662) 575-5599
Fax :(662) 575-5555
Email: info@miraclegrandhotel.com

โรงแรมมราเคล
99 ถนนวภาวดรงสต
หลกส
กรงเทพฯ 10210
โทร. 02-575-5599

3. Address and phone numbers of the CRI Residence (in English and Thai):

CRI Residence
Chulabhorn Research Institute
54 Kamphaeng Phet 6
Talat Bang Khen, Lak Si
Bangkok 10210, Thailand
Tel. (662) 984-8620
Mob. (6681) 932-0632
Fax. (662) 984-8665

สถาบนวจยจฬาภรณ
54 ชร 6
ตลาดบางเขน หลกส
กรงเทพฯ 10210
โทร. 02-984-8620
โทร. 081-932-0632

4. Pick up at airport

A driver will be awaiting you on your arrival at exit #3 (after you go through immigrations, pick up your luggage, go through customs, and turn right into the arrival area. Walk for about 200 meters towards the waiting area. The driver will be holding a sign with your name on it. The meeting point is located just before the Airport Information desk (see photo below).

It will take approximately 60-90 minutes (depending on traffic) from the airport to your hotel.

3. Emergency contact numbers

Mr. Vutthi Prakaiphetkul
Manager
Chulabhorn Convention Center & CRI Residence
081-932-0632

Dr. Daam Settachan
Chulabhorn Research Institute
081-811-7512

4. Participants will be requested to pay for lunch at the time of registration on

November 7th. The cost is $30 USD covering lunch for both days. Coffee/tea breaks are complimentary. Please prepare the exact amount as we are unable to give you change.

5. Participants will receive a wireless account for accessing the Internet at the venue.

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*

APPENDIX VII. TRAINING MATERIALS (PRESENTATIONS)

Introductory Overview

Asia Pacific Economic Cooperation Workshop

Regulatory Cooperation – Introductory level training on risk assessment and risk management to provide tools for the development of sound chemical regulations

Presentation by: Dr. David MacIntosh
APEC risk assessment and risk management workshop
November 7-8, 2013
Bangkok, Thailand

1

Definitions: Environment

- The circumstances, objects, or conditions by which one is surrounded

Adapted from Jonathan M. Links, Introduction to Environmental Health

2

Public Health Definition of the Environment

- All that which is external to the individual host. It can be divided into physical, biological, social and cultural factors, any or all of which can influence health status in populations.
  - Last, J.M. (ed.). 1995. A Dictionary of Epidemiology (3rd edition). New York. Oxford University Press.

Adapted from Jonathan M. Links, Introduction to Environmental Health

3

Definitions: Health

- A state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.
  - WHO. 1948. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 1946 and entered into force on 7 April, 1948.

Adapted from Jonathan M. Links, Introduction to Environmental Health

4

Environmental Health

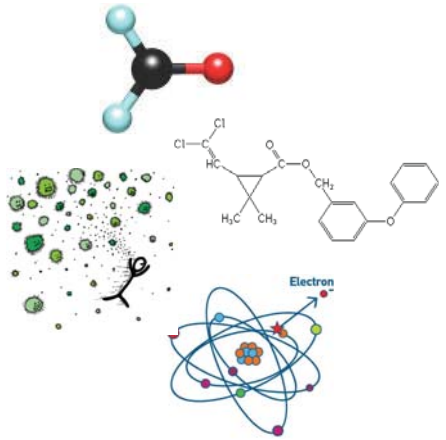
- Environmental health addresses all the physical, chemical, and biological factors external to a person, and all the related factors impacting behaviors. It encompasses the assessment and control of those environmental factors that can potentially affect health. It is targeted toward preventing disease and creating health-supportive environments.
  - WHO definition of environmental health
- Factors that:
  - Improve health
    or
  - Contribute to disease, impair performance, limit safety, or introduce risk of injury

Adapted from Jonathan M. Links, Introduction to Environmental Health

5

Contributors to Our Environment

- Chemical
  - Air pollutants, toxic wastes, pesticides, volatile organics
- Biological
  - Disease organisms present in food, water, air and on surfaces
  - Insect and animal allergens
- Physical
  - Noise, ionizing and non-ionizing radiation



6

Chemical Industry Products

- Integral part of daily life in today's world
- Important in all economic sectors of the global economy
- Contribute to more productive and comfortable lives for people
- Sound management essential to avoid significant risks to human health and ecosystems and corresponding costs to national economies

UNEP Global Chemicals Outlook, September 2012

7

Growth of the Chemical Industry

- Global output increased 20-fold from 1970 to 2010.
- Fastest growth in economies in transition
  - Annual growth rates 2000 - 2010
    - China and India: 24% and 14% annual growth rate
    - US, Japan and Germany: 5% to 8%
  - Trends projected to continue

UNEP Global Chemicals Outlook, September 2012

8

Growth of the Chemical Industry

Table 1. Chemical Production: Predicted Growth, 2012-2020

	Percent change, 2012-2020	
North America	25%	
United States		25%
Canada		27%
Mexico		28%
Latin America	33%	
Brazil		35%
Other		31%
Western Europe	24%	
Emerging Europe	35%	
Russia		34%
Other		36%
Africa & Middle East	40%	
Asia-Pacific	46%	
Japan		22%
China		66%
India		59%
Australia		23%
Korea		35%
Singapore		35%
Other		44%

UNEP Global Chemicals Outlook, September 2012

Growth of the Chemical Industry

Figure 1. Chemical Industry Output: Developed Regions*

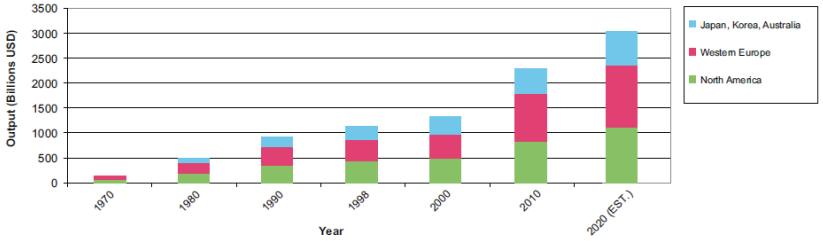
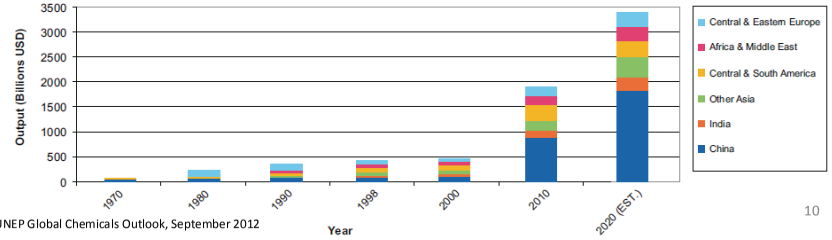


Figure 2. Chemical Industry Output: Developing Regions* & Countries with Economies in Transition



UNEP Global Chemicals Outlook, September 2012

Chemical Industry Companies

- Large and small companies
  - Some are among the largest industrial companies in the world
  - Others are small – companies with less than 50 employees make 95% of the 50,000 chemicals produced in the US
- Employs over 10 million people world-wide, but employment has dropped 7.5% from 1990 to 2000 (technology, automation)
- Produce tens of thousands of chemicals
- 200 to 300 new chemicals in significant quantities annually

Overview of the chemicals industries (OECD 2001 – Environmental Outlook for the Chemicals Industry.)

Chemical Volumes

- Smaller number of high production volume chemicals; large number of lower production volume chemicals

Table 3
Existing chemical substances in percentage by number of substances and volume within the European Union and Japan

Tonnes/year	by number in %		by volume in %	
	EU	JAPAN*	EU	JAPAN*
>1 million	1.34	0.7	75.68	77.9
>100,000 to 1 million	3.5	2.3	19.84	16.2
>10,000 to 100,000	6.12	5.8	3.46	4.2
>1,000 to 10,000	14.73	16.0	0.83	1.3
>100 to 1,000	28.45	32.7	0.16	0.3
>10 to 100	45.86	42.5	0.03	0.0

(EU data provided by the European Commission are unofficial; figures for Japan are estimates provided by the Japanese Ministry of International Trade and Industry)
*These are estimated figures and may not cover all chemicals in Japan.
Source: Theins, N. (2000); Nagata, Y. (2000)

Overview of the chemicals industries (OECD 2001 – Environmental Outlook for the Chemicals Industry.)

Health and Environmental Impacts

GCO

HEALTH AND ENVIRONMENTAL EFFECTS OF CHEMICAL EXPOSURES: AN INCREASINGLY COMPLEX CHALLENGE

The release of chemicals continues to affect all aspects of natural resources including the atmosphere, water, soil and wildlife. Chemicals released to the air can act as air pollutants as well as greenhouse gases and ozone depleters and contribute to acid rain formation. Chemicals can contaminate water resources through direct discharges to bodies of water, or via deposition of air contaminants to water. This contamination can have adverse effects on aquatic organisms, including fish, and on the availability of water resources for drinking, bathing, and other activities.

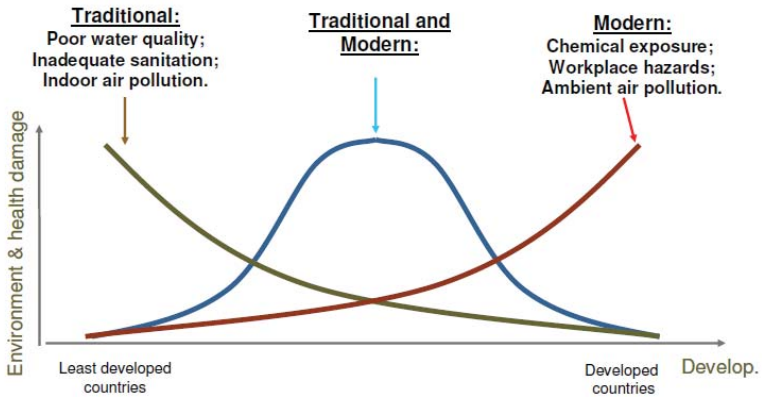
It is common for soil pollution to be a direct result of atmospheric deposition, dumping of waste, spills from industrial or waste facilities, mining activities, contaminated water, or pesticides. Soil contamination impacts include loss of agricultural productivity, contamination of food crops grown on polluted soil, adverse effects on soil microorganisms, and human exposure either through food or through direct exposure to

Of the 5.7 million metric tons of pollutants released or disposed of in North America in 2006, 1.8 million metric tons were of chemicals considered persistent, bioaccumulative or toxic, 970,000 metric tons were known or suspected carcinogens and 857,000 metric tons were of chemicals that are considered reproductive or developmental toxicants.

mirex, toxaphene, PCBs, and polychlorinated dibenzo-p-furans and polychlorinated dibenzofurans (PCDD/PCDF). Additional chemicals were added to the list more recently: alphahexachlorocyclohexane; beta hexachlorocyclohexane; chlordecone; technical endosulfan and its related isomers; hexabromobiphenyl; hexabromodiphenyl ether and heptabromodiphenyl ether (commercial octabromodiphenyl

UNEP Global Chemicals Outlook, September 2012

Evolution of Environmental Health Risks



Gutschmidt 2011 – Training on Risk Assessment of Chemicals at National Level in a Global Context

Global Burden of Disease from Chemicals

- Pruss-Ustun et al. 2011
- Loss of 7.4 million years of health life annually
- Unintentional poisoning causes more than 350,000 deaths each year (94% in low and middle income economies)
- 6% of the total burden of disease world wide
- Likely to be an underestimate

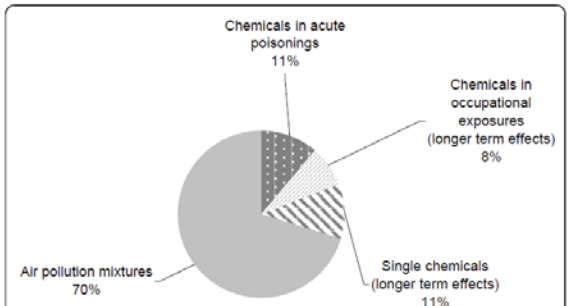


Figure 2 Distribution of known burden of disease (in DALYs).

Pruss-Ustun et al. 2011, Environmental Health, 2011, 10:9; http://www.ehjournal.net/content/10/1/9

Global Burden of Disease from Chemicals

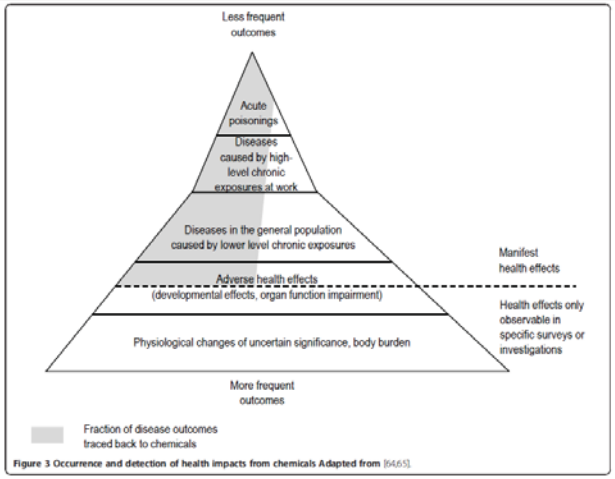


Figure 3 Occurrence and detection of health impacts from chemicals Adapted from [64,65].

Pruss-Ustun et al. 2011, Environmental Health, 2011, 10:9; http://www.ehjournal.net/content/10/1/9

Opportunities for Managing Chemical Exposure

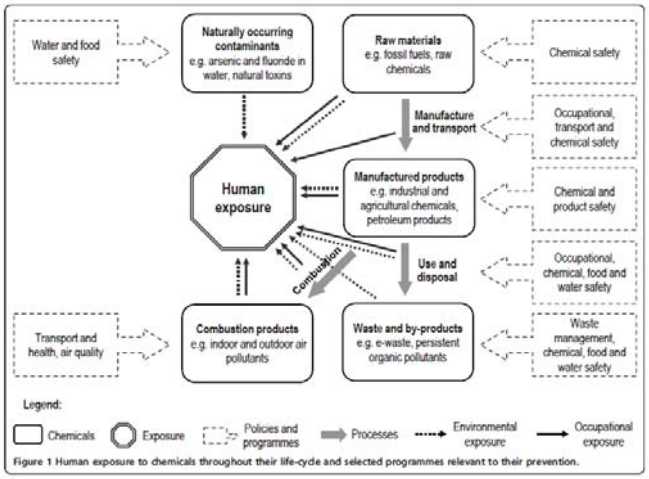


Figure 1 Human exposure to chemicals throughout their life-cycle and selected programmes relevant to their prevention.

Pruss-Ustun et al. 2011, Environmental Health, 2011, 10:9; http://www.ehjournal.net/content/10/1/9

Selected International Programs

- Stockholm Convention on persistent organic pollutants
- Rotterdam Convention on exchange of environmental health information on priority chemicals
- Basel Convention on managing trans-boundary movement of hazardous waste
- International Health Regulations for coordination and management of public health emergencies of international concern, including chemical incidents
- Johannesburg Plan of Implementation to achieve by 2020 chemical production and use in ways that minimize significant adverse impacts on the environment and human health

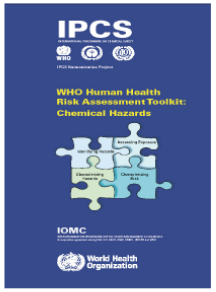
Examples of Existing Tools for Chemical Risk Assessment and Management

- World Health Organization Human Health Risk Assessment Toolkit: Chemical Hazards
- OECD Environmental Risk Assessment Toolkit
- World Bank Persistent Organic Pollutants (POPs) Toolkit
- Numerous documents and tools from economies
- Chulabhorn Research Institute/World Health Organization Distance Learning Tool for Risk Assessment and Risk Management (nearing completion)

Examples of Existing Tools for Chemical Risk Assessment and Management

Purpose and intended audience of the Toolkit

- Assist its users with the performance of human health risk assessments.
- Promotes the use of information developed by international organizations.
- Designed for addressing different risk assessment scenarios.
- Aimed at those conducting and using risk assessments (scientific and lay professionals).
- Targeted at developing countries and countries with economies in transition.
- However, it is of use for everyone involved in RA.



Gutschmidt 2011 – Training on Risk Assessment of Chemicals at National Level in a Global Context

Key Messages

- Environmental health is the study and management of factors in the environment that influence environmental health
- Chemical factors in the environment present a range of substantial benefits and can pose significant harm and risk to health
- Sound management essential to avoid significant risks to human health and ecosystems and corresponding costs to national economies
- This APEC Workshop is one of several efforts by international organizations to build capacity for chemical risk management in economies

Concepts on Risk Management and Risk Assessment

Presentation by: Dr. David MacIntosh
APEC risk assessment and risk management workshop
November 7-8, 2013
Bangkok, Thailand

1

Risk-Based Management of Chemical Hazards

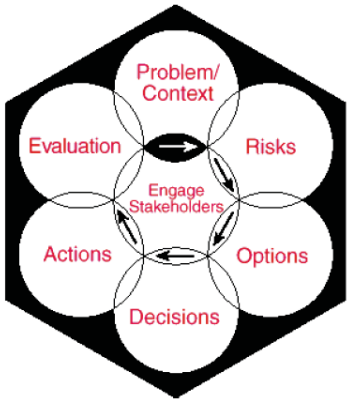
- Information on chemical toxicity and exposure is used to support a wide range of decisions about land use and other human activities.
- Consider these questions that relate to human health:
  - Is the water safe to drink?
  - Are chemicals released from a building a cause of illness in people nearby?
  - How much does the air pollution in a city contribute to illness and mortality?
  - When should food be harvested after the crops have been treated with a pesticide?
  - Is the foul smell inside that building going to make occupants of the building sick?
  - Are chemicals a cause of elevated rates of cancer of in a certain population?
- Consider these questions that relate to ecological integrity:
  - Is the diversity of organisms in a lake affected by chemicals in the sediment or water?
  - Are local emissions of mercury adversely affecting populations of predatory birds and mammals?
  - Will emissions from a proposed electricity generating station have a negative effect on the productivity of the local forest and agricultural fields?

Information Needed …

- Society's ability to provide answers to questions like those listed on the previous page depends in large part on the quality and quantity of information available about the hazards of chemicals and exposure to chemicals. The relevance of that information to the circumstances of interest is another important consideration.
- How does society protect human health and the environment from chemical hazards, even when the information needed to do so is not complete?

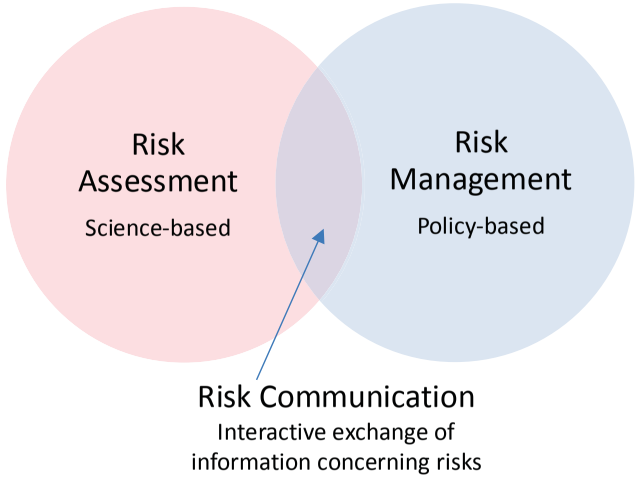
Risk-Based Management of Chemicals

- The answer is through a cycle of inter-related activities:



Scope of the Workshop

- Fundamental components of risk-based management of chemicals

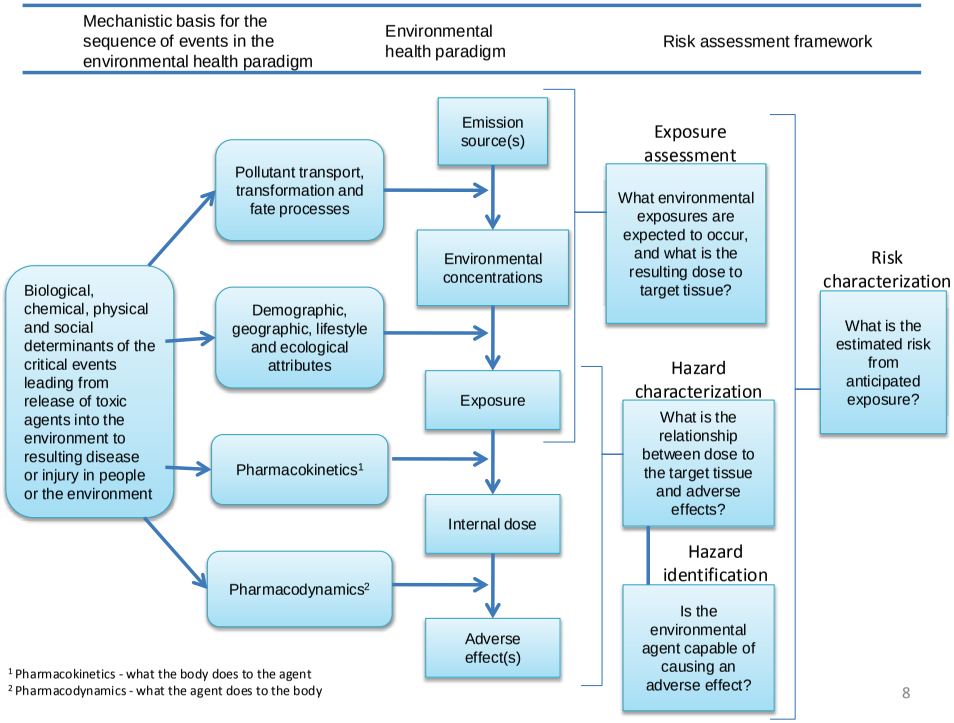


Inputs to Risk Management Decisions

45

The Risk Assessment Process

- Risk assessment is a process to estimate the nature and likelihood of adverse effects in people or the environment that may be exposed to chemicals in contaminated environmental media, now or in the future.
- Risk assessment is a scientific process, but also incorporates policy judgements
- In general, risk depends on:
  - How much of a chemical is present in an environmental medium (e.g., air, water, soil)
  - How much contact a person or other organism has with the environmental medium
  - The toxicity of the chemical



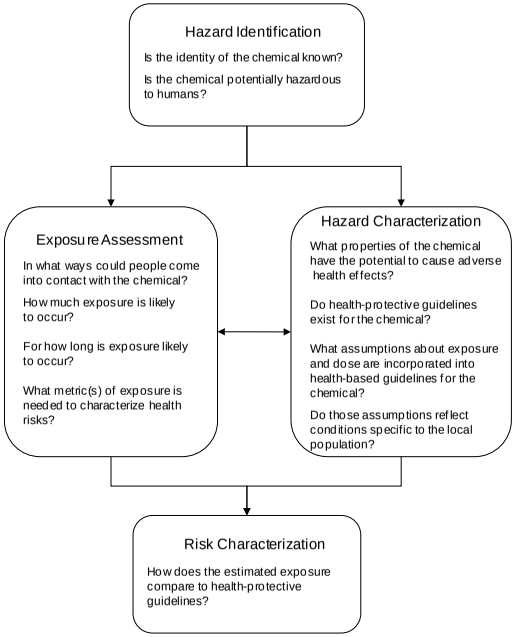
The Risk Assessment Process

- Problem Formulation – Determines the objective of the assessment including the chemicals, populations, and time frames of interest.
- Hazard Identification – Examines whether a chemical has the potential to cause harm to humans and/or ecological systems, and if so, under what circumstances.
- Hazard Characterization (or Dose-Response Assessment) – Examines the numerical relationship between exposure and effects.
- Exposure Assessment – Examines what is known about the frequency, duration, timing, and levels of contact with a chemical.
- Risk Characterization – Examines the likelihood of risk to health that is based upon the extent of exposure to a chemical and the toxicity of a chemical, and the strength of the data for supporting conclusions about the nature and extent of the risk.

Adapted from EPA 2011

Road Map for Risk Assessment

WHO Chemical Risk Assessment Toolkit



Risk Communication

- Risk communication is an open, interactive exchange of information among stakeholders.
- Risk communication is grounded in science-based approaches for communicating effectively in sensitive or controversial situations, including situations where concern is high and trust is low.
- As shown in the figure, effective communication of risk is an essential component of all stages of the risk analysis cycle.

Key Messages

- The objective of this workshop is to provide an introduction to risk-based approaches for the management of chemical hazards in the environment.
- The workshop will cover three inter-related topics: (1) risk assessment, (2) risk management, and (3) risk communication.
- Risk assessment is a science-based process to estimate the magnitude and likelihood of adverse effects associated with exposure to chemicals in contaminated environmental media, now or in the future.
- Risk management is the process which evaluates how to protect human health and the environment and leads to an action intended to control risk.
- Risk communication is an open, interactive exchange of information among stakeholders that facilitates the assessment and management of risk.

Hazard Identification

Presentation by: Dr. Lynn Panganiban
in collaboration with Dr. David MacIntosh
APEC risk assessment and risk management workshop
November 7-8, 2013
Bangkok, Thailand

Learning Objectives

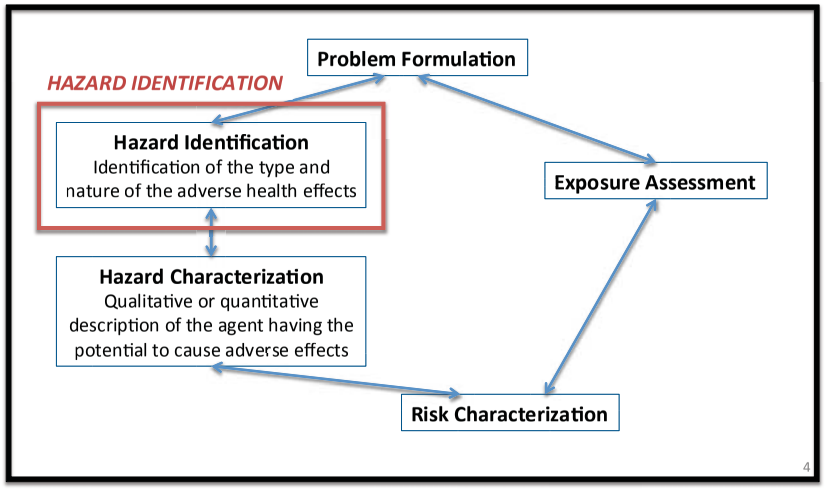
- By the end of this module, workshop participants should have an understanding of:
  1. How to identify and describe the hazardous properties of a chemical substance.
  2. Resources from international organizations that are available to further identify and characterize a chemical of interest.

Key Messages

- The goal of hazard identification is to determine the possible adverse effects of an agent or situation to which an organism, system or (sub) population could be exposed.
- *Hazard identification* describes the properties of a chemical which make it a concern for health
  - Chemicals are identified using standardized systems for classification from international and national organizations.
  - Health hazards of interest include cancer, neurological, immunological, dermal, respiratory, organ-specific and other effects
  - Environmental hazards of interest include toxicity, persistence, and bioaccumulation
- Information on health and environmental hazards for many agents are available from authoritative international, national and scientific sources.

Introduction

RISK ASSESSMENT



Introduction

HAZARD IDENTIFICATION

Is the identity of the chemical known?

Is the chemical potentially hazardous to humans?

5

Introduction

HAZARD IDENTIFICATION

KEY COMPONENTS :

- **Toxicokinetics :**

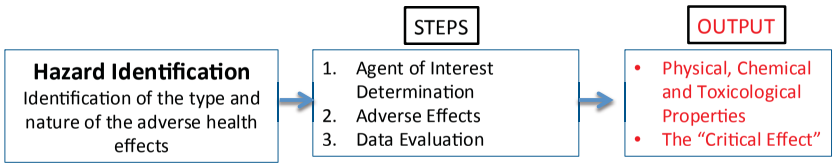
Deals with the absorption, distribution, metabolism, excretion (adme) characteristics of chemicals

- **Toxicodynamics:**

Deals with mechanisms of action of chemicals resulting to adverse effects

6

Introduction Cont.



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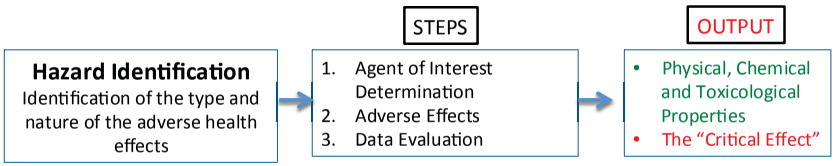
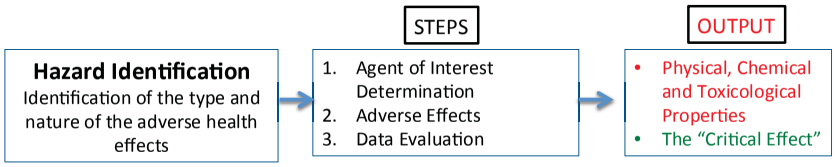
Determining Agent of Interest



Physico-chemical and toxicological properties:
Volatility, Vapor Pressure, Solubility, Melting Point, Boiling Point

8

Adverse effects



Hazardous Effects/Critical Effect:

Structure-Activity Relationship
Animal Toxicologic Tests
In-vitro Studies
Epidemiologic Data
Environmental Toxicology

9

Adverse Effects

- A chemical may be associated with one or more hazards to human health. Adverse effects can be:
  - Acute or Chronic
  - Temporary or Permanent
  - Life threatening

10

Adverse Effects

- Several schemes for classification of hazard information have been developed. In general, chemicals are classified according to human health hazards that they pose, such as:
  - Neurological
  - Developmental
  - Reproductive
  - Respiratory
  - Cardiovascular
  - Carcinogenic

Carcinogenic versus Non-carcinogenic Outcome

11

Environmental Hazards

Environmental fate
- Photodegradation
- Stability in water
- Transport and distribution between compartments
- Bioaccumulation and biomagnification

Adverse effects on aquatic and wildlife
- Ecotoxicology (fish, invertebrates, terrestrial animals)

12

Sources of Information

Internal Sources

- Company documents
- People who work with the chemical
- Ingredient listings
- Chemical packaging
- Chemical safety cards
- Material safety data sheets

External Sources

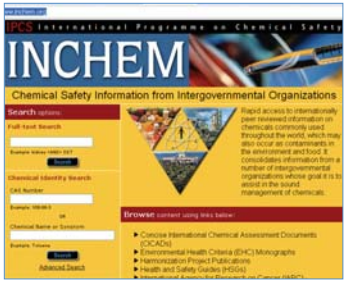
- Emission scenario documents
- Full text search using INCHEM
- Permits of building plans
- Dialogues with local community

13

International Sources of Hazard Identification Information

- OECD eChemPortal

- WHO IPCS INCHEM



14

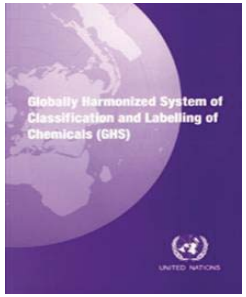
International Sources of Hazard Identification Information

Hazardous Substances Data Bank (TOXNET)
http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB)

15

International Sources of Hazard Identification Information

The Globally Harmonized System of Classification & Labelling of Chemicals (GHS)
http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html



Harmonized criteria for classifying substances and mixtures according to their health, environmental and physical hazards

Harmonized hazard communication elements

16

International Sources of Hazard Identification Information

Table 4: Human health effects included in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Health effect	*Number of hazard categories*	*Criteria for categories*
Acute toxicity	5	LD_{50} and LC_{50}
Skin corrosion/irritation	3	Corrosive, irritant, mild
Serious eye damage/irritation	1	Irreversible effects
Respiratory sensitizer	3	Evidence for effects in humans
Skin sensitizer	3	Evidence for effects in humans
Germ cell mutagenicity	2	Evidence for effects in humans
Carcinogenicity	2	Evidence for effects in humans
Toxic to reproduction	2	Evidence for effects in humans
Effects on or via lactation	1	Concern for effects
Specific organ toxicity (acute exposure)	3	Strength of the evidence
Specific organ toxicity (repeated exposure)	2	Strength of the evidence
Aspiration hazard	2	Evidence for effects in humans

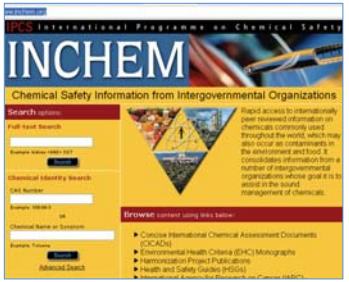
LC_{50}, median lethal concentration; LD_{50}, median lethal dose

17

Adverse Effects Example: Non-carcinogenic

- OECD eChemPortal

- WHO IPCS INCHEM



CHEMICAL: Formaldehyde

Skin , eye, gastrointestinal, lung irritant effect

Allergic reactions

18

51

Adverse Effects Example-Carcinogenicity

1. The threat carcinogenicity, like many other compounds, is determined through a **weight of evidence approach**.
2. The weight of evidence increases with:
   - An increase in the number of animal species, strains, sexes, and number of experiments showing carcinogenic response.
   - An increase in the number of tissue sites affected by the chemical.
   - A clear dose response relationship.
   - A dose-related decrease of the time to tumor development.
   - When there is a dose related increase in the proportion of malignant versus benign tumors.
   - When there is an increase in an unusual type of tumor or tumors in an unusual site.

19

Adverse Effects Example-Carcinogenicity

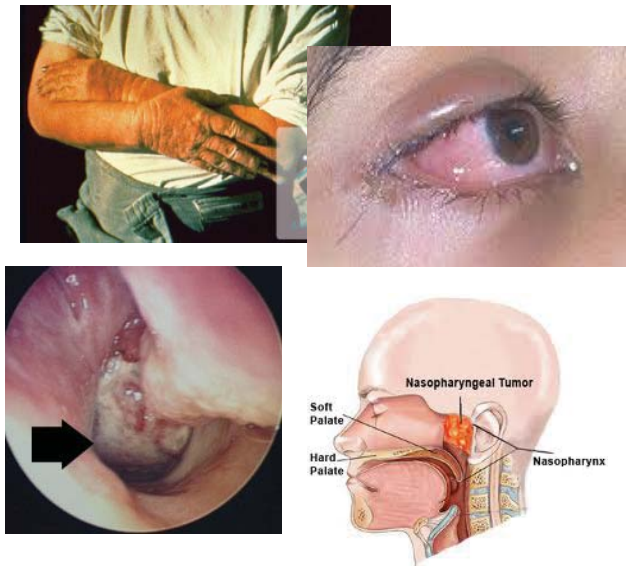
3. The International Agency for Research on Cancer (IARC) categorizes chemicals and other agents into one of five categories based on the strength of evidence that an agent could alter the age-specific incidence of cancer in humans:
   - Group 1: the agent is *carcinogenic* to humans
   - Group 2A: the agent is *probably carcinogenic* to humans
   - Group 2B: the agent is *possibly carcinogenic* to humans
   - Group 3: the agent is *not classifiable as to its carcinogenicity* to humans
   - Group 4: the agent is *probably not carcinogenic* to humans

20

Adverse Effects Example- Carcinogenicity

Evidence for carcinogenicity: **FORMALDEHYDE**

"Evaluation: There is sufficient evidence in humans for the carcinogenicity of **formaldehyde**. There is sufficient evidence in experimental animals for the carcinogenicity of **formaldehyde**. Overall evaluation: **Formaldehyde** is carcinogenic to humans (Group 1). [IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol 88 Summary of Data Reported and Evaluation. (Last updated: September 7, 2004). Available from, as of June 22, 2006: http://monographs.iarc.fr/ENG/Monographs/vol88/volume88.pdf **PEER REVIEWED** "



Data Evaluation

- Background
- Confidence and Assumptions

Background

Animal Data

Advantages	Disadvantages
Easy to Establish Causation: Exposure➔ Effect	Relevance of animal data to humans
	Relevance of extrapolation for high dose to low dose
	Homogeneity of test animals vs. heterogeneity of human population
Able to control exposure conditions	

Background

Epidemiological Data

Advantages	Disadvantages
Species of primary concern	Exposures often poorly defined
	Long latency of disease
	Low statistical power and sensitivity
	Confounding Factors (multiple exposures)

25

Background

COMMON TOXICITY DEFAULTS

Test animals are appropriate models for humans.
(Studies show that some animal tumor responses do not occur in humans)

High-dose exposures in animals accurately predict potential adverse effects at lower doses in humans.
(Differences in metabolism, physiology, and many other factors change the way animals and humans react at different doses)

The most sensitive sex, strain, species and site of action are proper bases for risk assesment.
(Certain species are not always appropriate models of the Human response because of differences in body chemistry and physiology)

26

Background

1. It is essential to evaluate all interspecies differences carefully before concluding that human toxicity from animal toxicity results for a suspect chemical.

2. Results from epidemiological studies provide information about the effects of a suspect chemical *directly* in humans, and are usually given more weight than animal studies.

27

Confidence and Assumptions

1. Assumptions

- Lifetime incidence in humans is the same as in animals receiving an equivalent dose, when that dose is calculated on a body weight or surface area basis.
- Humans are as sensitive as the most sensitive animal species.

28

Confidence and Assumptions

2. Confidence

- There is a strong association between exposure and disease.
- Findings are consistent (association and specificity) in more than one study.
- The exposure data are reliable and supported by biological or ambient data.
- There is a clear dose-response relationship.

Confidence and Assumptions

2. Confidence

- The study is of sufficient statistical power and significance.
- There is adequate and reliable documentation of disease incidence.
- The temporal relationship between exposure and manifestation of the disease is biologically plausible.

30

Output of Hazard Identification

1. List of Properties

- Chemical
- Physical
- Toxicological

2. The Critical Effect

- The relevant adverse effect that is produced at the **lowest** exposure or dose

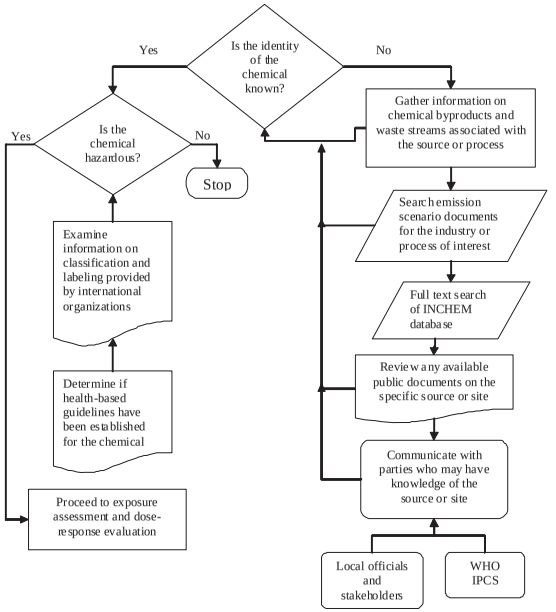
3. Example- Formaldehyde

- Volatile Organic Compound
- Used in fertilizer, paper, plywood, urea-formaldehyde resins, and preservatives
- Affected Organs: Skin, GI Tract, Respiratory, Immune System

4. Critical Effect

- Known carcinogen

31



Roadmap for Hazard ID

Source: WHO Toolkit for Human Health Risk Assessment: Chemical Hazards

32

Hazard Characterization

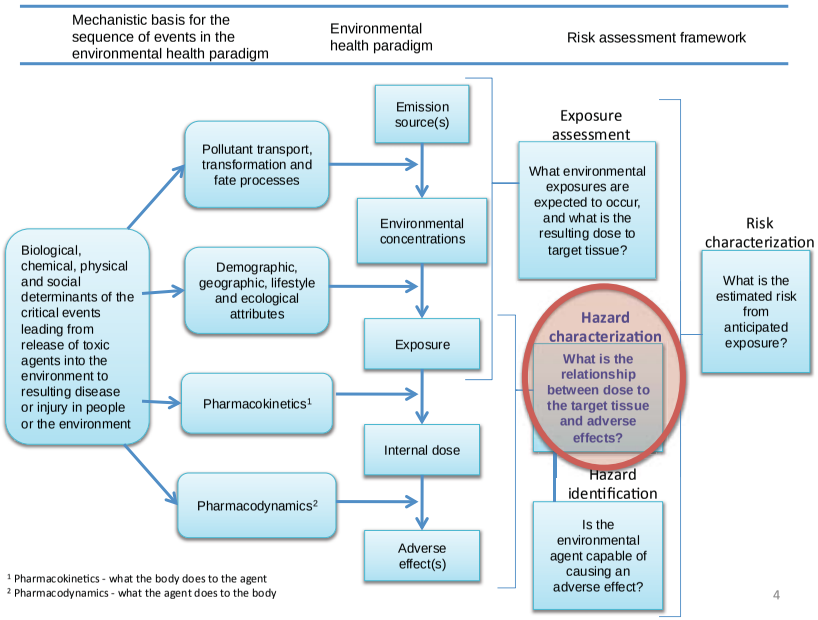
Presentation by: Dr. Salmaan Hussain Inayat Hussain
in collaboration with Dr. David MacIntosh
APEC risk assessment and risk management workshop
November 7-8, 2013
Bangkok, Thailand

Learning Objectives

- By the end of this module, workshop participants should have an understanding of:
  1. The meaning of a "dose-response" relationship.
  2. The metrics that are used to characterize the toxicity of a chemical for human health risk assessment.
  3. Resources from international organizations that are available to further identify and characterize a chemical of interest.

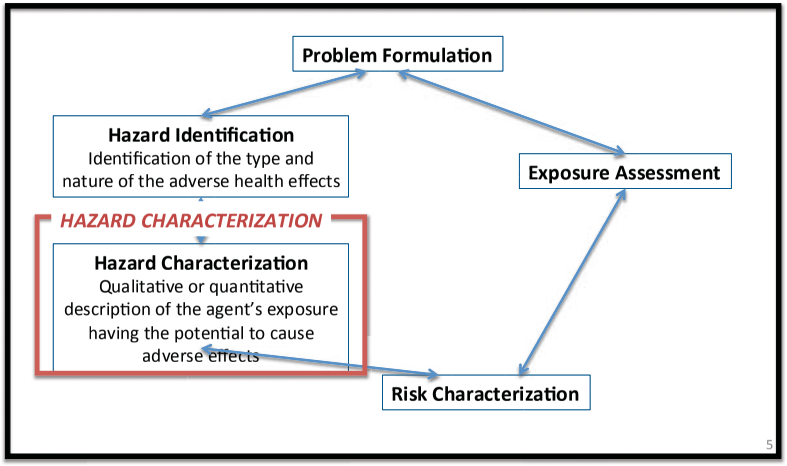
Key Messages

- ***Hazard characterization*** describes the toxic effects of an agent in relation to dose
  - ***Qualitative*** descriptions include whether effects are reversible, the result of acute or chronic exposure
    - whether expressed immediately or much later following exposure
  - ***Quantitative*** descriptions are generally expressed as guidance values which are derived from either studies of animals (toxicology) or people (epidemiology)
  - Carcinogenic and non-carcinogenic agents receive different hazard characterizations
- Safety factors and uncertainty factors are utilized in hazard characterization to decrease the chance that the risk to sensitive populations will be underestimated.
- Quantitative reference values for many agents are available from authoritative international, national and scientific sources.

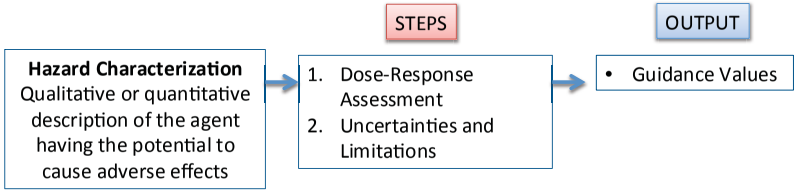


Introduction

RISK ASSESSMENT



Introduction Cont.



Dose

THE KEY CONCEPT in Toxicology

Father of Modern Toxicology

***Paracelsus*—1564**

All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and a remedy.

Dosis sola facit venemun

DOSE

- Definition: The amount of that agent that comes into contact with a living organism
- Dose Units
  - mg/kg (quantity per unit mass eg ingestion)
  - mg/m^2 (quantity per unit area eg skin)
  - mg/m^3 or ppm (mg/L) (quantity per unit air/water eg inhalation)
    - a ppm is equivalent to…..
      - One drop of gasoline in a standard 60 litre car gas tank
      - a single cent in 10, 000 dollars

Determinants of Dose
Workplace or Environmental

Dose

amount of toxicant reaching the target

Exposure

surrogate for dose

DOSE

The toxic response magnitude is proportional to the concentration of the chemical at the target site.

The concentration of a chemical at the target site is proportional to the dose.

ADME control the amount of a chemical that reaches the target site.

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion

DOSE-RESPONSE

Definition

- The quantitative relationship between the amount of exposure (dose) and the incidence of adverse effect (response).

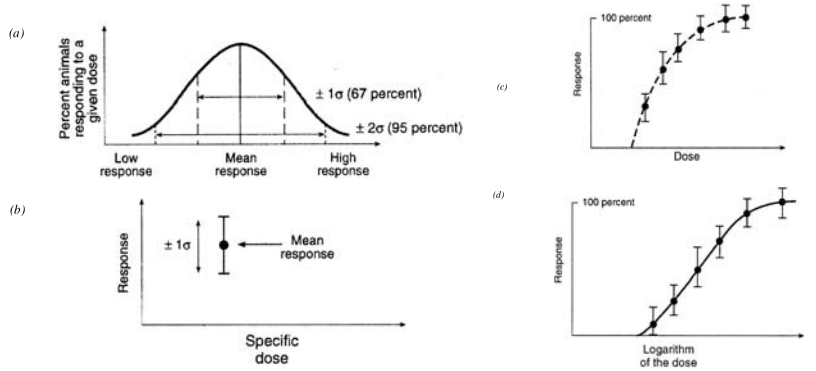
Uses

- To determine health-based guidance values
  - To determine a margin of exposure (MOE) in risk management
    - To estimate the magnitude of risk to a human health

The dose-response curve

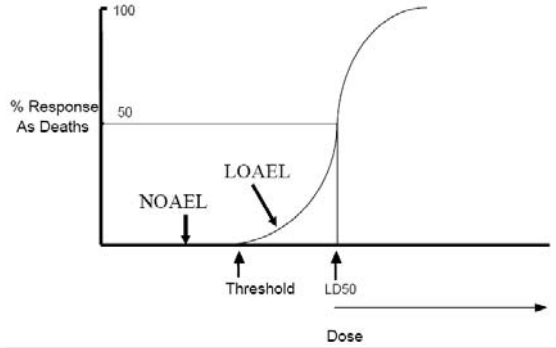
- As the dose increases, the measure response increases

DOSE-RESPONSE



Dose-Response Relationship

"The Dose Makes the Poison"

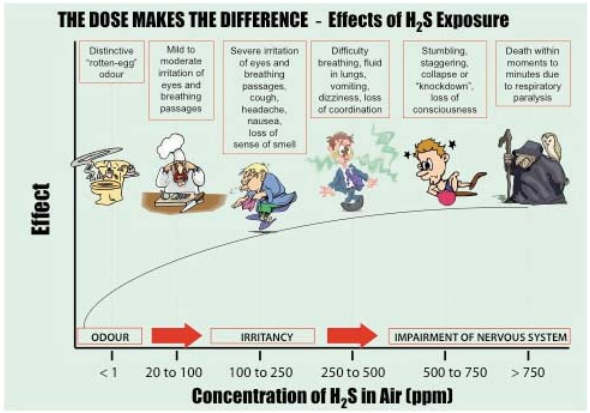


The LD50 is the median dose associated with the death of 50% of the population

Dose effect…

% Alcohol in Blood	Observed Effect
0.05	Stimulant, social relaxation
> 0.1	Incoordination
0.3	Unconsciousness
0.4	Possible lethal level

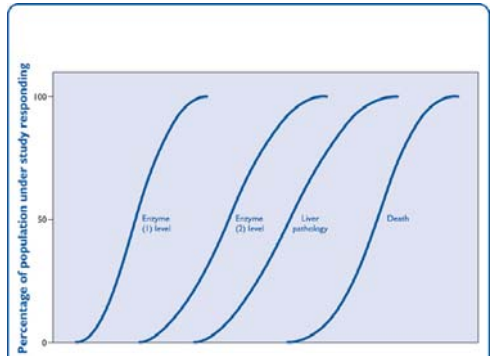
http://toxlearn.nlm.nih.gov



PEL= 10ppm

http://www.intrinsik.com/environment/docs/Sour_Gas_and_Your_Health-Intrinsik-2009.pdf

The Critical Effect



IMPORTANT DOSE CONCEPT

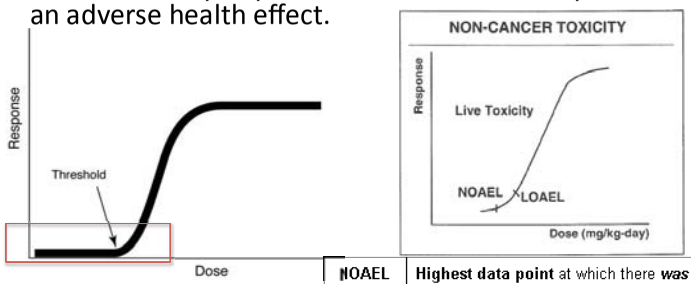
- THRESHOLD DOSE VERSUS NON-THRESHOLD DOSE

17

The Threshold Concept NON-CANCER

Threshold Concept: There is a dose below which there is no significant risk of occurrence of a health effect

- A range of exposure from zero to some finite amount can be tolerated by any individual with essentially no chance of an adverse health effect.



NOAEL	**Highest data point** at which there ***was not*** an observed toxic or adverse effect
LOAEL	**lowest data point** at which there ***was*** an observed toxic or adverse effect

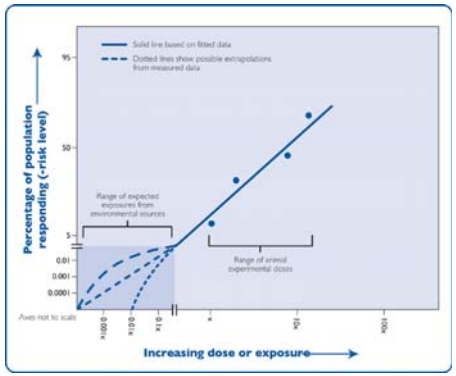
18

The No Threshold Concept CANCER

No Threshold Concept:

- The probability of response is proportional (linear) for all doses above zero
- No level of exposure which poses zero risk
- Commonly used with carcinogens

Figure 7: Hypothetical curve for an animal carcinogenicity study



Adapted from: Levy & Wegman 1988.

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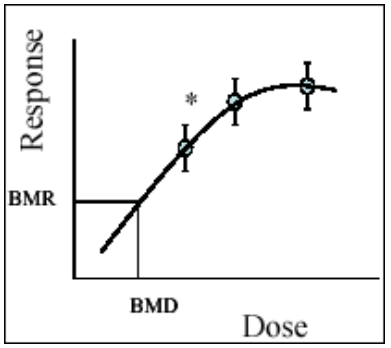
19

Benchmark Dose (BMD)

Benchmark Dose (BMD): the dose at which a certain percentage of population is expected to express the response.

- Common benchmark response (BMR) is 10%
- Advantages:
  - Can extrapolate
  - Can use for cancer and non-cancer outcomes
  - Can provide better statistical uncertainty analysis



20

Other Dose Response Models

- Continuous dose-response models
- Quantal dose-response models
- Severity
- Modeling with covariates
- Biologically based dose-response models
- For details on these models, please consult: EHC 239, available at: http://www.who.int/ipcs/publications/ehc/methodology_alphabetical/en/index.html

21

DOSE-RESPONSE NOAEL SELECTION

Based on the dose-response relationship

- Set the maximum quantity, at which any biological and statistical significant toxic effects are not found, as NOAEL.
  - If a NOAEL can not be determined, then select a LOAEL (Lowest Observed Adverse Effect Level). The NOAEL (or LOAEL) should be represented as the dose per 1 kg of body weight per day.

If more than 1 NOAEL can be obtained from several toxic test data

- Select the lowest NOAEL considering the sensitivity of the animals used in the test, the exposure duration, exposure route etc.
  - However, when several test results show the same effect in the same target organ, selection of the lowest NOAEL is not always the best
    - In this case, one can choose an appropriate NOAEL with careful examination of each of the test results (WISDOM REQUIRED)

22

DOSE-RESPONSE NOAEL SELECTION

NOAEL from epidemiological studies is rare

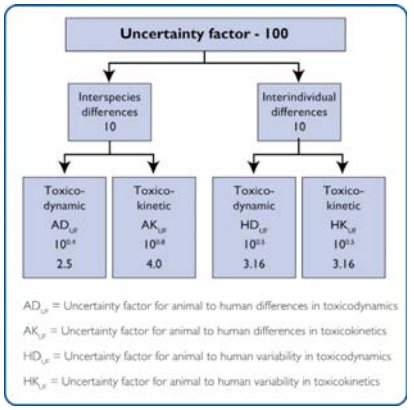
- Sometimes LOAEL is identified from epi studies and may be used

NOAEL (or LOAEL) are generally obtained from animal toxic test data (sometimes epi studies)

- includes some inevitable uncertainties or variability relating to the difference in sensitivity among individuals, the differences in sensitivity between animals and humans or the duration of exposure.
- These uncertainties (variability) should be represented as Uncertainty Factors (UFs) and the NOAEL (or LOAEL) should be divided by them to derive a reference or health based guidance value.

23

Figure 23: Proposed subdivision of default uncertainty factors to be used in risk assessment



Reproduced from IPCS 2009b with permission from WHO.

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24

Types of Uncertainty (JAPAN NITE DOCUMENT)

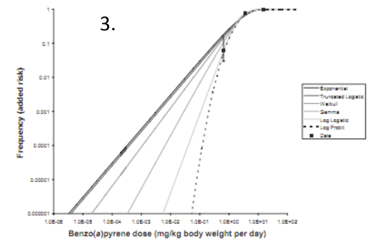
- Intraspecies variability: 10
- Interspecies variability: 10
- Extrapolation from LOAEL to NOAEL: 10
- Duration of Exposure (Extrapolation Subchronic to Chronic effects):
  - 1 month – shorter than 3 months: 10
  - 3 months - shorter than 6 months: 5
  - 6 months – shorter than 12 months: 2
  - 12 months or longer: 1
- Type of effect (Carcinogenicity): 10

Uncertainty and Limitations

Uncertainty arises from at least three sources:
- Environmental or Study Error
- Sampling or analytical Error
- Model Error or incomplete scientific knowledge

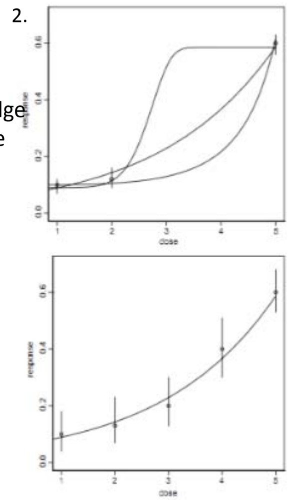
- Use p-values and confidence intervals to illustrate statistical significance and power.
- Refrain from extrapolating wherever possible.

3.



Example: Variability in outcomes at low-doses.

2.



Example: Two data sets illustrating the idea of model uncertainty

Reference Material 2: Examples of Uncertainty Factor used domestically and internationally

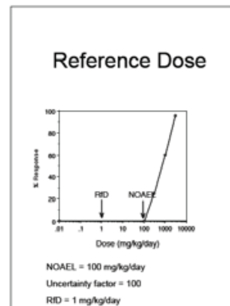
	NITE CERI "Guideline on Initial Risk Assessment Ver.2.0", 2007.[1)]	Cabinet Office, Government of Japan Food Safety Commission "Glossary regarding Food Safety (Revised version, addenda)" 2006.[2)]	Ministry of Health, Labour and Welfare Health Sciences Council Section Meeting on Living Environment, and Drinking Water "Reviews regarding Water Quality Standards" 2003.[3)]	Ministry of the Environment "Initial Environmental Risk Assesment of Chemicals Vol 5" Guideline for Initial Risk Assessment of Chemicals 2006.[4)]	GHS Inter-Ministerial Committee Outlook on Risk Assessment for Consumer Products Based on Exposure for GHS Labelling, 2007.[5)]	U.S. EPA A REVIEW OF REFERENCE DOSES AND REFERENCE CONCENTRATION PROCESSES. EPA/630/P-02/002F, 2002.[6)]	WHO/IPCS Environmental Health Criteria 210: Principles for assessing the risk to human health from exposure to chemicals, 1999.[7)]	ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) ICH Harmonised Tripartite Guideline Impurities: Guideline for Residual Solvents Q3C(R3),1997.[8)]	ECB (European Chemical Bureau) EUSES2.0 Background Report III, Model Calculations page III-191, Table III-108, 2004.[9)]	ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) Technical Report No. 86, 2003.[10)]	Australia Department of Health and Ageing Environmental Health Risk Assessment, Guidelines for assessing human health risks from environmental hazards, 2004.[11)]
Interspecies	10	10	10	10	10	when data available, TK Mouse; 7, Rat; 4, Guinea pig; 3, Rabbit; 2 } TD ×3	10 → TD $10^{0.4}$(2.5), TK $10^{0.6}$(4.0)	Rat: 5 Mouse: 12 Dog: 2 Rabbit: 2.5 Monkey: 3 Other animals: 10	Rat: 4, Mouse: 7, Guinea pig: 3, Rabbit: 2.4, Monkey: 2, Dog: 1.4 } ×2.5	Mouse: 7 Rat: 4 Monkey: 2 Dog: 2 Inhalation area: 1	10
Intraspecies	10	10	10		10	10	10 → TD $10^{0.5}$(3.2), TK $10^{0.5}$(3.2)	10	Workers: 5 General population: 10	(systemic effects, local effects) General population: 5 Workers: 3	10
Exposure duration	1 month: 10 3 months: 5 6 months: 2 12 months: 1		Up to 10	10	1～10	Subchronic to Chronic: 10 Not applicable to a shorter period than Subchronic	(10)	Half-life *) or more:1 Mid-long term**) ; 2 Mid term***) ; 5 Short term ; 10	Subacute to Subchronic: 3 Subchronic to Chronic: 2 Subacute to Chronic: 6	Subacute to Chronic: 6 Subchronic to Chronic: 2 Local Effects by Inhalation: 1	
LOAEL to NOAEL	10		Up to 10	10	1～10	10	3 or 10	10		3	10
Incompleteness of DB	*)		Up to 10			Depends on condition 3 or 10	Take into account (value larger than 1)				1～10*)
Characteristics of toxicity (such as carcinogenicity with threshold value)	Carcinogenicity with threshold: 10		Up to 10 *) 10 **)	Up to 10 *) Normally 10 (1～10) **)			Up to 10	1 for fetal toxicity associated with maternal toxicity 5 for fetal toxicity without maternal toxicity 5 for a teratogenic effect with maternal toxicity 10 for a teratogenic effect without maternal toxicity	Take into account *) No specific value		1～10
Remarks [Uncertainty Factors (UFs) and others]	*) Can be added depending on the type and quality of text at evaluator's judgment. If the UFs exceed 10,000 the data will not be used. Definition of test duration: 1 month = 1 - less than 3 month, 3 months = 3 - less than 6 months, 6 months = 6 - less than 12 months, 12 months = 12 months and more	Generally the setting of ADI use 100 which is the mix of interspecies and intraspecies, and depending on the quality of data, adopt larger factors (such as 500, 1000, 1500).	*) if the characteristics of toxicity is severe, **) if carcinogenicity exists.	Should be set as the factor to use in calculating the MOE. *) if N(L)OAEL is set using non-carcinogenic effects but possibly carcinogenic to human. **) if N(L)OAEL is set using carcinogenic effects.		The Technical Panel recommends limiting the total UF applied for any particular chemical to no more than 3000 and avoiding the derivation of a reference value that involves application of the full 10-fold UF in four or more areas of extrapolation. *)in the absence of any other specific toxicokinetic or toxicodynamic data, a default factor of 3 (in conjunction with HEC derivation) or 10 is applied.	TD: toxicodynamics, TK: toxicokinetics No description during the test, however, it is taken into consideration with drinking water quality setting.	*) 1 year for rodents or rabbits. 7 years for cats, dogs, and monkeys. **) 6-month study in rodents, or a 3.5-year study in non-rodents. ***) 3-month study in rodents, 2-year study in non-rodents.	In addition extrapolation from route to route is considered. *) It is considered as the uncertainty in the extrapolation of the dose-reaction, including the uncertainty associated with the characteristic of the effect and quality of the database.	Extrapolation between routes (Oral to Inhalation, Inhalation to Dermal) are stated as "not set".	*) Representation of the "quantity and quality of scientific data".

GUIDANCE ON A CONSUMER PRODUCT RISK ASSESSMENT FOR GHS LABELLING (2008) National Institute of Technology and Evaluation Chemical Management Center, Japan

Determining Guidance Values

Reference dose= $\frac{\text{NOAEL or BMD}}{\text{UF}}$

1. To determine the guidance value, the NOAEL or BMD is modified to decrease the chance that the risk to sensitive populations will be underestimated
2. Uncertainty factors (UF) are applied for:
   - Variability
     - Interspecies differences and human variability
   - Uncertainty
     - Lack of studies considering specific endpoints or long term exposure or use of a LOAEL
   - Values for each uncertainty factor typically range from 3 to 10



Guidance Values

1. Guidance Value: A dose or concentration, which is derived after allocation of the reference dose among the different possible media (routes) of exposure.

	Term	Abbreviation	Use	Units
2.	Acceptable Daily Intake	ADI	*Systemic Toxicants*	mg/kg body weight/ day
	Tolerable Daily Intake	TDI	*Systemic Toxicants*	mg/kg body weight/ day
	Reference Dose	RfD	*Systemic Toxicants*	mg/kg body weight/ day
	Provisional Tolerable Weekly Intake	PTWI	*Systemic Toxicants*	mg/kg body weight/ week
	Provisional Tolerable Monthly Intake	PTMI	*Systemic Toxicants*	mg/kg body weight/ month
3.	Cancer Slope Factor	CSF	*Carcinogenic Toxicants*	(mg/kg body weight per day)$^{-1}$
	Drinking Water Guidelines	--	*Regulatory Purposes*	µg/L
4.	Air Quality Guidelines	--	*Regulatory Purposes*	µg/m^3
	Maximum Residue Limit	MRL	*Regulatory Purposes*	mg/kg

29

62

CARCINOGEN DOSE RESPONSE

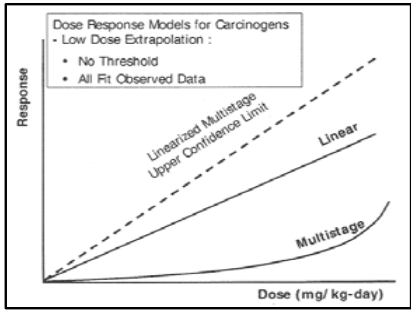
- The risk of cancer is characterized as a linear relationship with dose for cancer causing chemicals
- The carcinogenic potency of a chemical is characterized as the slope of a line fit to the relationship between exposure to the chemical and prevalence of cancer in populations.
- In practice, an upper-bound estimate of the coefficient, such as the 95th percentile, is selected to account for uncertainty in model fit and to provide a conservative estimate of the true but unknown actual carcinogenic potency

30

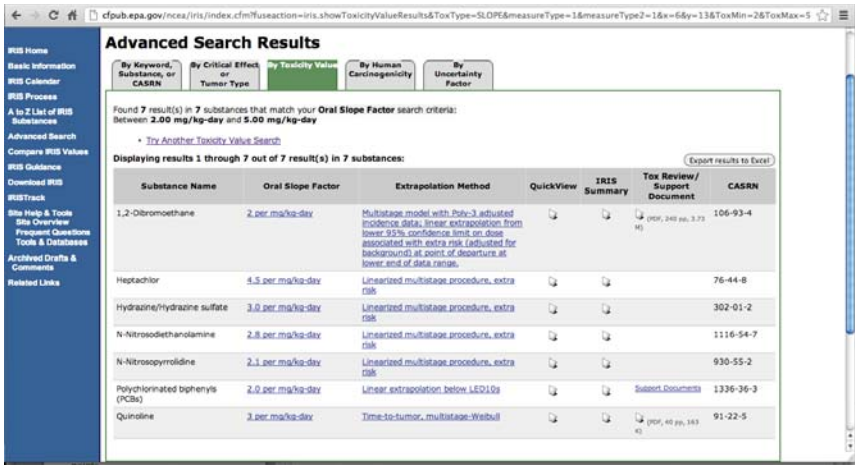
Cancer Slope Factor Non-threshold Approach

1. The Cancer Slope Factor (CSF) is determined by fitting a line between exposure to the chemical and prevalence of cancer in populations.

2. Uncertainty Factor:
   - 95% upper statistical confidence bound for the slope of the dose response curve.
3. CSF:
   - Unit is inverse dose or exposure
   - TCE: 0.4 (mg/kg-day)$^{-1}$



31



32

Output of Hazard Characterization

1. Guidance Values

- Examples:
  - Acceptable/ Tolerable Daily Intake (ADI/TDI)
  - Acute Reference Dose (ARfD)
  - Chronic Reference Concentration (RfC)
  - Cancer Slope Factor (CSF)
  - Drinking Water Limit
  - Food Residue Limit (MRL)
  - Worker's Time Weighted Average (TWA)

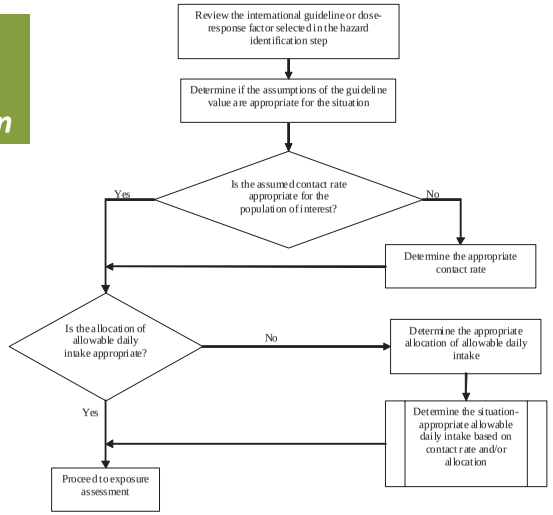
2. Example- Chlorpyrifos

- ADI- 0.01 mg/kg/day
- ARfD- 0.1 mg/kg/day

33

Roadmap for Hazard Characterization

Source: WHO Toolkit for Human Health Risk Assessment: Chemical Hazards



34

63

International Sources of Guidance Values

Sources of guidance values for chemicals developed by international organizations.

Reference	Available at:
Inventory of IPCS and other WHO pesticide evaluations and summary of toxicological evaluations performed by the joint Meeting on Pesticide Residues (JMPr) through 2010	http://www.who.int/foodsafety/chem/jmpr/publications/jmpr_pesticide/en/index.html
Evaluations of the Joint FAO/WHO Expert Committee on Food Additives	http://apps.who.int/ipsc/database/evaluations/search.aspx
WHO's Alphabetical list of CICADs	(http://www.who.int/ipcs/publications/cicad/cicads_alphabetical/en/index.html, accessed 23 August 2010

35

International Sources of Media Specific Guideline Values

Guidelines	Organization	Reference	Available at
Drinking-water quality guideline values	WHO, 2008	*Guidelines for drinking-water quality,*	http://www.who.int/water_sanitation_health/dwq/gdwq3rev/en/index.html
Drinking-water quality guideline values	WHO, 2008	*Guidelines for drinking-water quality*	http://www.who.int/water_sanitation_health/dwq/GDWAN4rev1and2.pdf
Air quality guidelines	WHO, 2000	WHO (2000) *Air quality guidelines for Europe*	http://www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf
Air quality guidelines	WHO, 2000	*Air quality guidelines—global update 2005: particulate matter, ozone, nitrogen dioxide and sulfur dioxide.*	http://whqlibdoc.who.int/hq/2006/WHO_SDE_PHE_OEH_06.02_eng.pdf, accessed 23 August 2010
Maximum residue limits (MRLs) of pesticides in food	FAO/WHO, 2010	FAO/WHO (2010) *Pesticide residues in food: maximum residue limits, extraneous maximum residue limits*	http://www.codexalimentarius.net/mrls/pestdes/jsp/pest_q-e.jsp
Maximum limits (MLs) of contaminants in food	FAO/WHO, 2010	FAO/WHO (2010a) *Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)*	http://apps.who.int/ipsc/database/evaluations/search.aspx

36

Exposure Assessment

Presentation by: Dr. David MacIntosh
APEC risk assessment and risk management workshop
November 7-8, 2013
Bangkok, Thailand

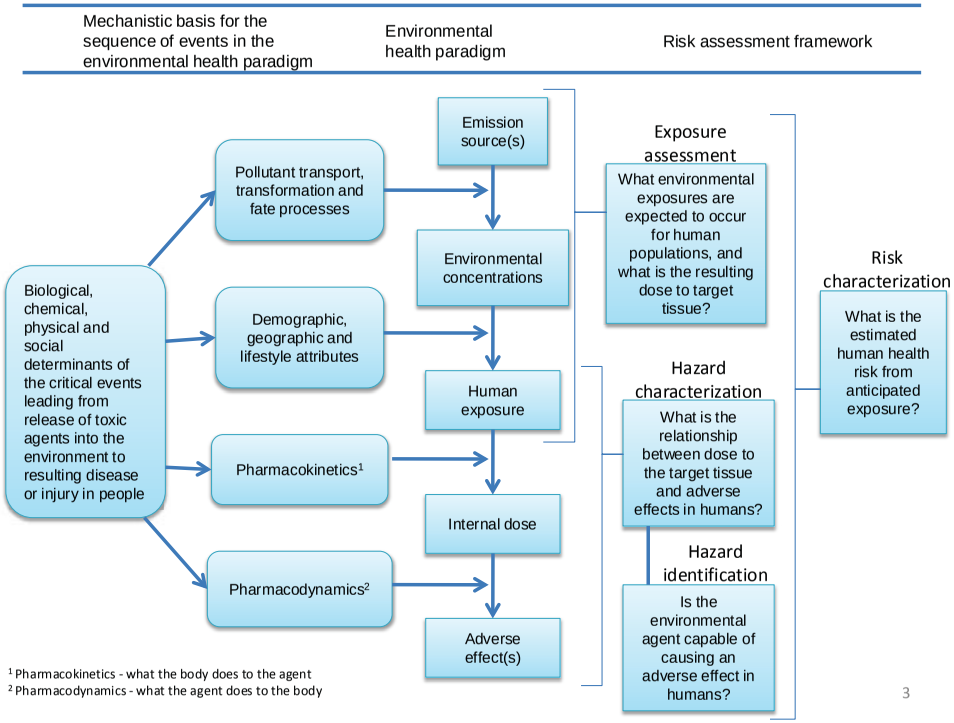
Learning Objectives

By the end of this module, workshop participants should have an understanding of:

- The purpose of exposure assessment for health risk assessment
- The primary attributes of exposure
- The routes and pathways by which people and other organisms can be exposed to hazardous substances
- Common metrics of exposure: concentration, intake rate, and dose
- General approaches to how exposure is evaluated and their corresponding strengths and limitations
- How knowledge of exposure can support a risk management process
- International resources that provide additional exposure information

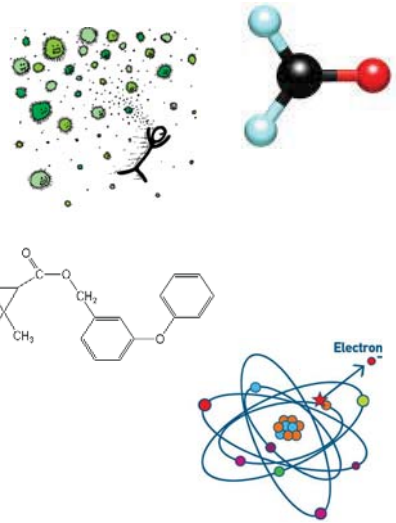
Exposure Defined

- What is exposure?
  - Exposure is contact between a hazardous agent and a target such as a person, plant, animal, or other receptor of interest. Contact takes place at a lining of the organism such as the lung, skin, and eyes.
  - Contact generally occurs when hazardous agents are in air, water, food, soil, or products that contain a hazardous substance.
  - Source
    - WHO 2000
    - http://www.inchem.org/documents/ehc/ehc/ehc214.htm
- Exposure assessment
  - Exposure assessment is the process of estimating or measuring the magnitude, duration, and frequency of exposure to an agent, along with the number and characteristics of the population exposed. Ideally, an exposure assessment describes the sources, pathways, routes, and uncertainties in the assessment.



Hazardous Substances

- Risk assessments require estimates of exposure for a wide variety of hazardous substances
  - Chemical hazards: volatile organic compounds, pesticides, semi-volatile organics, gases, aerosols, heavy metals, etc.
  - Biological hazards: virus, fungi, bacteria, allergens, infectious agents
  - Physical hazards: ionizing radiation, heat, electromagnetic fields, noise
- Risk assessments commonly focus on hazardous substances one at a time, but must also consider simultaneous exposure to multiple substances that have the same toxicological properties (e.g., organophosphate insecticides)
- Co-occuring exposure to multiple hazardous substances with different toxicological properties are sometimes the subject of risk assessment – e.g., carcinogens, neurotoxicants, and liver toxins.

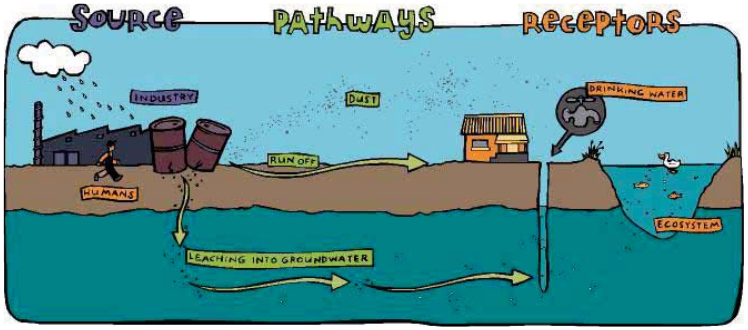


Exposure and Risk

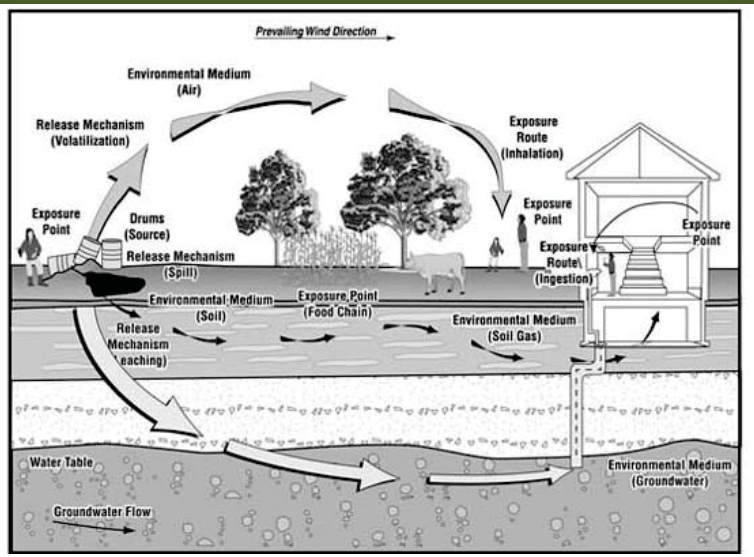
- Exposure is the critical link between emissions of a hazardous substance and risk
- Risk is a function of exposure and toxicity.
  - When there is no exposure, there can be no risk.
  - Low exposure to an substance with high toxicity yields low risk. Likewise, high exposure to a substance with low toxicity also yields low risk.
  - High exposure and high toxicity can produce a level of risk that warrants further attention and evaluation of approaches for managing the risk.

Exposure Pathway

- The course that an agent follows from the source to the receptor
- Exposure pathways can be complete or incomplete
- If the exposure pathway is incomplete, the agent doesn't reach the receptor, reducing the risk
- Understanding the exposure pathway is critical for identifying opportunities to reduce intake of a hazardous agent



Exposure Pathway

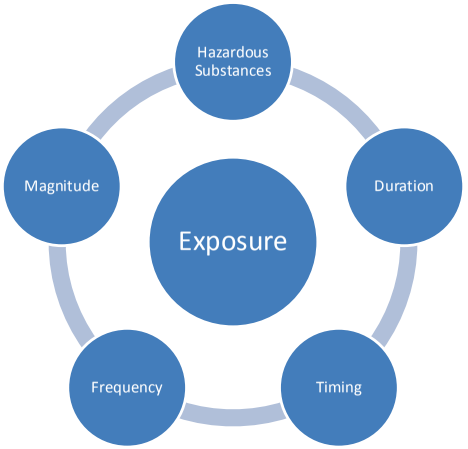


Exposure Routes

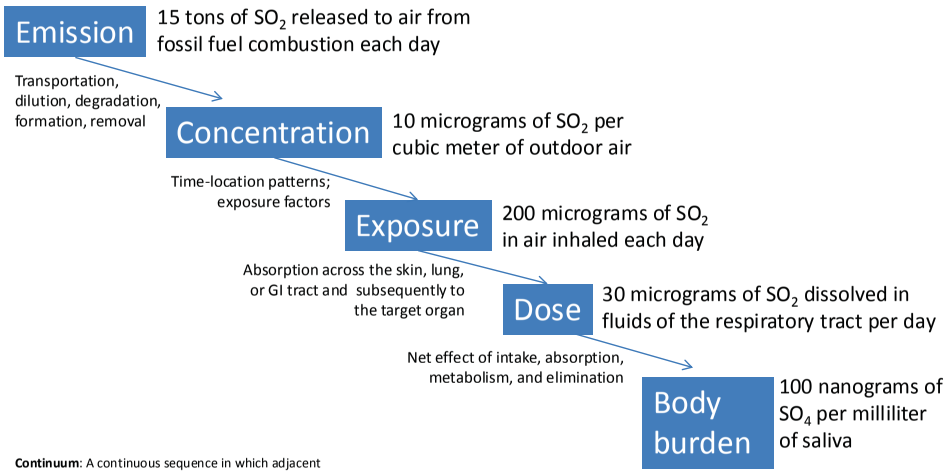
- Hazardous agents can enter the body through three routes of exposure
- Inhalation
  - Agent is present in outdoor or indoor air of locations visited by a receptor
  - Absorption could occur through the respiratory tract
- Ingestion
  - Agent is present in water, food, soil, or dust that is consumed intentionally or unintentionally
  - Absorption could occur through the gastrointestinal tract
- Dermal absorption
  - Agent is present in a liquid, solid, air, or a product that is contact with the skin
  - Absorption could occur through the layers of the skin
- Route of exposure can be an important consideration in the potential for adverse effects of exposure to an agent

Characteristics of Exposure

- Magnitude
  - The amount of a hazardous substance in an environmental medium or consumer product
  - The rate of contact with the substance
- Duration
  - The period of time over which an individual or population may be exposed
  - Ranges from short (seconds) to long (lifetime)
- Frequency
  - The persistence of exposure over a certain duration of time
  - Contact could be rare, intermittent, or continuous
- Timing
  - Vulnerable period
  - Childhood
  - Pregnancy



Continuum of Exposure Metrics



Continuum: A continuous sequence in which adjacent elements are not perceptibly different from each other, although the extremes are quite distinct.

Quantifying Exposure

- Three basic approaches for quantifying exposure
  - Each approach considers different data
  - Each approach has different strengths and weaknesses
  - Using the approaches in combination can strengthen the credibility of an exposure assessment
- Point of Contact Measurement
  - Measuring the chemical at the point of contact with people or the environment
  - Measuring the duration, frequency and timing of contact
- Scenario Evaluation
  - Separately evaluating exposure concentrations and time of contact
  - Combining that information to estimate exposure
- Reconstruction
  - Estimate exposure from body burden and dose after the exposure has taken place

Point of Contact Measurements

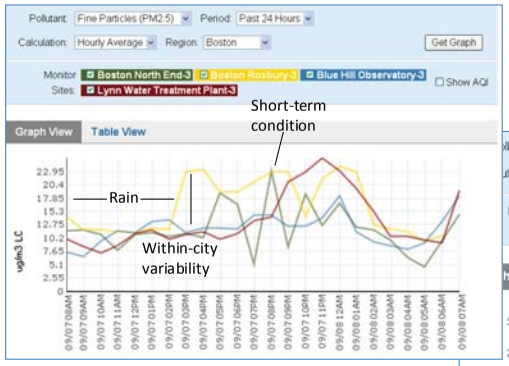
- Measuring the amount of a chemical at the point of contact with people or the environment
  - Usually reported as a concentration
- Whether measured or modeled, in the field or in a controlled setting, exposure concentrations always represent a certain time and location
- Important to understand the spatial and temporal dimensions of an exposure concentration in comparison to the corresponding dimensions of the assessment question
  - Instantaneous or very short term)
  - Integrated over time
    - Time series
    - Discrete

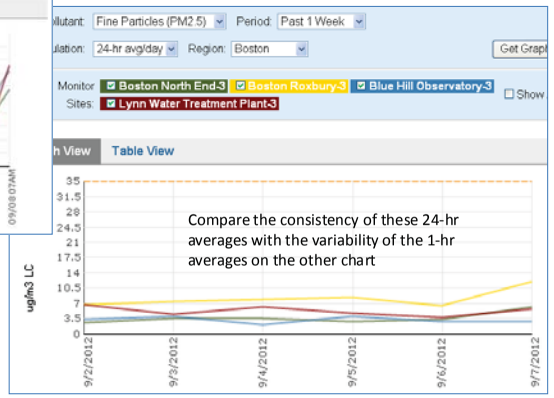
Personal air


Food and water


Skin

Example of Temporal and Spatial Dimensions





Scenario Evaluation

- Exposure requires that a hazardous agent and a person are present in the same location at the same time
- Scenario evaluation refers to combining separate analyses of concentrations and time-location patterns
- Concentrations and time-location patterns can be determined from measurements or models
- Exposure can be quantified in several different forms
  - Time-weighted average concentration
  - Cumulative concentration (concentration x time)
  - Intake rate
- These terms are often synonyms for exposure: exposure concentration, exposure dose, potential dose, administered dose

Time-Weighted Average Exposure

- Time-weighted average exposure
  - An average of location-specific concentrations weighted by the amount of time a person spends in each location

– TWA Exposure = $\sum_{i=1}^{n} (C_i \cdot f_i)$

where,

C = concentration

f = fraction of time spent in location i

i = an individual location

n = the total number of locations

Cumulative Exposure

- Examples
  - Pack-years for characterizing exposure from lifetime tobacco use
    - One pack-year = any combination of cigarette consumption and duration that is equivalent to 20 cigarettes smoked everyday for one year
    - Equivalencies for other forms of tobacco
    - Calculators available
  - ppm-years for characterizing lifetime exposure to benzene
    - One ppm-year = any combination of benzene concentration and duration that is equivalent to 8-hour average benzene personal air concentration of 1 ppm over one year of full-time work
  - Working Level Month (WLM) for characterizing lifetime exposure to radon
    - 1 WLM = any combination of radon concentration in air and duration that is equivalent to 100 picocuries of radon per liter of air for 170 hours
- Because time is an explicit component of this metric, we are now transitioning from concentration into exposure and dose

Exposure Rates

- Concentrations and contact with environmental media are combined to estimate the amount of an agent delivered to a lining of the body per unit time.
- This metric of exposure is often termed exposure rate, intake, exposure dose, or administered dose
- Units are typically
  - Amount (weight, number) per time
  - Amount per time per body weight
- Exposure rate = $\frac{\text{Exposure Concentration x Exposure Factor}}{\text{Body Weight}}$

Exposure Factors

4.8.6 Exposure factors

Exposure factors are generic or default values that describe contact rates with media, including inhalation rate, drinking-water consumption and food consumption. Exposure factors also include anthropometric features of people, such as body weight and body surface area. Default exposure factors published by WHO are summarized in Table 19.

Table 19: Summary of selected exposure factors published by WHO.

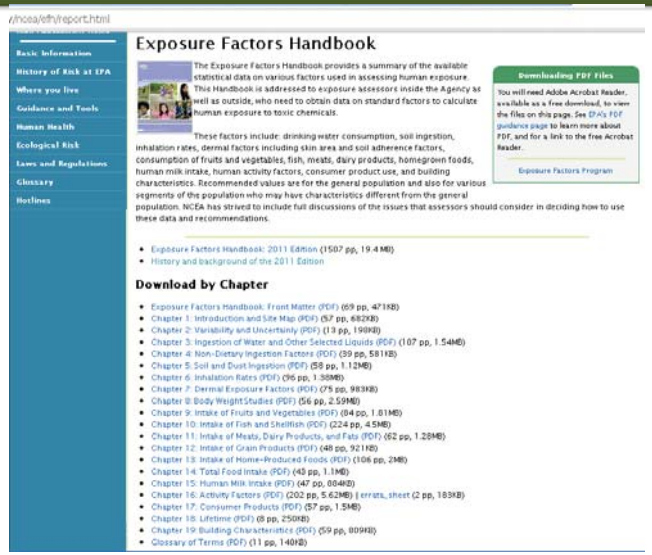
Exposure factor	*Value*	*Reference*
Inhalation rate	22 m^3/day	IPCS (1994)
Drinking-water consumption	2 litres/day	WHO (2008a)
	1.4 litres/day	IPCS (1994)
Body weight	60 kg	WHO (2008a)
	64 kg	IPCS (1994)
Food consumption	Diets for clusters of countries	WHO (2010b)

Source: WHO Human Health Risk Assessment Toolkit: Chemical Hazards, 2010

Exposure Factors Handbook

- U.S . Environmental Protection Agency, National Center for Environmental Assessment
  - Major part of the EPA Office of Research and Development (not a regulatory program)
  - Produces a comprehensive compilation of exposure factor research and recommendations for exposure factors
- Adult and child versions of the handbook
- Exposure Factors Handbook website
  - Links to the adult and child handbooks
  - Guide to current literature
  - Summary of current exposure factor research
- Let's take a quick look …

Exposure Factors Handbook



Dose

- Conceptually, dose is the exposure rate over a length of time that is biologically (toxicologically) relevant
- Average daily dose (ADD) is a common dose metric
- ADD = $\frac{\text{Exposure Conc x Exposure Factor x Exposure Duration x Exposure Frequency}}{\text{Body Weight x Averaging Time}}$
- When calculating ADD, averaging time is generally either the period of exposure or the length of a typical lifetime.
- Let's look at an example of calculating the ADD for both the period of exposure and a lifetime

Calculating Period Average Daily Dose

- Calculate the ADD over the exposure period for this hypothetical scenario: arsenic is present in drinking water of a community at a concentration of 22 micrograms per liter. Each member of the community consumes 0.2 liters of water three times a day, resides in the community for 30 years, lives to be 70 years old, and weighs 65 kilograms.
- ADD = $\frac{\text{Exposure Conc x Exposure Factor x Exposure Frequency x Exposure Duration}}{\text{Body Weight x Averaging Time}}$

$= \frac{\text{22 ug/L x 0.2 L/drinking event x 3 drinking events/d x 30 years}}{\text{65 kg x 30 years}}$

= 0.2 ug/kg/d

The average daily dose over the exposure period for a member of the community is 0.2 microgram of arsenic per kilogram body weight per day.

Calculating Lifetime Average Daily Dose

- Calculate the ADD over the exposure period for this hypothetical scenario: arsenic is present in drinking water of a community at a concentration of 22 micrograms per liter. Each member of the community consumes 0.2 liters of water three times a day, resides in the community for 30 years, lives to be 70 years old, and weighs 65 kilograms.
- ADD = $\frac{\text{Exposure Conc x Exposure Factor x Exposure Frequency x Exposure Duration}}{\text{Body Weight x Averaging Time}}$

$= \frac{\text{22 ug/L x 0.2 L/drinking event x 3 drinking events/d x 30 years}}{\text{65 kg x 70 years}}$

= 0.09 ug/kg/d

The lifetime average daily dose for a member of the community is 0.09 microgram of arsenic per kilogram body weight per day.

Reconstruction: Biomarkers of Exposure

- Measurements of chemicals in biological tissue or fluids
  - compounds of interest or their metabolites
  - blood, urine, hair, nails, exhaled breath
- Advantages
  - Characterize total dose of a contaminant from all sources of exposure for a particular time
  - Can be more predictive of health risk than external measures of exposure
  - Useful for status and trends analysis as well as identifying the environmental and demographic determinants of exposure
- Disadvantage - difficulty in characterizing the individual sources which contribute to total exposure

24

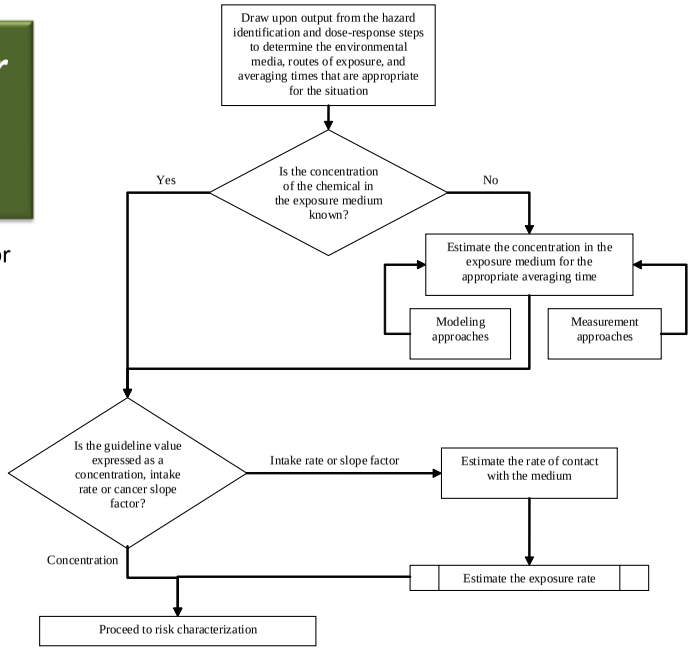
Role of Exposure in Assessing Risk

- Health protective benchmarks provide a standard against which we can determine whether exposure is acceptable (or not), high or low, in a range that warrants further evaluation.
- Health protective benchmarks are often expressed in units of exposure – for example, the average daily dose of a chemical that is likely to be without appreciable risk of adverse effects over a lifetime
- Therefore, comparing an estimate of exposure to a health protective benchmark can provide a preliminary characterization of risk
- These concepts will be addressed further in the risk characterization section of the workshop

25

Roadmap for Exposure Assessment

Source: WHO Toolkit for Human Health Risk Assessment: Chemical Hazards



26

International Resources - General

Table 17: International sources of guidance on exposure assessment.

Document title	*Reference*
Human exposure assessment (EHC 214)	IPCS (2000)
Human exposure assessment: an introduction	Berglund et al. (2001)
Dietary exposure assessment of chemicals in food	FAO/WHO (2008)
Occupational and consumer exposure assessments	OECD (1993)
Principles of characterizing and applying human exposure models (Harmonization Project Document No. 3)	IPCS (2005b)
Biomarkers and risk assessment: concepts and principles (EHC 155)	IPCS (1993a)
Biomarkers in risk assessment: validity and validation (EHC 222)	IPCS (2001b)

Links to the documents on this page and the next page can be found in the WHO EHC 214 Human Exposure Assessment
http://www.inchem.org/documents/ehc/ehc/ehc214.htm

International Resources – Routes and Media

Table 16: International sources of information on media and routes of exposure.

Topic	*Document title*	*Reference*
Food additives and contaminants	*Principles and methods for the risk assessment of chemicals in food*	FAO/WHO (2009)
Pesticide residues in food	*Principles and methods for the risk assessment of chemicals in food*	FAO/WHO (2009)
Dermal absorption	*Dermal absorption* (EHC 235)	IPCS (2006c)
Drinking-water quality guidelines	*Guidelines for drinking-water quality*, 3rd edition, incorporating first and second addenda	WHO (2008a)
Air quality guidelines	*Air quality guidelines for Europe*, 2nd edition	WHO (2000)
Air quality guidelines	*Air quality guidelines—global update 2005: Particulate matter, ozone, nitrogen dioxide and sulfur dioxide*	WHO (2006)

Links to the documents on this page and the previous page can be found in the WHO EHC 214 Human Exposure Assessment
http://www.inchem.org/documents/ehc/ehc/ehc214.htm

Key Messages

- The purpose of exposure assessment is to determine the route by which people or ecological receptors come into contact with a hazardous substance and the magnitude of that exposure, including the frequency and duration.
- Exposure can occur through ingestion, inhalation, and absorption through the skin. The type and likelihood of effect from intake of a hazardous substance can differ by route of exposure.
- Exposure is commonly quantified in one of several forms: exposure concentration; exposure rate; average daily dose
- Exposure may be based on measurements or mathematical models of the amount of the contaminant in various media (air, water) and an estimate of human intake of these media under different activity patterns.
- Knowledge about the path that a hazardous substance follows through an environment is important for (i) understanding sources that contribute to exposure and (ii) identifying opportunities to manage risk.
- Information on background levels of hazardous substances in environmental media and default values for breathing rates, consumption of water and food, and absorption across the skin are available from authoritative international, national, and scientific organizations.

Risk Characterization

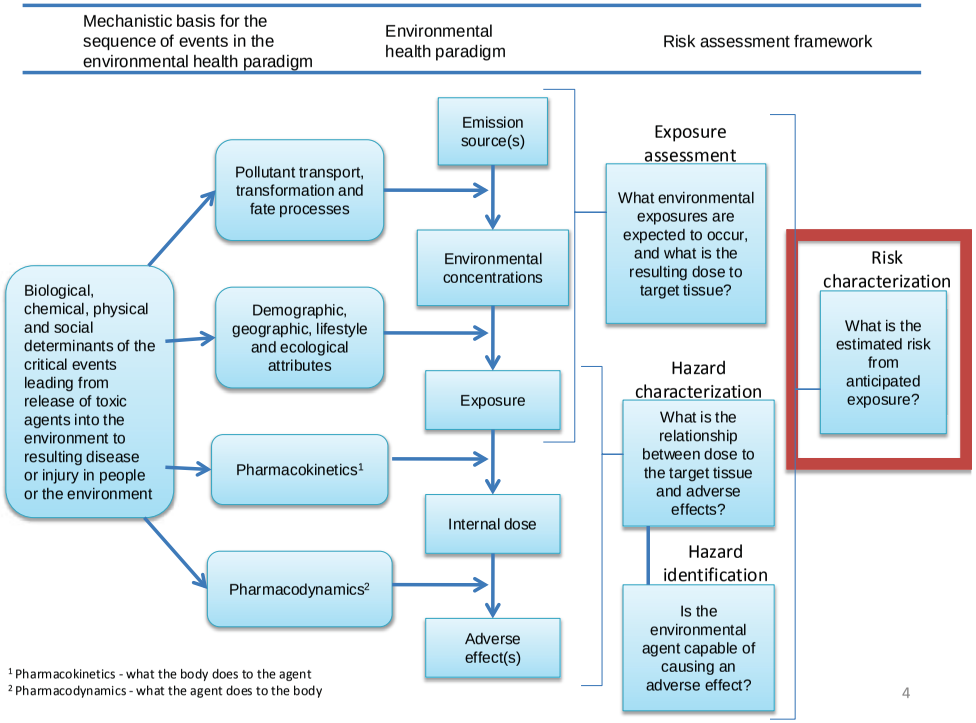
Presentation by: Dr. David MacIntosh
APEC risk assessment and risk management workshop
November 7-8, 2013
Bangkok, Thailand

Learning Objectives

- By the end of this module, participants should have an understanding of:
  - The purpose of risk characterization
  - Integrating the results of hazard identification, hazard characterization, and exposure assessment
  - Common metrics used to describe risk
  - Approaches for discussing uncertainties, assumptions, and scientific judgments

Key Messages

- Risk characterization, the last step in a risk assessment, is a qualitative or quantitative statement about the likelihood of harm associated with exposure to an agent including the identification and consideration of attendant uncertainties.
- Likelihood of harm is determined by combining results of the hazard characterization step and the exposure assessment step.
- Frequently used quantitative measures of risk are the hazard index, excess lifetime cancer risk, and margin of exposure.
- Risk can also be characterized quantitatively by comparing exposure concentrations for an agent in an environmental medium to corresponding guideline values derived from authoritative organizations such as the World Health Organization and national agencies
- The output of risk characterization should be presented in a manner that ensures that the risk manager and risk communicator understand the biological meaning and uncertainties of the risk assessment and how these can impact on their responsibilities.



Risk = Hazard x Exposure

Risk Characterization-The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions

Risk= Hazard x Exposure

5

Major Components of Risk Characterization

- State the objective of the assessment
- Quantitative or qualitative statement of likelihood of harm
- Discussion
  - Assumptions and uncertainties
  - Identify alternative interpretations
  - Distinguish scientific conclusions from policy judgments

6

Statement of Objective

- What population has the potential to be at risk?
- What is the time period of concern?
- Where is the exposure located and through what media?
- What is the agent(s) of concern?
- What are the health effects of concern?

7

State Likelihood of Harm

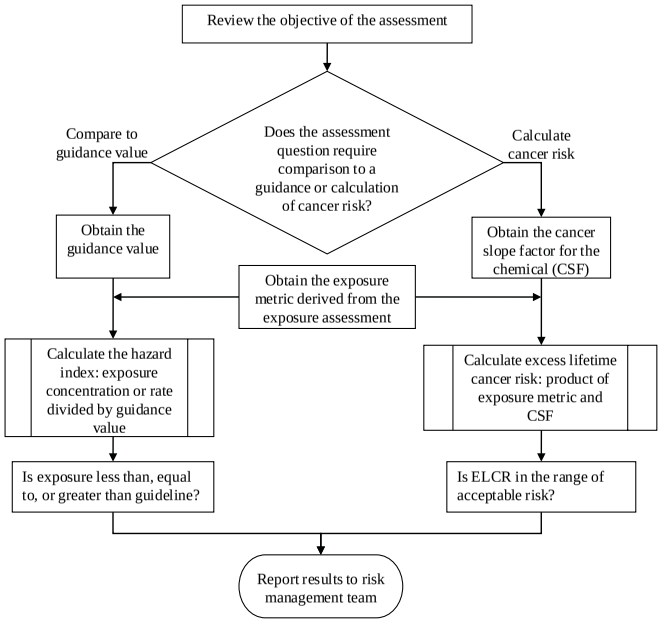
- Typically a probabilistic statement based upon comparing the amount of exposure to applicable benchmarks
- Examples of risk statements from various countries (YY to be filled in)

8

Applicable Benchmarks

- Conventions for *de minimus* or acceptable risk
- Health protective guidance levels
- Guideline levels for concentrations of chemicals in specific media, such as air, water, soil, sediment, and food
- Normative levels such as concentrations and exposures that are typical and presumably tolerated or accepted
- Sources: international and national organizations; scientific literature

Roadmap for Risk Characterization



Source: WHO Toolkit for Human Health Risk Assessment: Chemical Hazards

Conventions for de minimus Risk

	Human, Non-Cancer	Human, Cancer	Ecological
Convention	Exposure rate below threshold for adverse effect	Probability of a tumor is acceptably low	Exposure concentration below threshold for adverse effect

Health Protective Guidance Levels

	Human, Non-Cancer	Human, Cancer	Ecological
Convention	Exposure below threshold for adverse effect	Probability of a tumor is acceptably low	Exposure concentration below threshold for adverse effect
Hazard Characterization Input	ADI, TDI, RfD, RfC, BMD, etc.	Cancer slope factor (CSF)	Predicted No Effect Concentration (PNEC)
Exposure Input	Period average daily dose (PADD)	Lifetime average daily dose (LADD)	Predicted environmental concentration (PEC)
Risk Metric	Hazard quotient (HQ)	Excess lifetime cancer risk (ELCR)	Hazard quotient (HQ)
Calculation	HQ = PADD/ADI (or other)	ELCR = LADD x CSF	HQ = PEC/PNEC

Characterization of Non-Cancer Risk

- Hazard Quotient (HQ)
- A metric for evaluating the risk associated with exposure to chemicals that may cause (non-cancer) effects
- Calculated as the ratio of average daily to a guideline value
- Guideline values for a wide range of chemicals are available from international and national resources (refer to the Hazard Characterization section of the workshop)

$$\text{Hazard Quotient} = \frac{\text{Average Daily Dose}}{\text{Guidance Value}}$$

HQ < 1	The chemical exposure is less than the benchmark; unlikely to result in adverse effect
HQ > 1	The exposure is greater than the benchmark; potential risk

13

Example: Hazard Quotient

- Recall our example of period average exposure to arsenic in drinking water that was presented in the exposure section of the workshop
- Objective: characterize the risk of systemic effects to human health associated with that exposure
- Average Daily Dose: 0.2 micrograms of arsenic per kilogram body weight per day
- Guidance values
  - 2 µg/kg/d – Joint FAO/WHO Expert Committee on Food Additives
  - 0.3 µg/kg/d – U.S. Environmental Protection Agency

$$\text{Hazard Quotient} = \frac{\text{Average Daily Dose}}{\text{Guidance Value}}$$

FAO/WHO Benchmark

$$\text{Hazard Quotient} = \frac{0.2\ \mu g/kg/d}{2\ \mu g/kg/d}$$

$$= 0.1$$

HQ less than 1

EPA Benchmark

$$\text{Hazard Quotient} = \frac{0.2\ \mu g/kg/d}{0.3\ \mu g/kg/d}$$

$$= 0.67$$

HQ less than 1

14

Characterization of Cancer Risk

- Excess lifetime cancer risk (ELCR)
- A metric for quantifying risk associated with exposure to chemicals that may cause cancer
- Calculated as the product of dose and the cancer slope factor
- Information on carcinogenicity of chemicals is available from international and national resources (refer to the Hazard Characterization section of the workshop)

ELCR = Lifetime Average Daily Dose x Cancer Slope Factor

ELCR < 10^{-6}	Excess lifetime cancer risk less than 1 in a million is typically considered *de minimus* or negligible
ELCR > 10^{-4}	Excess lifetime cancer risk greater than 1 in ten thousand is a common benchmark for gathering additional information or relaxing conservative assumptions that may be used in a screening analysis

15

Example: Excess Lifetime Cancer Risk

- Recall our example of period average exposure to arsenic in drinking water that was presented in the exposure section of the workshop
- Objective: characterize the risk of systemic effects to human health associated with that exposure
- Lifetime Average Daily Dose: 0.09 micrograms of arsenic per kilogram body weight per day
- Guidance values
  - 1.5 per mg/kg/d - U.S. Environmental Protection Agency

ELCR = Lifetime Average Daily Dose x Cancer Slope Factor

= 0.09 ug/kg/d x 1 mg/10^3 ug x 1.5 per mg/kg/d

= 1.35 X 10^{-4}

The extra risk of cancer associated with lifetime exposure to arsenic in drinking water is 1.35 in 10,000 or approximately 0.01%

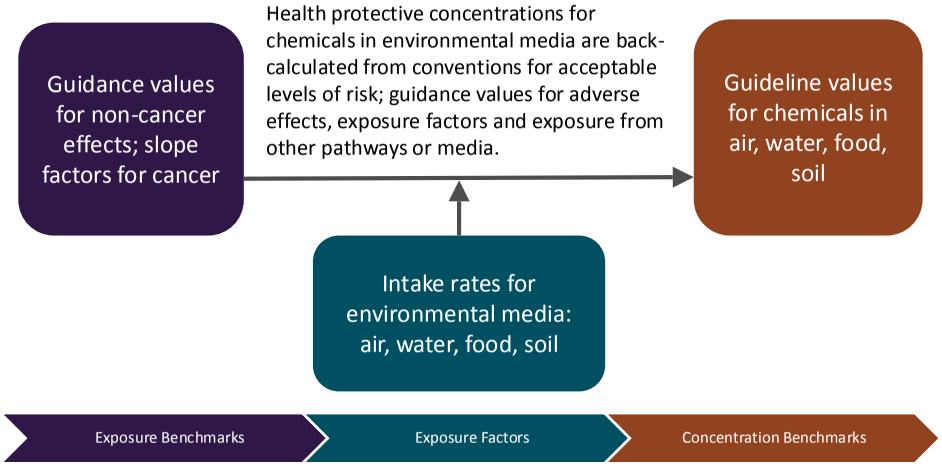
16

Characterization of Ecological Risk

- Hazard Quotient= PEC/PNEC

HQ < 1	No immediate concern
HQ = 1-10	Of concern if supply volumes increase
HQ= 10-100	Further data require
HQ > 100	Reduce risk immediately

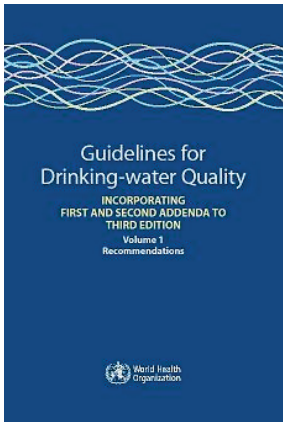
Media-Specific Chemical Concentrations as Benchmarks



Types of Media-Specific Guideline Values

Type of Benchmark	Type of Effect	Benchmark	Description of the Benchmark	Units	Note	Source
Media-specific Concentrations	Non-cancer and cancer. Benchmark value is the lower of the two concentrations that yield exposure equivalent to the non-cancer or cancer risk convention for acceptable risk	Air quality guidelines	An estimate of the concentration of selected pollutants in outdoor air that is intended to be health protective; separate values for different averaging times	$\mu g/m^3$ or ppb	Particulate matter, sulfur dioxide, nitrogen dioxide, carbon monoxide, ozone and lead	WHO
		Ambient air quality standards				USEPA and others
		Drinking water quality guidelines	An estimate of the concentration of contaminants in drinking water that is intended to be health protective	mg/L, µg/L, ppm, ppb	Considers intake from other media	WHO
		Maximum Contaminant Levels for drinking water			Considers intake from drinking water only	USEPA and others
		Risk-based concentrations	An estimate of the concentration of contaminants in air, water, and soil that is intended to be health protective	Various	Large number of contaminants considered; values do not consider intake from other media	USEPA and others

Example of Media-Specific Guideline Values



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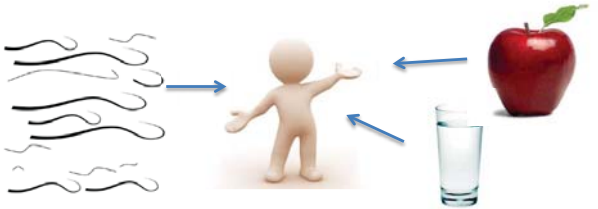


2. Contact Rate Variability:

- Water consumption
- Inhalation
- Food consumption
- Dermal contact

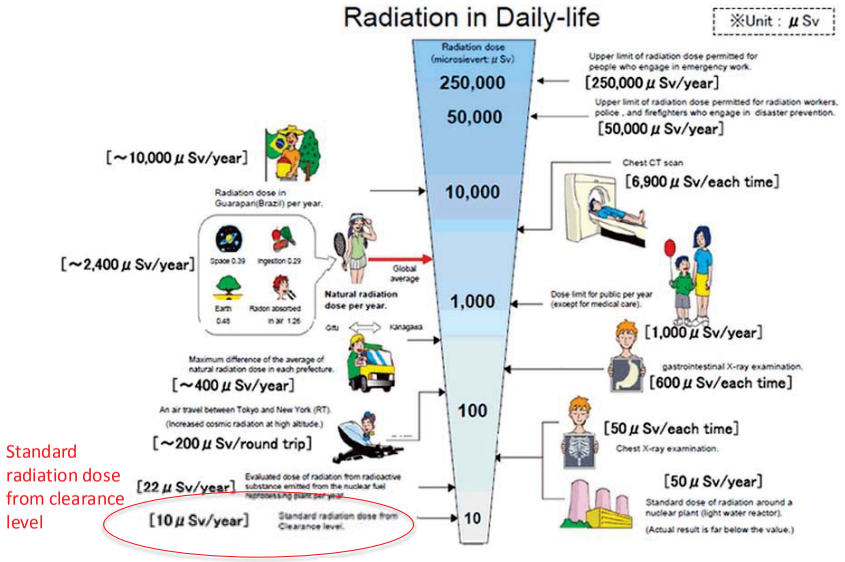
3. Exposure Rate Variability:

- Natural sources
- Cultural practices
- Lifestyle choices

Normative Levels as Benchmarks

- Concentrations and exposures that are typical and presumably tolerated or accepted
- An approach for providing context to quantitative estimates of exposure and risk
- Information on normative levels is available from international and national resources
  - WHO Environmental Health Criteria series
  - WHO CICAD series

Example of Normative Levels



Source: Japan Ministry of Education, Culture, Sports, Science and Technology

Discussion

- Risk characterization should include an evaluation of the overall quality of the assessment
- Fair and open presentation of the uncertainties in the calculations and a characterization of how reliable (or how unreliable) the resulting risk estimates really are
- Describe the degree of confidence the assessors have in the estimates and conclusions
- identify the strengths and uncertainties of the risk assessment
  - Quality and quantify of available data
  - Gaps in the data on exposure or dose-response
  - Understanding of biological mechanisms
  - Scientific judgments that were used to bridge gaps in information
- Types of uncertainties and assumptions typically addressed in risk characterization
  - Agreement between animal toxicology and human studies that address dose-response relationships
  - Realism of exposure scenarios
  - Whether the assumptions made are likely to overestimate or underestimate risk

International Resources

Table 9: WHO documents on principles of human health risk assessment for chemicals.

Document title	*Reference*
Principles for the assessment of risks to human health from exposure to chemicals (EHC 210)	IPCS (1999a)
Human exposure assessment (EHC 214)	IPCS (2000)
Principles and methods for the assessment of risk from essential trace elements (EHC 228)	IPCS (2002)
Elemental speciation in human health risk assessment (EHC 234)	IPCS (2006a)

Table 10: International sources of information on harmonization of risk assessment methodology.

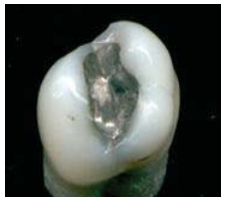
Document title	*Reference*
IPCS risk assessment terminology. Part 1: IPCS/OECD key generic terms used in chemical hazard/risk assessment; Part 2: IPCS glossary of key exposure assessment terminology (Harmonization Project Document No. 1)	IPCS (2004)
Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment (Harmonization Project Document No. 2)	IPCS (2005a)
Principles of characterizing and applying human exposure models (Harmonization Project Document No. 3)	IPCS (2005b)
Skin sensitization in chemical risk assessment (Harmonization Project Document No. 5)	IPCS (2008b)
Uncertainty and data quality in exposure assessment. Part 1: Guidance document on characterizing and communicating uncertainty in exposure assessment. Part 2: Hallmarks of data quality in chemical exposure assessment (Harmonization Project Document No. 6)	IPCS (2008a)

Key Messages

- Risk characterization, the last step in a risk assessment, is a qualitative or quantitative statement about the likelihood of harm associated with exposure to an agent including the identification and consideration of attendant uncertainties.
- Likelihood of harm is determined by combining results of the hazard characterization step and the exposure assessment step.
- Frequently used quantitative measures of risk are the hazard index, excess lifetime cancer risk, and margin of exposure.
- Risk can also be characterized quantitatively by comparing exposure concentrations for an agent in an environmental medium to corresponding guideline values derived from authoritative organizations such as the World Health Organization and national agencies
- The output of risk characterization should be presented in a manner that ensures that the risk manager and risk communicator understand the biological meaning and uncertainties of the risk assessment and how these can impact on their responsibilities.

Risk Management

Presentation by: Dr. Mario Yarto
in collaboration with Dr. David MacIntosh
APEC risk assessment and risk management workshop
November 7-8, 2013
Bangkok, Thailand


Learning Objectives

By the end of this module, participants should have an understanding of:

- Risk management and its relationship with risk assessment
- The objective of risk management
- The socio-economic factors and considerations that are involved in risk management
- The role of cost-benefit analysis in risk management
- The types of management options that are often available to risk managers
- Consultations with stakeholders

Introduction

- Risk management involves development and implementation of actions that can eliminate or reduce environmental exposures to a level where the associated risks are 'acceptable'

- Key issues addressed in risk management are:
  - *Deciding what level of risk is acceptable*
  - *Evaluating alternative control options, their feasibility and cost*
  - *Considering risks in relation to benefits*

Comparing Risk Assessment and Risk Management

Attribute	Risk Assessment	Risk Management
Objective	Analysis of the magnitude and likelihood of risk to human health and the environment	Determination of whether and what actions are needed to achieve an acceptable level of risk
Inputs and Considerations	Scientific information such as chemical transport and fate, toxicology, engineering, and statistics	Scientific, legal, economic, political, sociological and technological information
Methodology	Widely accepted step-wise process; quantitative; science-based.	No generally accepted approach; non-quantitative; non-scientific.
Approach to dealing with incomplete information	Explicit consideration of uncertainty which is incorporated into the quantitative results of an assessment	Addressing what level of risk is acceptable; feasibility and costs of control options, and evaluating benefits of lowering risks in relation to costs.
Output	Quantitative estimate of theoretical risk	Decision whether or not to control risk and if so, how

Relationship Between Risk Assessment and Risk Management

- Risk assessment and risk management are related to each other in several ways
- Three primary relationships are:
  - *Risk management decisions are based in part on the results of a risk assessment.*
  - *Certain risk assessment conventions can also be considered to be value judgments that are typically considered to be in the domain of risk management.*
  - *Risk assessors have an important role in risk management processes.*

What Level of Risk is Acceptable?

- How Safe is Safe Enough?
  - A fundamental question when talking about risk issues
  - The process of risk management will eventually lead to a choice of an action that will achieve the desired level of safety
  - The determination of acceptable or tolerable levels of risk may be prescribed or may be determined on a case-by-case basis
- Predetermined Acceptable Levels of Risk
  - Developed through societal processes
  - Examples
    - Legislative standards
    - Guideline and guidance values (see Risk Characterization module)
    - Industry derived norms
- Acceptable Levels of Risk Determined on a Case-by-Case Basis
  - Will raise the question "Acceptable to Whom?"
  - The risk management decision may depend on who is responsible for making the decision
    - Government officials
    - Community representatives
    - Regulated organizations

Framework for Risk Management

- Framework
  - Define the problem and put it in context
  - Analyze the risks associated with the problem
  - Examine options for addressing the risks
  - Make decisions about which options to implement
  - Take actions to implement the decision
  - Conduct an evaluation of the action's effectiveness
- Guiding Concepts
  - Collaborate with stakeholders such as the affected community
  - Use an iterative approach if new information is gained that changes the need for risk management

Define the Problem and Put It in Context

- Formulating the problem to be managed is an important step in risk management
- The major components of problem formulation are:
  - Identifying and characterizing an environmental health problem, or a potential problem, caused by chemicals or other hazardous agents or situations
  - Putting the problem into its public health and ecological context
  - Determining risk management goals
  - Identifying risk managers with the authority or responsibility to take the necessary actions
  - Implementing a process for engaging stakeholders

Identifying Risk Management Goals

- Identifying risk management goals is important for guiding the evaluation and selection of an appropriate risk management option
- The goals of risk management goals are varied. Major categories of goals include:
  - Risk-related objectives
    - Reduce or eliminate risks from exposure to hazardous substances
    - Reduce the incidence of an adverse effect
    - Reduce the rate of habitat loss
  - Economic considerations
    - Control risk without a loss of jobs
    - Protect the environment without reducing property values
  - Attain public or community values
    - Protect the most sensitive population, e.g., people with pre-existing illness
    - Protect children
    - Protect beloved or endangered animals or plants

Risk Management Options

- In broad terms, the overarching categories of options for managing risk are:
  - transferring risk to another organization such as an insurance company
  - retaining risk by a government, community or company
  - elimination of risk by removing the risk agent
  - reducing risk by controlling exposure
- The number of options for reducing risks to human health and the environment has evolved from command-and-control regulations only to now include alternatives such as education, incentives, monitoring, surveillance and research
- Approaches for reducing risks of chemicals include:
  - Encouraging pollution prevention
  - Limiting pollutant emissions
  - Taxing sources of pollutants based on the pollutants they release
  - Enforcing compliance
  - Educating/informing affected communities
  - Establishing market incentives
  - Monitoring pollutant levels
  - Health surveillance
  - Removing the source of risk

Analyzing Options

- Potential options for achieving the risk management goals should be assessed according to their technical and non-technical attributes
  - Technical attributes such as effectiveness, feasibility, benefits and costs
  - Non-technical attributes such as legal, social, cultural and political implications
- Key questions to ask about each option include:
  - What are the expected benefits?
  - What are the expected costs?
  - Who gains the benefits and who bears the costs?
  - How feasible is the option, given the available time and resources, as well as legal, political, statutory and technology limitations?
  - Does the option increase certain risks while reducing others?

Making a Decision

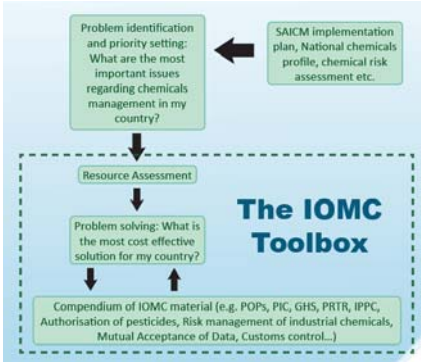
- The goal of risk management is to arrive at a decision that is equitable, minimizes risks and maximizes benefits.
- With these concepts in mind, a good risk management decision:
  - Addresses a clearly articulated problem in its public health or ecological context.
  - Emerges from a decision-making process that elicits the views of those affected by the decision, so that differing technical assessments, public values, knowledge, and perceptions are considered.
  - Is based on careful analysis of the weight of scientific evidence that supports conclusions about a problem's potential risks to human health and the environment.
  - Is made after examining a range of regulatory and non-regulatory risk management options.
  - Reduces or eliminates risks.
  - Can be implemented effectively, expeditiously, flexibly, and with stakeholder support.
  - Can be shown to have a meaningful impact on risks of concern.
  - Can be revised and changed when significant new information becomes available.

Taking Action

- A good risk management decision is one that can be implemented effectively, expeditiously, flexibly and with stakeholder support.
- Implementation of risk management decisions is typically driven by requirements established by regulatory agencies. Companies, local governments and communities generally are responsible for the actual actions.
- Examples of risk management actions
  - Facilities reducing or eliminating emissions of pollutants to ambient air, workplace air, bodies of water and soil by upgrading air pollution control technology, upgrading wastewater treatment, and improving manufacturing processes.
  - Governments providing market incentives that favor greater use of less polluting sources of energy and green procurement
  - Governments developing chemical inventories and registrations, PRTRs, and health surveillance programs
  - Employees working with employers to identify workplace practices and processes that improve safety and productivity
  - Community groups working with local officials and businesses to monitor the success of risk reduction activities

Example – IOMC Toolbox

- IOMC Toolbox for Decision-Making in Chemicals Management
- An internet-based problem solving tool that will enable countries to identify the most relevant and efficient tools to address specific national problems in chemicals management
- IOMC: Inter-Organization Programme for the Sound Management of Chemicals



Website: www.who.int/iomc/toolbox/en

Evaluating Results

- Evaluating effectiveness involves comparing the actual benefits and costs of a risk management action to the estimates made in the decision-making stage.
- Evaluation effectiveness provides important information about
  - Whether the actions were successful, accomplished what was intended, and yielded the benefits and required the costs estimated earlier
  - Whether any modifications are needed
  - How stakeholder involvement contributed to the outcome
  - What lessons can be learned to guide future risk management decisions
- Key steps in evaluating results are:
  - Plan for evaluation during the implementation phase of the risk management action
  - Gather information needed for the evaluation, usually measurement and monitoring data
  - Be prepared to review and adjust risk management actions if new information of importance becomes available

Risk Management Tools (1)

- The policy instruments which a country selects for national chemicals management can influence its ability to respond to concrete problems affecting its population and the quality of its environment.
- The selection of policy instruments also has practical and resource implications.
- Examples of RMT include:
  - *Pollutant Release and Transfer Registers (PRTR)*
  - *Chemicals Inventories*
  - *Classification and Labelling of Chemicals*

Risk Management Tools (2)

A **PRTR** is a national or regional environmental database or inventory of hazardous chemical substances released to air, water and soil, and transferred off-site for treatement or disposal

- Industrial facilities quantify and report the amount of substances released or transferred
- Some PRTRs also include estimates of releases from diffuse sources, such as agriculture and transport, and from the end use of products.

Risk Management Tools (3)

- PRTR data are made available to the public, in published documents, in annual reports, or on the internet.
- Data may be presented geographically
- Data may be presented by industry sectors, by facility, by a pollutant, chemical substance or groups of substances
- National PRTRs may vary in terms of the substances and pollutants reported, industry or business categories that must report, and destination of releases.

Risk Management Tools (4)

The role of stakeholders in the design and operation of a PRTR

- ***Industry***: determine, collect and report their releases and transfers. Also useful for comparison with other in the same business. It is a good practice to identify more effective chemicals management practices and improvements to processes.
- ***The Public, NGOs and the Scientific and Economic Communities***: access to environmental information according to the right-to-know principle. Useful for research purposes and disssemination to public society.
- ***Government***: a PRTR assists the public sector to track the generation, release and fate of emissions over time, to examine progress in reduction measures and for priority setting purposes.

Risk Management Tools (5)

Useful links to PRTR information

- **Japan**
- **Switzerland**
- **North America**
- **North America (2)**
- **UNITAR** **http://www2.unitar.org/cwm/publications/cbl/prtr/index.htm**

Risk Management Tools (6)

- **Chemicals Inventory**: It is a listing of industrial chemicals manufactured in, or imported by, a country and is used primarily to disntinguish between new and exisiting chemicals.
  - Created from information submitted to government authorities
  - Content may vary depending on national needs
  - Nearly always has a legal instrument as its basis

Risk Management Tools (7)

What to include in an inventory:

- CAS Registry Number, Index Name and Synonyms
- Formula and molecular structure
- Chemical class
- Quantities Produced & Imports
- Ecotoxicological data
- Environmental persistence
- Bioaccumulation
- Toxicity in aquatic systems

Examples

- New Zeland
- South Korea
  ncis.nier.go.kr/newchem/eng
- USA

Risk Management Tools (8)

Labelling and Classification

- The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) is an internationally-agreed tool for chemical hazard communication.
- GHS incorporates harmonized chemical hazard classification criteria and provisions for standarized labels and safety data sheets.
- Provisions of the GHS affect chemical hazard communication in four key sectors at the national level; they include:
  - industrial workplace,
  - agriculture,
  - transport,
  - consumer products.

Risk Management Tools (9)

- Integrated Pest Management
- Life Cycle Assessment
- Pollution Prevention/Cleaner Production
- Registration Schemes

Other options

- International Conventions
- Regional (APEC) and bilateral cooperation

Risk Managment tools (10)

- Stockholm Convention
  - Targets Persistent Organic Pollutants (POPs)
  - Legally binding instrument
  - National Implementation Plans
  - Lists 22 substances
    - *Pesticides*
    - *Industrial chemicals*
  - Capacity Building
    - *Inventory development*
    - *Waste and stockpiles*
  - BET/BAP
    - *Harmonized framework to miminize releases of unintentional POPs*
  - POPs Review Committee

Risk Managment tools (10)

- Rotterdam Convention
  - Targets pesticides (32) and industrial chemicals (11) subject to international trade.
  - Prior Informed Consent (PIC) procedure for facilitating an exchange of information
  - Legally binding instrument
  - Chemicals Review Committee

Risk Managment tools (10)

- Basel Convention
  - Control of Transboundary Movements of Hazardous Wastes and their Disposal
  - Legally binding instrument, which aim is addressed through a number of general provisions requiring States to observe the fundamental principles of environmentally sound waste management
  - Capacity building and technical guidelines
    - Waste classification
    - Enforcement
    - Mercury
    - Co-processing
    - E-waste

Risk Managment tools (11)

- Strategic Approach to International Chemicals Management
  - Policy framework to foster the sound management of chemicals
  - Overarching Policy Strategy
    - Risk reduction
    - Knowledge and information
    - Governance
    - Capacity Building
    - Illegal international traffic
  - Global Plan of Action
    - Working tool that guides the implementation of SAICM
    - Work areas and associated activities
  - Quick Start Programme (QSP)
    - Kick off for initial enabling activities

Risk Communication

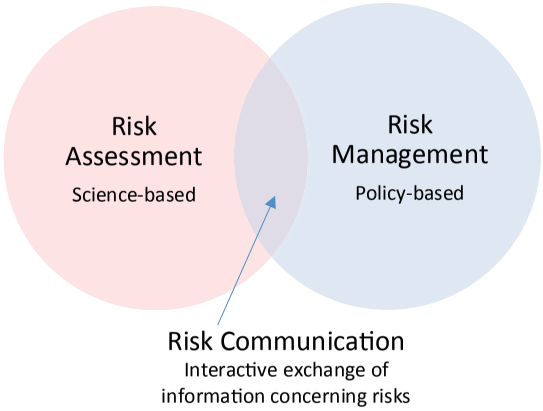
Presentation by: Dr. Mario Yarto
in collaboration with Dr. David MacIntosh
APEC risk assessment and risk management workshop
November 7-8, 2013
Bangkok, Thailand

Learning Objectives

By the end of this module, participants should have an understanding of the:

- Importance and place for skill in risk communication
- Principles of risk communication
- Key elements of effective risk communication
- Resources available to gain a deeper understanding of risk communication

Risk Communication in Relation to Risk Assessment and Risk Management



Risk Communication: What and Why?

Risk communication is a science-based approach for communicating effectively in sensitive or controversial situations, including situations where concern is high and trust is low.

Numerous events can lead to sensitive or controversial situations, including the presence of hazardous agents in work places or communities.

An open, interactive exchange of information among stakeholders is important for effective resolution of these situations.

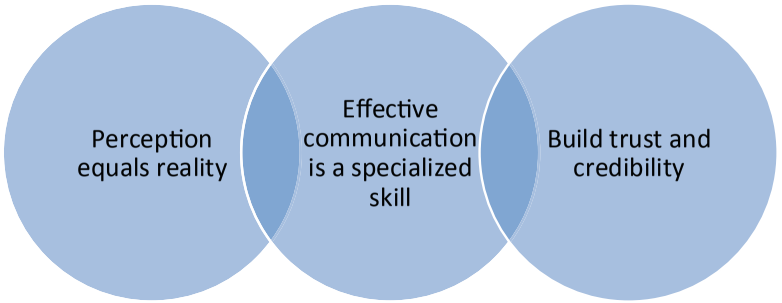
Principles of Risk Communication

- People who are effective at communicating risk information understand the important principles of exchanging information in sensitive situations
- In this module, the basic principles are divided into two groups.
  - The first group includes three 'practical concepts' that are essential attributes of effective risk communication.
  - The second group includes the psychological and sociological theory upon which risk communication training and practice is based.

Practical Concepts

- Perception equals reality. In other words, what people believe to be real is real to them and influences how they feel and act.
- Effective communication requires skill. That skill is different from technical competence.
- The goal of risk communication is to gain trust and credibility with the audience.

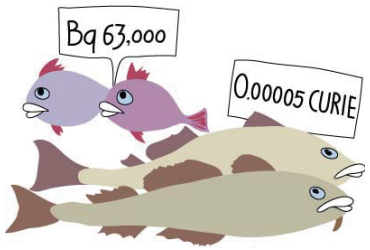
Practical Concepts



Perceptions of Risk

- Effective communication of risk requires us to recognize and address people's perceptions of risk.
- When interacting with people personally affected by a chemical incident, you should anticipate their perceptions of the risks and be prepared to deal with their concerns.
- Several factors can influence their perceptions; the most important of these are shown on the next slide

Factors that Influence Perceptions



Low Degree of Fear and Outrage	High Degree of Fear and Outrage
Voluntary	Involuntary
Natural	Man-made
Familiar	Exotic
Not memorable	Memorable
Common	Rare
Controlled by individual	Controlled by others
Fair	Unfair
Morally irrelevant	Morally relevant
Detectable	Undetectable
Visible benefit	No visible benefit
Trusted source	Untrusted source

0.00005 Curie is a much larger amount of radiation than 63,000 Becquerel

Positive Influence on Perceptions

- In discussing risk, you need to address three topics that most audiences want to understand:
  - Hazards: What can go wrong or has gone wrong?
  - Probability: How likely is it that the hazards will lead to exposure?
  - Consequence: What will happen as a result of the current situation and foreseeable situations?

Skillful Communication

- The use of effective risk communication skills is essential for transmitting necessary information and building trust among stakeholders. This requires:
  - Disciplined and sustained use of risk communication principles and skills
  - Consistent application among all stakeholders and in all formats (in person, written, media interviews, telephone, presentations)
  - Incorporation of situational and cultural awareness

Goal-Oriented Communications

- There are three major goals of risk communication:
  - Create a communications environment based on trust and credibility
  - Produce an informed audience that is involved, interested, reasonable, thoughtful, solution-oriented, and collaborative
  - Build confidence in your organization's professionalism, commitment, and expertise

Summary of Theory of Risk Communication

Theory	Effect	Solution
• Risk Perception	• Frustration and outrage	• Anticipate and address the factors that influence perception
• Mental Noise	• Blocks communication	• Use clear, concise messages
• Negative Dominance	• Distorts communication	• Develop positive wording for messages
• Trust Determination	• Enhances or detracts from message	• Show that you care

Seven Cardinal Rules of Risk Communication

- In addition to understanding the practical concepts and theory of risk communication, experience has demonstrated that there are several essential rules of effective risk communication.
- Accept and involve the public as a legitimate partner in assessment and management of risk
- Plan communications carefully and evaluate their effectiveness as you proceed
- List to the specific concerns raised by the public
- Always be honest, direct, and open
- Coordinate your activities and collaborate with credible third-party sources as much as possible
- Meet the needs of the media so that they rely upon you for credible information, rather than others
- Speak clearly and with compassion; in other words, say what you mean and mean what you say.

Delivering a message

Presentations: Speeches to public groups.

Benefit: offers the audience a chance to ask questions; reaches many people at one time.

Limitations: if poorly presented, can distort community perception; cannot sufficiently address individual concerns; can become argumentative or confrontational.

Open Houses/Availability Sessions: Informal meeting where public can talk to staff on a one-to-one basis.

Benefit: allows for one-to-one conversation; helps build trust and rapport.

Delivering a message

Small Group Meetings: Sharing information with interested community members and government officials.

Benefit: allows two-way interaction with the community.

Limitations: may require more time to reach only a few people; may be perceived by community groups as an effort to limit attendance; be sure your information is identical or you may be accused of telling different stories to different groups.

Newsletters: To inform community of ongoing activities and findings.

Benefit: explains findings; provides background information.

Limitations: can backfire if community members do not understand or misinterpret contents.

Delivering a message

News Release: Statement for the news media to disseminate information to large numbers of community members.

Benefit: reaches large audience quickly and inexpensively.

Limitations: may exclude details of possible interest to the public; can focus unneeded attention on a subject.

Public Meetings: Large meeting open to the public where experts present information and answer questions and community members ask questions and offer comments.

Benefit: allows community to express concerns and agency to present information.

Limitations: can intensify conflicts, rather than resolve controversies.

Delivering a message

Exhibits: Visual displays to illustrate health issues and proposed actions.

Benefits: creates visual impact.

Limitations: one-way communication tool, no opportunity for community feedback.

Fact Sheets: To introduce new information.

Benefit: brief summary of facts and issues; provides background for information discussed during a meeting.

Limitations: one-way communication tool; needs to be well-written and understandable.

Delivering a message

Briefings: Can be held with key officials, media representatives, and community leaders; generally not open to the public.

Benefit: allows key individuals to question risk assessment staff before release of public information.

Limitations: should not be the only form of community communication; bad feelings may arise if someone feels that they were left off the invite list.

Community mailings: Sends information by mail to key contacts and concerned/involved members of the community.

Benefit: delivery of information quickly; may require less planning than a meeting.

Limitation: no opportunity for feedback.

Thank you for your attention!

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APPENDIX VIII. TRAINING MATERIALS (CASE STUDIES)

Risk Assessment Case Studies

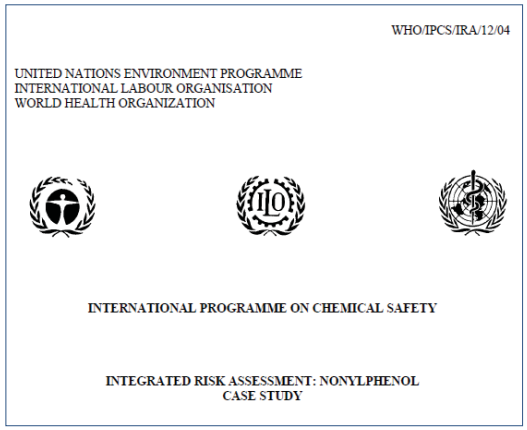
Presentation by: Dr. David MacIntosh
APEC risk assessment and risk management workshop
November 7-8, 2013
Bangkok, Thailand

Learning Objectives

- To learn more about key concepts of risk assessment through examples
- To practice using the roadmaps provided in the WHO Toolkit for Human Health Risk Assessment: Chemical Hazards
- To share experiences with other workshop participants

Nonylphenol Case: Background

Take 5 minutes to review background information on nonylphenol presented in pp. 9-11 of the WHO integrated risk assessment case study. Emphasize the highlighted portions of the document.



WHO/IPCS/IRA/12/04

UNITED NATIONS ENVIRONMENT PROGRAMME
INTERNATIONAL LABOUR ORGANISATION
WORLD HEALTH ORGANIZATION

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

INTEGRATED RISK ASSESSMENT: NONYLPHENOL
CASE STUDY

Charge Questions: Nonylphenol Background

- Is nonylphenol typically used in products in the public domain?
- What is the primary source or pathway of nonylphenol emissions into the environment?
- Is nonylphenol likely to be widely distributed among air, water, and soil? Why or why not?
- Are nonylphenol concentrations in surface water likely to be about the same everywhere?
- Is nonylphenol likely to present as much of a risk to people as to ecological receptors?

Charge Questions: Nonylphenol Problem Formulation

- Discuss the scope of the chemical(s) considered in the risk assessment by Fenner et al. 2002. Do they consider only the 'parent' compounds? Why or why not?
- What is the temporal scope of the assessment: acute or chronic exposures and effects?

Charge Questions: Nonylphenol Exposure

- Do Fenner et al. rely on a model or measurements for their assessment of exposure?
- What form of exposure does Fenner et al. consider (concentration, dose, absorbed dose, etc.?)
- Where are the exposure assessment results presented in the paper?
- Did Fenner et al. do any analysis to evaluate the validity of their exposure assessment results?

Charge Questions: Nonylphenol Hazard Characterization

- Describe the toxicity values from which Fenner et al. derived guideline values
- What uncertainty or extrapolation factors, if any, were applied to derive guideline values?
- Rank the various chemical forms of nonylphenol considered in this paper in order of highest to lowest toxicity

Charge Questions: Nonylphenol Risk Characterization

- Describe the method by which the risk of the individual nonylphenol-related compounds was characterized
- Describe how the risk of adverse effects from the mixture of nonylphenol-related compounds was characterized
- Fenner et al. describe the uncertainty associated with their risk charcterization. Identify and describe the "two conservative" and "one non-conservative" assumption they mention in the second full paragraph of the final page of the paper.
- Compare the Fenner et al. predicted environmental considerations (PEC) of nonylphenol to the values described in the WHO nonylphenol report. Discuss whether or not the Fenner et al. PECs are conservative.

Environ. Sci. Technol. **2002**, *36,* 1147−1154

Including Transformation Products into the Risk Assessment for Chemicals: The Case of Nonylphenol Ethoxylate Usage in Switzerland

KATHRIN FENNER, CORNELIS KOOIJMAN, MARTIN SCHERINGER,* AND KONRAD HUNGERBÜHLER

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A method for applying the risk assessment approach using ratios of predicted environmental concentrations (PECs) and predicted no-effect concentrations (PNECs) to mixtures of parent compounds and their environmental transformation products is presented. Nonylphenol ethoxylates (NPnEOs) and a selection of their most relevant transformation products are investigated as a case study illustrating the method. The PEC values of NPnEO and its transformation products are calculated with a regional multimedia fate model including the transformation kinetics of the NPnEO degradation cascade. PNEC values are derived from a selection of toxicity data on NPnEO and its transformation products. The toxicity of the emerging mixture of NPnEO and its transformation products is then estimated under the assumption of concentration addition (similar mode of action). On this basis, PEC-to-PNEC ratios for the aquatic environment and the sediment are calculated for the individual components of the mixture and the mixture itself. For this purpose, average release rates of NPnEO and its transformation products from Swiss sewage treatment plants were used. While the PEC values of the individual components do not exceed the corresponding PNEC values, the risk quotient of the mixture in water is greater than 1. In sediment, the mixture does not exceed a risk quotient of 1. A combination of sensitivity and scenario analyses is employed to identify the upper and lower bounds of the results.

Introduction

Many chemicals are transformed to structurally related transformation products in the environment before they are mineralized. Each of these transformation products displays its own toxicity and persistence. Accordingly, the EU Technical Guidance Document on the risk assessment of notified new substances (TGD) states a need to include such transformation products into risk assessment for chemicals (ref *1*, Part II, p 253). However, common practice of risk assessment does not cover the transformation products of industrial chemicals for several reasons: (i) the relevant transformation products have to be identified and characterized, (ii) the transformation kinetics has to be explored, (iii) the group of chemicals forms a complex mixture that is difficult to assess, and (iv) toxicity data for transformation products is often lacking. (For pesticides, the regulatory requirements in Europe are more stringent than for other industrial chemicals in that the identification, analysis, and risk assessment of all relevant metabolites is mandatory for their registration (*2, 3*).) All of these tasks pose methodological problems and increase the time and effort required for the assessment. Accordingly, there are only a limited number of studies dealing with the risk assessment of transformation products of industrial chemicals (e.g., refs *2* and *4*−*8*).

One approach to include transformation products into the risk assessment of their parent compounds is to identify important transformation products, such as DDE formed out of DDT or nonylphenol stemming from nonylphenol ethoxylates, and to perform a risk assessment for these substances individually (*2, 9*). However, this approach does not account for a variety of other transformation products being present at the same time nor does it cover the toxicity of this mixture of different chemicals.

In an alternate approach, Fenner et al. (*7*) and Quartier and Müller-Herold (*8*) have included the transformation kinetics into the assessment. They have calculated the environmental exposure to parent compounds and transformation products as they are being formed in the degradation cascade. Here, as a next step, we include the effect assessment into this approach so that a risk assessment in terms of a risk quotient (quotient of predicted environmental concentrations (PEC) and predicted no-effect concentrations (PNEC)) can be accomplished. We investigate the still widely used nonylphenol ethoxylates (NPnEO) and their transformation products, including short-chain NPEOs, nonylphenoxy carboxylic acids, and nonylphenol, as a case study (short: NPEs).

First, we calculate predicted environmental concentrations of the different chemicals with an open regional multimedia fate model that reflects the conditions in Switzerland and includes the transformation kinetics of NPnEO (*10*). Next, the toxicity of the emerging mixture of NPnEO and its transformation products is assessed under the assumption of a similar mode of action of the single compounds and, therefore, concentration addition (*11, 12*). The combination of fate modeling and mixture toxicity assessment leads to a risk quotient for the entire group of chemicals. Finally, to explore the reliability of the results, we carry out a sensitivity and scenario analysis and compare the results to those from two other risk assessments of nonylphenol and nonylphenol ethoxylates (*9, 12*).

The overall aim of the study is to demonstrate how the concomitant release and formation of transformation products can be included into the risk assessment of parent compounds and to argue in favor of such an inclusion into the practice of risk assessment.

Methods

Multimedia Model for Switzerland. To calculate predicted environmental concentrations (PECs), a regional steady-state (level III) model for Switzerland including the environmental media soil (s), water (w), air (a), and sediment (sed) has been set up (Figure 1). It describes the multimedia behavior and fate of NPnEO *and* of all of its transformation products, as well as the transformation reactions shown in Figure 2. Each transformation reaction is represented in the model calculations in terms of media-specific fractions of formation, θ_i^{xy}, which indicate the relative amount of a precursor x that is transformed into a transformation product y. The math-

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10.1021/es015576i CCC: $22.00
Published on Web 03/13/2002

TABLE 1. Model Dimensions and Transport Parameters for Switzerland (CH)

Compartment Dimensions					
phase depth	value (m)	compartment volume CH	value (m^3)	interfacial area CH	value (m^2)
soil (h_s)	0.1	soil (v_s)	3.96×10^9	air/soil	3.96×10^{10}
water (h_w)	3	water (v_w)	5.20×10^9	air/water	1.73×10^9
air (h_a)	1000	air (v_a)	4.13×10^{13}	total (area)	4.13×10^{10}
sediment (h_{sed})	0.02	sediment (v_{sed})	3.47×10^7		

Environmental Properties Different from Values in Ref *13*		
parameter	symbol	value
rain rate CH	u^{rain}	4×10^{-3} m/d
wind velocity	u^{wind}	4.32×10^5 m/d
water outflow CH	U^{water}	1.46×10^8 m^3/d

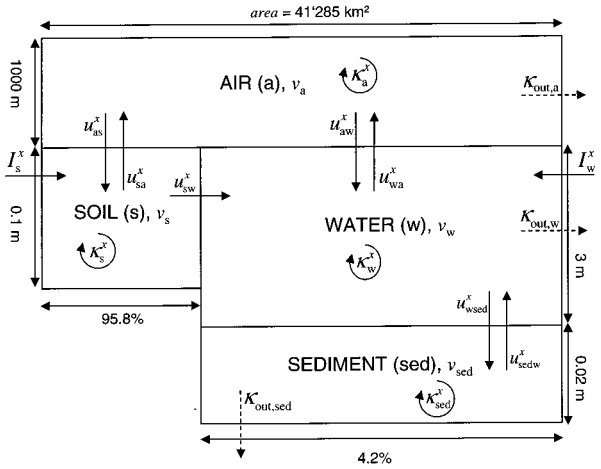

FIGURE 1. Open four-compartment model for Switzerland. In each compartment (soil (s), water (w), air (a), and sediment (sed)), all chemicals *x* undergo first-order degradation (κ_i^x) and transformation ($\kappa_i^{xy} = \theta_i^{xy}\kappa_i^x$), advective and diffusive transfer processes between the compartments (u_{ik}^x), and advective transport out of the system ($\kappa_{out,i}$). Substances are emitted into the model system as secondary effluents into water (I_w^x) and, adsorbed to sewage sludge, into soil (I_s^x).

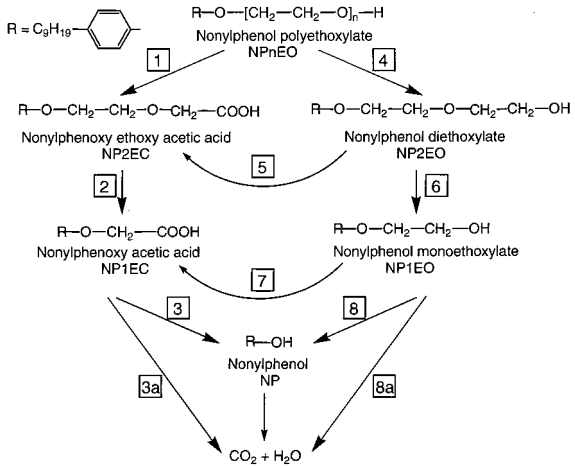

FIGURE 2. Simplified transformation scheme of NPnEO in wastewater treatment plants and in natural environments according to refs *12* and *34*. Numbers of reactions are used in Table 2.

ematical implementation is the same as described elsewhere (*7*) and is presented in more detail in the Supporting Information (Section A).

Intermedia transfer processes are similar to those in refs *13* and *14*, whereas all media dimensions and some environmental properties have been modified to be specific to Switzerland. The media dimensions and all parameters deviating from the globally averaged properties in ref *13* are given in Table 1. In addition, a surface mixed sediment layer (SMSL) has been introduced as a fourth medium, and the model has been changed to represent an open system (i.e., it is assumed that the chemical can be removed from the system through advective transport in air and water and through burial into the permanent sediment). The quantification of the transfer processes in the SMSL model and of the removal processes is described in the Supporting Information (Section A).

Solving the model for steady-state conditions as described in the Supporting Information (Section A) results in a concentration vector $\mathbf{c}^{stst}$ (in mol/m^3), which contains the steady-state concentrations for each chemical *x* in each compartment *i*. These are used as predicted environmental concentrations (PECs) to calculate the risk quotients.

Risk Quotient for a Mixture of Parent Compound and Transformation Products. For a single compound *x*, the risk to the organisms living in a given environmental compartment is commonly expressed as risk quotient (RQ^x), which compares the concentration c^x of the compound *x* in that compartment to some measure of its toxicity (e.g., EC_l^x (EC = effect concentration, *l* = effect level in percent of affected organisms)).

To describe the environmental risk posed by the mixture of a chemical and its emerging transformation products, ways of predicting the risk of the mixture from the toxicity of the individual components are needed. To this end, the concept of mixture toxicity, up to now mainly used for the assessment of mixtures that were initially released as such, is applied. The components of a chemical mixture can act either interactively (synergistically or antagonistically) or without interaction (through similar or dissimilar modes of action) on a given target organism. Because information about the interaction between components is often lacking and difficult to deduce from the chemical structures, no interaction is assumed in most cases as a first estimate (*15*, pp 107−111). Two basic concepts can be distinguished in this case. The first is independent action (IA; also, response addition), assuming that the mixture components act independently on different receptor systems. The second is concentration addition (CA), which means that the mixture components have the same mode of action and the same slope of their dose−effect curves so that, at each concentration level, one component can be substituted by an equi-effective amount of another component.

For calculating the risk of the mixture of parent compound and transformation products, we assume CA (for a discussion of this assumption and the mode of toxic action of NPEs, see Supporting Information, Section B). CA has been shown experimentally (*16*) and numerically (*17*) to overestimate the mixture toxicity of independently acting chemicals by maximally a factor of 10. Therefore, CA might be considered

an appropriate approach for a routine effect assessment of most types of chemical mixtures (*16*).

Given CA, the concentrations of all of the components of a mixture can be transformed into an equivalent concentration c_{EQ}^{ref} of a reference compound by summing up the concentration of each component multiplied by its relative potency RP^x. The relative potency RP^x is defined as the ratio of the toxic potency of the reference compound (EC_l^{ref}) divided by that of the compound x (EC_l^x). The total risk of the mixture can then be assessed by comparing the equivalent concentration c_{EQ}^{ref} with a given toxicity threshold of the reference compound (eq 1).

$$RQ_{mix} = \frac{c_{EQ}^{ref}}{EC_l^{ref}} = \frac{\sum_x c^x RP^x}{EC_l^{ref}} = \frac{\sum_x c^x \frac{EC_l^{ref}}{EC_l^x}}{EC_l^{ref}} = \sum_x \frac{c^x}{EC_l^x} = \sum_x RQ^x \quad (1)$$

Equation 1 shows the usual expression for the mixture risk quotient (*1*, *12*, *15*, *18*) indicating that, under the assumption of concentration addition, the risk for exposure to a mixture can be expressed as the sum of the single risk quotients RQ^x of all of the toxicants of concern. Equation 1 implies that several subthreshold (i.e., ineffective) exposures could have a cumulative adverse effect.

In the methodology suggested here, the concentration of the single substances is not measured but predicted by means of the previously described multimedia model. Therefore, predicted environmental concentrations PEC^x are used instead of measured concentrations c^x to determine the risk quotients. Also, not the measured effect concentrations EC_l^x are used as toxicity thresholds but predicted no-effect concentrations $PNEC^x$, which are extrapolated from the EC_l^x values by applying extrapolation factors EF^x that account for inter- and intraspecies variability, acute to chronic extrapolation, and extrapolation from observed effects to predicted no-effect levels, thus $PNEC = EC_l^x/EF^x$. Accordingly, the definition for the mixture risk quotient RQ_{mix} as used here is

$$RQ_{mix} = \sum_x \frac{PEC^x}{PNEC^x} = \sum_x RQ^x \quad (2)$$

According to the EU TGD (*1*), an EF of 1000 is applied if only acute toxicity data ($L(E)C_{50}$) are available for a substance. This EF can be lowered (100, 50, or 10) if long-term studies have been conducted. The value of the EF then depends on the number of trophic levels for which long-term endpoints were measured and on whether the species with the lowest NOEC (no-observed effect concentration) also shows the lowest acute toxicity (*1*).

Case Study: Nonylphenol Ethoxylates

Usage of Nonylphenol Ethoxylates in Switzerland. Nonylphenol ethoxylates (NPE) are high production volume chemicals that have been used for over 40 years as detergents, emulsifiers, and dispersing agents. NPE containing products are used in many sectors, including textile processing, pulp and paper processing, oil and gas recovery, steel manufacturing, and power generation (*12*). In Switzerland, NPE were banned from use in domestic cleaning agents in 1987. However, industrial NPE usage still exceeds 400 tons per year in Switzerland (*19*). The current use leads to a total NPE amount of 240 t treated yearly in Swiss sewage treatment plants, of which approximately 45% (i.e., 108 t/y) are still found in the secondary effluents (60%) and digested sewage (40%) (*20*). A detailed derivation of the yearly releases of the different NPE components in secondary effluents of Swiss sewage treatment plants is given in the Supporting Information (Section C). It results in the following estimated releases of the different NPE components: 18.7 t/y of long-chain NPnEO, 14.7 t/y of short-chain NP1/2EO (approximate ratio 3:1), 30.7 t/y of carboxylic acids NP1/2EC (approximate ratio 1:6), and 2.7 t/y of NP in secondary effluents, as well as 18.7 t/y of NP applied to the soil with the sewage sludge. These releases are used as model inputs.

TABLE 2. Fractions of Formation in Soil, Water, and Sediment[a]

reaction no. (r) in Figure 2	fractions of formation in soil ($theta_{r,s}$)	fractions of formation in water ($theta_{r,w}$)	fractions of formation in sediment ($theta_{r,sed}$)
1	0.7	0.7	0.5
2	1	1	1
3	0	0	0.5
4	0.3	0.3	0.5
5	0.5	0.5	0.5
6	0.5	0.5	0.5
7	0.5	0.5	0.5
8	0	0	0.25

[a] In air, no transformation reactions according to the scheme in Figure 2 are expected. The fractions of formation were determined from transformation schemes taken from refs *34*–*38*.

Fate of NPnEO and Its Transformation Products in the Natural Environment. The partition coefficients and half-lives of the compounds, which are required as substance-specific input parameters for the exposure model, are listed in Table A3 in Section D of the Supporting Information. Half-lives were collected from a broad set of original publications and were adjusted to an average temperature of 283 K.

The relative importance of the degradation pathways of NPnEO (see Figure 2) depends on the environmental conditions (see Table 2). If there is enough oxygen present, as is the case in surface water and upper soil layers, the carboxylation of NPnEO to NP1EC and NP2EC is favored. Therefore, the fractions of formation $\theta_{1,s}$ and $\theta_{1,w}$ are estimated to be 0.7 (see Table 2). In aerobic media, NP is expected to mineralize quickly. So, the fractions of formation of NP in aerobic compartments, $\theta_{3,s}$, $\theta_{3,w}$, $\theta_{8,s}$, and $\theta_{8,w}$, are set to 0 (note, however, that the mineralization of NP1EC and NP1EO proceeds through NP).

In the sediment, where there are anaerobic spots, NP formed out of NP1EC or NP1EO may be more persistent. Because the exact fraction of persistent NP being formed is not known, the formation of persistent NP from NP1EC and NP1EO and direct mineralization of NP1EC and NP1EO are assumed to be equally important ($\theta_{3,sed}$ is set to 0.5 and $\theta_{8,sed}$ to 0.25). Further, under anaerobic conditions, the formation of NP2EO from NPnEO becomes more important than under aerobic conditions; therefore, the fraction of formation $\theta_{4,sed}$ is set to 0.5.

The importance of oxidation of NP2EO to NP2EC and of NP1EO to NP1EC is not known exactly, so the fractions of formation $\theta_{5,i}$ and $\theta_{7,i}$ are set to 0.5 for all media i (see Table 2).

In air, efficient degradation by attack of OH radicals is assumed. The pathways of this process are, therefore, not modeled explicitly.

Toxicity of NPnEO and Its Transformation Products. To derive a predicted no-effect concentration (PNEC) for every single substance, a broad set of toxicity data was evaluated, containing data from databases in refs *9*, *12*, *21*, and *22*. The EU study (*9*), Servos (*21*), and Staples et al. (*22*) distinguish between data points that are considered valid and well-

TABLE 3. Selected Toxicity Values of NPnEO and Its Transformation Products[a]

	NPnEO[b]	NP2EC	NP1EC	NP2EO	NP1EO	NP[c]
endpoint	LC_{50}	LC_{50}	LC_{50}	LC_{50}	LC_{50}	LC_{50}
test duration [h]	96	48	96	48	48	96
concentration [μg/L]	900	990	2000	110	110	20.7
ref	39	40	Williams, J. B. et al., 1996 in ref *21*	39	39	Brooke, L. T., 1993a, in ref *21*
extrapolation factor (EF)	1000	1000	1000	1000	1000	1000
PNEC in water (μg/L)	0.90	0.99	2.00	0.11	0.11	0.021
PNEC in sediment (μg/kg)	83.3	3.43	6.93	86.0	79.8	27.0

[a] Lowest acute lethal concentrations (LC_{50}) were taken from a database that was compiled from refs *9*, *12*, *21*, and *22*. [b] Values for NP9EO and NP15EO were used. [c] CAS Registry Number: 84852−15−3.

documented and those that should be used with care. Here, only "valid" data were included.

It is known that, besides general acute and chronic toxicity, NPE also cause estrogenic responses in aquatic organisms that occur at concentrations similar to those at which chronic effects occur (*23*). However, the relative intensity of this effect for the different compounds is still an unresolved issue (see ref *23* vs ref *24*). The risk through estrogenic behavior is, therefore, not yet addressed in this study.

For all substances, PNEC values in water were deduced from acute toxicity data by applying an EF of 1000 (see Table 3). Derived that way, the PNEC values in water reproduce the tendency of increasing toxicity with decreasing chain length reported by Servos (*21*), with NP being the most toxic compound. Accordingly, the relative potencies (RP^x) occurring in eq 1 reflect the relationships between the acute toxicity data.

PNEC values for the sediment were derived from the PNECs in water by using the equilibrium partitioning approach (*25*). The resulting values in μg/kg sediment are also listed in Table 3.

Only for two chemicals, NP and NPnEO, there are, according to the TGD (*1*), sufficient chronic data available for deriving the aquatic PNEC from these chronic data. Using these data for NP and NPnEO leads to different PNECs (given in Section E of the Supporting Information) and, as a consequence, also to different relative potencies of the components of the mixture. These relative potencies now reflect the relationships between the chronic NOECs of NP and NPnEO, on the one hand, and the acute data, combined with an implicitly assumed acute-to-chronic ratio, of the other four compounds, on the other hand.

We think that the first choice, that is, comparing the chemicals with respect to experimental data for the same endpoint (acute toxicity) and with a fixed EF, leads to more reliable relative potencies, which, in turn, are required for the mixture toxicity assessment. Therefore, we use the PNEC values based on EF = 1000 in our "standard scenario". For comparison, we investigate the effect of the PNEC values derived from chronic NOECs for NP and NPnEO in the alternative scenario B1 (see following section on sensitivity and scenario analysis and Table 5; also see Section E in the Supporting Information).

A third approach for deducing PNECs is to analyze distributions of species sensitivities and to define the acceptable environmental concentration as the concentration at which 5% of the species is exposed above their toxicity threshold (*26*). In ref *12*, a hazardous concentration for 5% of the species (HC_5, 40 μg/L) is determined for NP from the log-probit transformed distribution of acute toxicity data. Extrapolation factors of 4 and 10 are applied that account for the acute-to-chronic ratio and for sublethal effects and species differences, resulting in a $PNEC_{dist}^{NP}$ of 1 μg/L. The PNECs of the other substances are deduced by using factors between 2 and 200, expressing the relative toxicities of the chemicals. (This approach assumes the same slope of the distributional curve as for NP for all chemicals.) These PNECs lie by a factor of 20−200 higher than those listed in Table 3 as standard values. This third set of PNEC values is discussed in the scenario analysis as scenario B2.

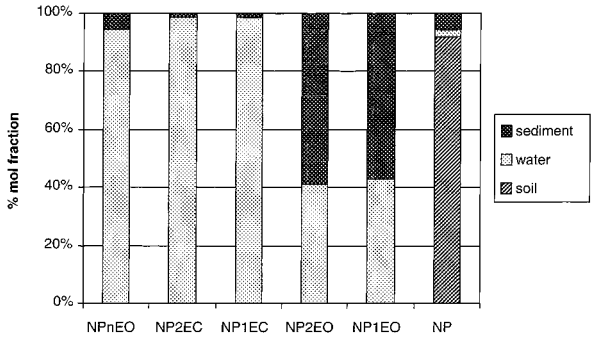

FIGURE 3. Mass fractions of NPE in the compartments soil, water, and sediment (on a molar basis). Fractions in air are below 0.1% for each compound (not shown).

Results

Predicted Concentrations. Figure 3 shows the mole fractions of NPnEO and its transformation products in the compartments soil, water, and sediment in the steady state. In air, no relevant amounts of any of the compounds were found. All compounds except NP partition mainly between water and sediment with the acids NP2EC and NP1EC found predominantly in water because of their higher water solubility. NP, being the only compound emitted to soil (adsorbed to sewage sludge), is mainly found in the soil compartment.

Water concentrations range from 0.012 μg/L for NP to 0.30 μg/L for NP2EC (see Table 4 for the concentrations of all compounds), while concentrations in sediment range from 0.15 μg/kg for NP1EC to 5.7 μg/kg for NP1EO.

To evaluate these results, the water concentrations obtained from the model are compared in Table 4 with measured concentrations for five locations in Swiss rivers (*27*). Only for the river Glatt measurements are given that include NP, the short-chain ethoxylates as well as the acids. Our calculated concentrations for these five compounds deviate from the measured concentrations in the Glatt by a factor of 1.2−5. For NP2EO and NP1EO, the calculated concentrations lie within the range of the measurements at all five locations, while the concentration calculated for NP lies below the detection limit of the measurements.

The tendency toward underprediction in the model results might be due to the fact that the calculations represent averages of all Swiss waters, while the measurements were conducted in rivers with characteristically high anthropogenic loads.

Sediment concentrations have not been extensively measured yet, so a comparison with the predicted concentrations is not possible here.

TABLE 4. Comparison of Calculated Steady-State Concentrations c_w^x, and Measured Concentrations of NPE in the River Glatt (Switzerland) and Other Swiss Rivers (27)

	c^{NPnEO}	c^{NP2EC}	c^{NP1EC}	c^{NP2EO}	c^{NP1EO}	c^{NP}
calculated concentrations [μg/L]	0.21	0.30	0.19	0.04	0.07	0.012
measured concentrations in the river Glatt [μg/L]		0.60	0.70	0.095	0.06	0.06
measured concentrations at five locations in Swiss rivers over the period 1997−1998 (μg/L)[a]				nd−0.31 (2.55)[b]	nd−0.35	nd−0.48

[a] nd: below detection limit of 0.03 μg/L. [b] Exceedingly high value, measured in small river with high loads of NPE.

TABLE 5. Calculated RQ^x Values in Water of Single Components x and RQ_{mix} of the NPE Mixture[a]

uncertain parameter	scenario description	RQ^{NPnEO}	RQ^{NP2EC}	RQ^{NP1EC}	RQ^{NP2EO}	RQ^{NP1EO}	RQ^{NP}	RQ_{mix}
	Standard	0.229	0.304	0.094	0.323	0.645	0.568	2.16
degradation rates	(A1) upper limit degradation rates	0.051	0.145	0.069	0.067	0.462	0.475	1.27
	(A2) lower limit degradation rates	0.363	0.448	0.065	0.524	0.664	0.646	2.71
PNEC extrapolation models	(B1) $PNEC^x$ calculated strictly according to TGD	0.010	0.304	0.094	0.323	0.645	0.151	1.53
	(B2) $PNEC^x$ taken from distributional assessment in (*12*)	1.03×10^{-3}	1.51×10^{-3}	0.94×10^{-3}	0.018	0.035	0.012	0.069
fractions of formation	(C1) equal shares for parallel reactions[b]	0.229	0.299	0.087	0.369	0.655	1.833	3.47
	(C2) enhanced formation of NP2/1EC from NP2/1EO in aerobic compartments[c]	0.229	0.317	0.107	0.323	0.591	0.567	2.13
	(C3) no NP formation in the sediment[d]	0.229	0.304	0.094	0.323	0.645	0.556	2.15

[a] Uncertain parameters such as degradation rates and fractions of formation as well as PNEC extrapolation models are varied in the different scenarios. The standard scenario relates to the input parameters as given in Tables 2 and 3 and in A3 in the Supporting Information. [b] $\theta_{1,i} = 0.5$; $\theta_{2,i} = 1$; $\theta_{3,i} = 0.5$; $\theta_{4,i} = 0.5$; $\theta_{5,i} = 0.5$; $\theta_{6,i} = 0.5$; $\theta_{7,i} = 0.33$; $\theta_{8,i} = 0.33$. [c] $\theta_{5,s} = \theta_{5,w} = 0.9$; $\theta_{7,s} = \theta_{7,w} = 0.9$. [d] $\theta_{3,sed} = 0$; $\theta_{8,sed} = 0$.

Risk Assessment. Risk quotients were calculated for water and sediment. The risk quotients of the individual compounds, RQ^x, and the mixture risk quotient, RQ_{mix}, in water are listed in Table 5 (scenario "standard"). The most relevant result here is that none of the single compounds' concentrations reaches the corresponding effect level (all RQ^x below 1), but the mixture exhibits a risk quotient of 2.2 and must, therefore, be considered potentially harmful. The biggest contributions to the overall risk stem from the three most toxic compounds, namely, NP, NP2EO, and NP1EO. This is still the case, although all their concentrations are lower than the concentrations of the other compounds (NPnEO and short-chain acids), which are less toxic than NP by a factor of about 50−100.

Risk quotients in sediment are generally lower. They vary between 0.021 for NP1EC and 0.071 for NP1EO. The sequence of compounds in order of decreasing risk in sediment is NP1EO, NP2EC, NP, NP2EO, NPnEO, and NP1EC. The mixture risk quotient lies below 1 with a value of 0.289.

In the following, investigations about uncertainty are conducted for water only because the mixture risk quotient in water lies above the critical limit.

Sensitivity and Scenario Analysis. The values of the risk quotients in water as given for the standard scenario in Table 5 depend strongly on the assumptions and input parameters that enter the calculation of the PEC and PNEC values. The uncertainty in the PEC values is largely due to uncertainty and variability in model input parameters such as the emission rates, the degradation rates, and the partition coefficients. It also depends on choices regarding the model geometry and the model algorithm such as the transformation scheme expressed by the fractions of formation θ_i^{xy}. The uncertainty in the PNEC values stems from uncertainty about the completeness of the collected toxicity data and from the model chosen to extrapolate from effect concentrations to no-effect concentrations. In the following, we discuss the influence of the most important uncertainties on the risk quotients RQ^x and RQ_{mix}.

First, the sensitivity of RQ_{mix} to changes in 68 input parameters related to the six chemicals was investigated (emission rates, degradation rates, partition coefficients, PNEC values, fractions of formation). For that purpose, the normalized sensitivity of RQ_{mix} to a one percent change in each input parameter was evaluated as described by Morgan and Henrion (*28*). All sensitivities exceeding 0.01 are shown in Figure 4. As expected, the RQ_{mix} is most sensitive to the PNEC values and emission rates because it is directly proportional to these two types of parameters. The order of these sensitivities corresponds to the extent that each compound contributes to RQ_{mix}.

The only relevant sensitivity other than to the PNEC values and emission rates is to the degradation rates and fractions of formation in water. As the degradation rates and fractions of formation contribute only indirectly to the PEC and RQ values, they are less influential though. One surprising result is the quite high influence of the Henry's law constant of NP. A possible reason for this is that its value of 11.0 $(Pa \cdot m^3)/mol$ is high enough that a slight change considerably influences the distribution of NP between water and air. This assumption is supported by the fact that NP has been measured in air occasionally (*29*).

To relate the model inherent sensitivities given in Figure 4 to the uncertainties found for the input parameters, we defined a number of different scenarios for each type of input parameter that the mixture risk quotient was found to be sensitive to (degradation rates, PNEC extrapolation model,

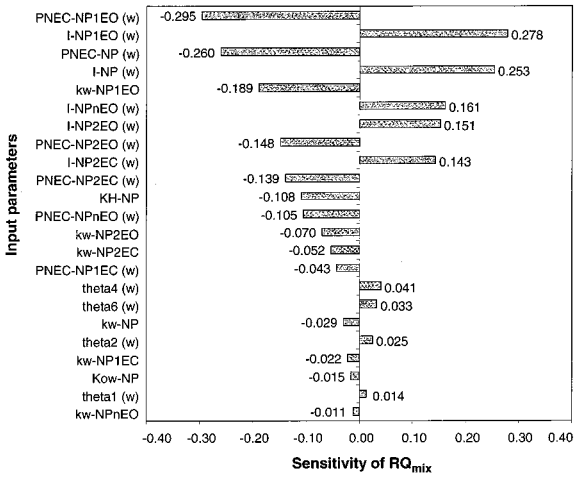

FIGURE 4. Sensitivity plot of RQ_{mix} toward emission rates (*I-x(i)* in graph), degradation rates (*ki-x* in graph), fractions of formation (theta r(*i*) in graph), partition coefficients (KH-*x* and Kow-*x* in graph), and PNEC values (PNEC-*x*(*i*) in graph). Only sensitivities exceeding 0.01 are shown.

fractions of formation) and calculated the corresponding RQ^x and RQ_{mix} values (see Table 5, scenarios A1−C3). For the emission rates, no alternative scenarios were defined because we believe that the current numbers best represent the present emission situation of NPnEO and NP in Switzerland.

Using only the fastest degradation rates from our data collection (scenario A1) reduced RQ_{mix} by about 41% to a value still above the critical limit of $RQ_{mix} = 1$. Using the slowest degradation rates (scenario A2) increased the RQ_{mix} by 25%. The biggest contributions to these changes stem from changes in RQ^{NP2EO}, RQ^{NPnEO}, and RQ^{NP2EC}. This is mainly due to a large spread in the degradation rate data of these compounds.

One alternative PNEC extrapolation model is to derive each $PNEC^x$ strictly according to data availability and TGD recommendations for extrapolation factors (scenario B1, as mentioned previously in the case study section). This led to higher PNEC values and, correspondingly, to lower risk quotients for NP and NPnEO and to a reduction of RQ_{mix} from 2.16 to 1.53.

A rather different picture is obtained (scenario B2) if the PNEC values are used that were obtained from the distributional assessment of toxicity values as it was conducted by Environment Canada (*12*). This is the only scenario where RQ_{mix} drops well below 1 to a value of 0.07 due to the fact that the PNEC values in scenario B2 lie by a factor of 20−200 higher than those of the standard scenario (see Discussion).

Scenario C1 for the case of different transformation schemes assumes an (in this case, hypothetical) worst-case information situation where nothing is known about the importance of the different pathways. Therefore, equal fractions of formation were attributed to all parallel reactions (i.e., 100% transformation in the case of single pathways, 50% transformation in the case of two parallel pathways, and 33.3% transformation in the case of three parallel pathways). This assumption was made for the soil, water, and sediment compartments equally. This scenario C1 leads to a considerably higher RQ_{mix} of 3.47, which is mainly due to the scenario's assumption that toxic NP is formed in all compartments. The other formation scenarios, C2 and C3, address two main uncertainties about the transformation scheme. Scenario C2 concerns the question to what extent the acids are formed through the oxidation of short-chain ethoxylates (reactions 5 and 7 in Figure 2) and to what extent they are formed directly from longer-chain ethoxylates (reactions 1 and 2 in Figure 2). Scenario C3 represents a situation in which the sediment environment is not sufficiently anaerobic for NP to be formed, so that NP1EO and NP1EC are directly mineralized (reactions 3a and 8a in Figure 2). Interestingly, in both scenarios, RQ_{mix} shows only small deviations from the standard scenario (±2%). Consequently, the importance of knowing the exact transformation scheme seems to be low as compared to other uncertainties.

Assuming that the different scenarios in Table 5 cover the most important uncertainties, we conclude that the uncertainty of RQ_{mix} is smallest due to uncertainties in the fractions of formation (variation of RQ_{mix} by ±2% in scenarios C2 and C3), usually within a factor of 2 for different sets of degradation rates, but on the order of at least 1 order of magnitude for different PNEC extrapolation models.

Discussion

We first discuss our results in the light of two other recent risk assessments for the same substance family. The first one is the EU risk assessment for nonylphenol (*9*) and the second one is a risk assessment for nonylphenol and its ethoxylates, conducted by Environment Canada and Health Canada (*12*).

In the EU risk assessment for nonylphenol, ethoxylates were only considered under the aspect that their biotransformation contributes to the biggest part of NP released into the environment but were not assessed themselves. The EU assessment investigates a variety of possible release scenarios of NPE from households and industry into water. Local and regional PECs for NP were calculated under standard worst-case assumptions (ref *1*, Part IV), thus reflecting hot spot situations and overestimating average concentrations in European rivers and lakes. On the toxicity side, a PNEC of 0.33 μg/L was used, which lies between the value chosen in this study (0.021 μg/L) and the value of the Canadian study (1 μg/L). Given these assumptions, the EU risk assessment identifies environmental risks for nearly all applications of NPEs as well as for the production of NP and NP derivatives (RQ values for NP range from <0.6 up to approximately 1400). Accordingly, a ban of NPE in all water-relevant use categories is suggested.

In our regional model for Switzerland, the risk quotient of nonylphenol alone is around 0.6. Obviously, if only NP was considered, no high risk would be deduced from our generic, regional risk assessment. However, in our analysis, we find that NP only accounts for 2.2% of the total mass in the water compartment and for only 26% of the total risk stemming from NPnEO and its transformation products. Because all of these compounds exist together as mixture in the environment, our results indicate that assessing the risk of the overall mixture (RQ_{mix}) is required.

In the Canadian study (*12*), concentrations in receiving waters for all compounds considered in our analysis were measured. These measured concentrations were used to calculate the risk from each single compound as well as the overall risk of the group of compounds. Regarding the risk quotients of the single compounds, the relative magnitude of our RQ^x values corresponds to the relative frequency with which the single compounds exceed a risk quotient of 1 in the Canadian study. Both studies agree that NP1EO poses the highest/most frequent single risk, followed by the other two more toxic compounds NP2EO and NP, and that the acids NP2EC and NP1EC exhibit lower single risks.

The comparison of our study with the EU risk assessment and the Canadian study and the results of the scenario analysis indicate that there are two factors that dominate the judgment about the risk of a specific chemical. First, we showed that it depends heavily on whether and, if so, on how many transformation products are considered. For the special case of NPnEO, whose transformation products are more toxic than the parent compound itself, the transforma-

tion products account for 89% of the overall risk. For other compounds, the effect might be less pronounced but still relevant.

Second, the judgment about the existence of risk depends on the PNEC extrapolation model chosen. In this respect, EU TGD guidelines are more restrictive than North American ones, which often use the distributional approach. PNEC values deduced with the distributional approach are usually larger for two reasons: (i) the distributional assessment relies on the idea that protection of 95% of all species is sufficient, while the TGD approach aims at protecting all species by basing the PNEC on the effect level of the most sensitive species (here, HC_5 of 40 μg/L (distributional) vs lowest LC_{50} of 20.7 μg/L (TGD)), and (ii) the distributional assessment uses lower extrapolation factors than the generic ones suggested in the TGD to account for the remaining uncertainties regarding acute-to-chronic ratio, sublethal effects, and species differences (here, 40 (distributional) vs 1000 (TGD)).

Another factor influencing the judgment about risk is the assumption of concentration addition. In cases where it is not applicable but is still used as an estimate of mixture toxicity, it will overestimate the toxicity by maximally a factor of 10. All in all, the mixture risk quotient in this study is subject to two conservative assumptions regarding PNEC extrapolation and evaluation of mixture toxicity and one nonconservative assumption in that possible estrogenic effects are excluded from the evaluation of the mixture toxicity at all.

Regarding the further applicability of the method presented here, the following assumptions need to be considered: (i) the use of averaged landscape parameters (no local conditions), the steady-state conditions, the selection of transformation products, and fractions of formation on the PEC side, and (ii) the assumption of concentration addition and the choice of extrapolation factors on the PNEC side.

With respect to these model limitations, the agreement between measured and modeled concentrations as well as the correspondence between the relative risks of the compounds in (*12*) and those found in our model calculations is considered sufficient. We therefore suggest that the method proposed here could be used, with due consideration of the aforesaid assumptions, to assess the risk of other compounds with environmentally relevant transformation products (e.g., odorants such as nitro musks (*30*), surfactants used in shower gels and shampoos (*31*), halogenated alkanes (*32*), or PAHs (*33*)).

Acknowledgments

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Supporting Information Available

Additional information on the model mathematics, the NPE releases, the toxicity of NPE, and the substance-specific model input parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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INTEGRATED RISK ASSESSMENT: NONYLPHENOL CASE STUDY

REPORT PREPARED FOR THE WHO/UNEP/ILO INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

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INTEGRATED RISK ASSESSMENT: NONYLPHENOL CASE STUDY

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1. INTRODUCTION

1.1 Background

The International Programme on Chemical Safety (IPCS) was initiated in 1980 as a collaborative programme of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). One of the major objectives of the IPCS is to develop and promote the use of improved methodologies for assessing the risks of chemical exposures on humans and the environment. For historical and practical reasons, human health and environmental risk assessment methodologies have generally developed independently. However, there is a need for an integrated, holistic approach to risk assessment that addresses real life situations of multi-chemical, multimedia, multi-route, and multi-species exposures. In response to this need, the IPCS (in collaboration with the US Environmental Protection Agency (US EPA), the European Commission (EC), and other international and national organizations) initiated activities to develop and promote the integration of assessment approaches to evaluate human health and ecological risks.

The term "integration" can have many meanings, and several opportunities exist within risk assessment generically for integration. In the IPCS project, **integrated risk assessment was defined as a science-based approach that combines the process of risk estimation for humans, biota, and natural resources in one assessment**. The overall goal of this project was to promote international understanding and acceptance of the integrated risk assessment process. Three specific objectives were identified to meet this goal: 1) enhance understanding of the benefits of integration, 2) identify and understand obstacles to integration, and 3) engage key scientific organizations to promote discussion of an integrated approach to risk assessment. To implement these objectives, IPCS in collaboration with a working group of international scientific experts developed a generic framework (see Figure 1.) to demonstrate and communicate how an integrated risk assessment could be conducted (WHO, 2001, 2001a; Suter et al., 2003; Munns et al., 2003a). In addition, four separate case studies were developed to demonstrate the use of the framework and to highlight the benefits of using an integrated approach (Ross and Birnbaum, 2003; Hansen et al., 2003; Sekizawa et al., 2003; Vermeire et al., 2003). The framework and case studies were evaluated at an international workshop in April 2001 (WHO, 2001, 2001b). Workshop participants identified a) a number of opportunities to integrate the risk assessment process; b) benefits and obstacles to using an integrated approach; and c) research recommendations to improve and facilitate integrated approaches (Munns et al., 2003b).

One recommendation of the April 2004 workshop was to conduct an integrated risk assessment on a specific chemical to demonstrate the practical applications, benefits, and obstacles to using an integrated approach when compared to independently conducted assessments for human health and the environment. The chemical, nonylphenol (NP), was chosen for this "demonstration integrated risk assessment." IPCS contracted with experts from the Institute of Risk Assessment, University of Utrecht, The Netherlands (in collaboration with

the Institute of Public Health and the Environment, Bilthoven, The Netherlands) to prepare the Nonylphenol case study using the IPCS generic framework for conducting integrated risk assessment.

This report summarizes the results of that effort. We hope that these collaborative efforts of the IPCS will help to establish the foundation for internationally accepted guidance for integration of risk assessment.

The draft Nonylphenol case study and related IPCS activities on integrated risk assessment were resented at the 10th International Congress of Toxicology held in Tampere, Finland, July 2004 (Munns et al., 2004; Suter et al., 2004; Sekizawa et al., 2004).

1.2 Strategic Approach For Development Of Case Study

The major objectives of this project was to compare a "demonstration" integrated risk assessment of Nonylphenol (NP) using the IPCS generic framework with data from independently conducted assessment on the environmental and human health effects of NP. This demonstration case study should build from the data used to conduct independent (non-integrated) assessments of the human and environmental risks of exposure to Nonylphenol. The following existing risk assessment reports on Nonylphenol were identified following an extensive literature search.

Reports with an ecological risk assessment:

- US EPA (1996) RM-1 document for para-nonylphenol.
- US EPA (2003) Ambient Aquatic Life Water Quality Criteria for Nonylphenol – Draft.

Reports with a human health risk assessment:

- None

Reports with both ecological and human health risk assessment:

- Environment Canada (2000), Priority Substances List Assessment Report, Nonylphenol and its ethoxylates.
- EC (2001), EU-RAR on 4-nonylphenol (branched) and Nonylphenol.

Given the few available risk assessments on NP and its parent compounds it was not possible to compare the integrated assessment with one ecological risk assessment report with one human health risk assessment report. Since the EU assessment was already partly integrated and also the most recent report, it was used for this project as the major source of information (supplemented with data from the other available assessment reports). Given the limited time-frame of this project, it was not feasible to re-evaluate the primary literature. The EU approach is based on the standard approach of problem formulation, dose-response assessment, exposure assessment and risk characterization. Due to the lack of independent human health and ecological risk assessment documentation, an evaluation of the benefits and drawbacks of IRA relative to the independent human health risk assessments and ecological risk assessments was

strictly speaking not possible. Instead, the used information was classified as ecological or human data. Conclusions resulting from these data were then integrated to form evaluations of the benefits of integration. If these integrated conclusions enhanced or improved the risk assessment, the process leading to these integrated conclusions as well as the conclusions themselves were listed as benefits of integration. Potential benefits per area of integration were searched in the following benefit categories: (1) coherent expression of assessment results, (2) interdependence of the results, (3) identification of sentinel organisms, (4) enhanced scientific quality of the assessment result and (5) efficiency in using and generating data. These categories were derived from the IPCS generic framework for integrated risk assessment which is illustrated in Figure 1 (HERA, 2003).

At the start of this project a selection was made of the most promising areas for integration. "Potential areas of integration" are processes or steps within a risk assessment that use either ecological data or human health data to generate a result, but could potentially benefit from using both (i.e., areas where ecological and human data could supplement each other and generate improved or new results). Several parts of the risk assessments of Nonylphenol did not qualify for this, either because data were too limited or because integration was not relevant. The following potential areas of integration were selected (1) problem formulation, (2) sources of emission, environmental concentrations and exposure estimates, (3) toxic kinetics, (4) estrogenic effects and (5) risk assessment for wildlife.

In Section 3, the relevance of each area of integration is briefly explained. The generic benefits of integration in that area are described along with the conclusions on the specific benefits of integration in each for the chemical Nonylphenol. The data used to derive these conclusions are also summarized. For each potential area of integration, summaries are provided for: a) the benefits already apparent in the EU-RAR; b) additional benefits gained by further integration and, in some cases; c) conclusions missed by not integrating.

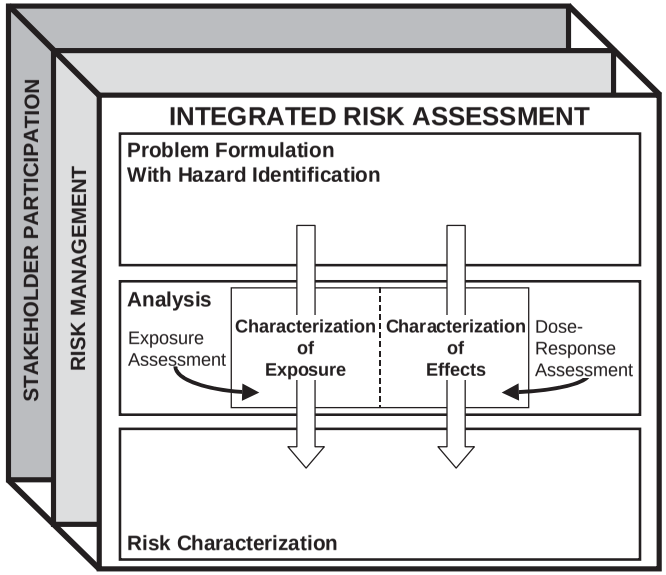

Figure 1. A framework for integrated human health and ecological risk assessment (modified from US EPA 1998). Risk assessors, risk managers, and stakeholders perform parallel activities which may interact at various stages.

2. INTRODUCTION TO NONYLPHENOL

This summary is based on the information in the EU risk assessment of nonylphenol.

Nonylphenol is used primarily as a building block for the monomers used in the production of resins and polymers. The data indicates that Nonylphenol is not used as a free additive in resins, plastics or stabilizers.

Of the 77,505 tons of nonylphenol (NP) produced in 1997 in Europe, 81 percent was produced continuously and 19 percent in batch production (four companies produce most of the Nonylphenol). Import exceeded export for an additional 5,000 tons in 1997. Nonylphenol is produced in Europe in three ways:

1. Phenol and mixed nonenes are reacted in the presence of a catalyst in a batch process. The catalyst used is montmorillonite clay/fulcat and phosphoric acid.
2. Phenol and mixed nonenes are reacted in the presence of a sulfonated ion exchange resin in a batch process.
3. Phenol and mixed nonenes are reacted in the presence of a fixed bed ion exchange resin in a continuous process.

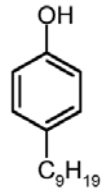

Figure 2: The molecular structure of nonylphenol.

The C_9H_{19} group can be a straight chain or be shorter and branched.
NP melts at 265 Kelvin, boils around 563 to 575 Kelvin. NP has a relative density of around 0.95 at 293 Kelvin and vapor pressure of 0.3 Pa at 298 Kelvin. Due to a low Henry's Law Constant and a low vapor pressure partitioning to air is low. NP is poorly soluble; solubility is around 6 mg/L at 293 Kelvin. NP has a pKa of 10 and will be in undissociated form in environmental water. NP has an n-octanol-partioning coefficient (Log K_{ow}) of around 4.48 (From EU-RAR).

Sixty percent of the NP is used for the production of nonylphenol ethoxylates, 37 percent for the production of resins, plastics, stabilizers, etc. and the remaining 3 percent for the production of phenolic oximes. All nonylphenol ethoxylates are produced from NP and ethylene oxide in batch processes. The length of the ethoxylate chain is varied by controlling the ratio of nonylphenol to ethylene oxide or by the reaction time. One company in the EU produces phenolic oximes from NP and exports all phenolic oximes out of Europe. Phenolic oximes are used as a reagent for the extraction and purification of copper from ore. The nonylphenol ethoxylates are functionally used as cleaning and washing agents, surface-active agents and foaming agents. The industry uses NP for industrial and institutional cleaning, textile auxiliaries, leather auxiliaries, emulsion polymerization, agricultural pesticides and paint production.

Nonylphenol ethoxylate containing products used in the public domain include: non-agricultural pesticides, cosmetics, cleaning products and office products such as correction fluids and inks. EU member states and industry have agreed to phase out nonylphenol ethoxylates in all detergent applications by the year 2000. As a result, the usage of NP is expected to drop in the future.

Small emissions of NP may occur during production, and escape to air or surface water. However, most wastes are first passed through a wastewater treatment plant. Most of the NP containing compounds, such as nonylphenol (poly)ethoxylates, is then aerobically degraded by bacteria into shorter nonylphenol ethoxylates or nonylphenol. In the wastewater treatment plant, it is estimated that half of the NP absorbs on particles. These particles then stay in the wastewater treatment plant as sludge or are emitted into the aquatic phase and settle on the sediment. For risk assessment calculations it was assumed in the EU RAR that all NP containing compounds in sludge are degraded into the more estrogenic NP. As the majority of the emissions of NP end up in the water compartment, the physico-chemical properties become relevant (Figure 2). NP is poorly soluble and unlikely to evaporate from the water. It remains in the aquatic phase and partitions to the sediment and biota such as fish. In the anaerobic sediment NP and its parent compounds (e.g. NP (poly)ethoxylates) are more resistant to degradation. Eventually, bacteria can mineralize NP. In the River Aire in England in 1995, downstream of the emission sites of textile processing industry, locally high concentrations of NP were found; up to 53 µg/L freely dissolved nonylphenol and up to 180 µg/L when including particles. Background concentrations on average in rivers in Germany in 1989 measured 0.038 µg/L, with peaks up to 1.3 µg/L. The Tees estuary in England receives water from heavily industrialized areas. In 1995 this estuary contained up to 3.1 µg/L freely dissolved nonylphenol and up to 5.2 µg/L of NP when including particles. NP has also been detected in rivers and lakes in Japan, the USA, and other countries.

Concern over the widespread usage of Nonylphenol has been increasing because of its toxicity to both marine and freshwater species, and its ability to induce estrogenic responses. The estrogenic effect of nonylphenol on fish and daphnids has been studied by a number of authors. Generally the work shows that nonylphenol and nonylphenol ethoxylates do exhibit estrogenic activity. For nonylphenol ethoxylates the activity was found to increase with decreasing chain length, with nonylphenol showing the greatest activity. Most of the tests indicate that estrogenic effects may start to occur at around 10-20 µg/L. Nonylphenol and some of its degradation products have been shown to have estrogenic activity in a number of *in vitro* (yeast, MCF-7 cells, ZR-75 cells) and *in vivo* assays (with rats and mice). The potency of this estrogenic activity in these assays ranged from 3 to 6 orders of magnitude less than that of estradiol. The effects of nonylphenol on fertility and reproductive performance have been investigated in a number of studies, but results are equivocal.

General Conclusions on the effects of NP in the EU-RAR (2001)

In the EU risk assessment report on nonylphenol of 2001 a No Observable Effects Concentration (NOEC) of 0.33 µg/L was derived, based on the endocrine disruptive potential of NP on fresh water fish. The PNEC for sediment of 0.039 mg/kg was derived using an equilibrium partitioning method. The conclusion of the EU RAR was that calculated background concentrations of NP are of concern and further measuring and testing is needed. In addition, there are many types of industries that cause locally high concentrations of NP and risk-limiting measures would be appropriate. Secondary poisoning on locally polluted sites is possible. The terrestrial and atmospheric compartments are not likely to be the source of meaningful amounts of exposure of organisms in the environment.

The calculated oral No Observable Adverse Effects Level (NOAEL) for repeated dose for humans was 15 mg/kg/day based on the endocrine disruptive effects in rats. Data from modeling suggest that there are concerns for human health with respect to local exposure, based on low margins between modeled exposures and the N(L)OAELs for repeated dose and reproductive toxicity. Living in the locality of a textile factory increases exposure by 4.42 mg/kg/day. Exposure via occupational paint usage (approximately 2 mg/kg/day) and industry sectors of manufacturing or using NP as intermediate should be reduced. In the worst-case scenario the total exposure would be approximately 6.4 mg/kg/day. The main routes of calculated exposure of humans to background pollution from the environment are from plant roots (70 to 80%) and fish (1 to 29%). Concern for mutagenicity and carcinogenicity is low. Exposure via consumer products is negligible. The calculated dose received from background pollution from the environment on a daily basis is $5.13*10^{-3}$ mg/kg/day, which is below levels of concern.

Nonylphenol is mostly an environmental health issue for aquatic organisms. Plants are exposed to NP from sludge. Terrestrial organisms are exposed via eating plant roots or exposed via secondary poisoning. There is a measure of concern for the terrestrial environment near industrial sites, which is below levels of concern. The exposure of humans to nonylphenol from background concentrations is of limited concern. Only a local high exposure could affect human health.

3. INTEGRATED RISK ASSESSMENT OF NONYLPHENOL

3.1 Problem Formulation Phase

3.1.1 Introduction

As indicated in Figure 1, the first step in the integrated risk assessment process is problem formulation, which delineates the overall goals, objectives, scope, and activities of the integrated assessment as well as the resources available to conduct the assessment. This analysis considers whether a risk assessment is needed, and who should be involved in the assessment/risk management process. It also helps to ensure that the assessment will provide the information necessary to support the environmental decision making process (i.e. risk management). Risk managers, risk assessors and other stakeholders all bring valuable perspectives to this assessment planning.

3.1.2 Potential benefits of integration Environmental Risk Assessment (ERA) and Human Health Risk Assessment (HHRA) knowledge

3.1.2.1 Assessment questions

Assessment questions are those that define the goals, breadth, and focus of the assessment.

Potential Integration benefits

1. Issues that are critical for both humans and the environment are more easily identified. Integration would greatly increase the chance of serendipitous recognition of problems for which evidence in any one sector is limited, but when all data are considered together, cause for concern may become evident.
2. Assessment of risks to humans is strengthened through evaluation of risks to other organisms that influence human health and welfare.
3. There will be greater consistency in the spatial and temporal scope (e.g., with regard to the information and processes used).
4. Data and knowledge gaps are identified at an early stage.

3.1.2.2 Impetus for the assessment

The impetus for the EU assessment was the requirement that all industrial chemicals be assessed for their risks to human health and the environment. The impetus for this integrated assessment was the desire of the WHO/IPCS to explore the benefits of integrated risk assessment by performing a demonstration case study.

3.1.2.3 Assessment Endpoints

Changes in the health of humans, ecosystems, or selected species (chosen to represent an ecosystem) must be quantified. Health is a qualitative endpoint but must be expressed in a measurable way. For example, endpoints such as the production of vitellogenin in male fish; mutagenicity skin irritation in rats can be used to quantify the effect of the stressor on these organisms or systems. More potential endpoints are listed in Table 2.

Potential Integration benefits

1. Susceptible endpoints in animals or ecosystems could indicate unidentified endpoints in humans (the reverse is also possible, but is more unlikely).
2. Knowledge on the fate of the compound and the target organisms can be used to predict potential adverse effects on the health of species within an ecosystem. Respectively, knowledge on the fate of the compound and the target organs can be used to predict potential adverse health effects on the health of a species due to organ toxicity.
3. Ecologists and human health assessors can discuss the relevance of all chosen endpoints.

3.1.2.4 Conceptual Model

The core of an integrated risk assessment is the conceptual model. The conceptual model is the condensation and formulation of how the assessors (and interested parties) think the stressor reaches and distributes over the environment and affects organisms in the environment (see Figure 3 for the EU conceptual model). Ecologists and human risk assessors should work together to evaluate the common routes of exposure of the stressor in order to enhance each other's view and understanding of the stressor's behavior. The relation between emission of the stressor and endpoints measured must be well characterized.

Potential Integration benefits

1. Both human and ecological risk assessors scrutinize the quality of information on the common pathways of emission, distribution, and exposure.
2. There will be better consensus between ecologists and human health assessors on the fate of the stressor.
3. Indirect exposure pathways via the environment to the humans are more likely to be identified since humans are modeled as just one more receiving species in the web of exposure pathways.
4. When relevant and possible, multiple sources of exposure such as consumer products, emissions, and natural emissions are incorporated into the model.
5. Only one conceptual model is produced; the ecological conceptual model and the human health conceptual model are one and are based on the same assumptions and data.

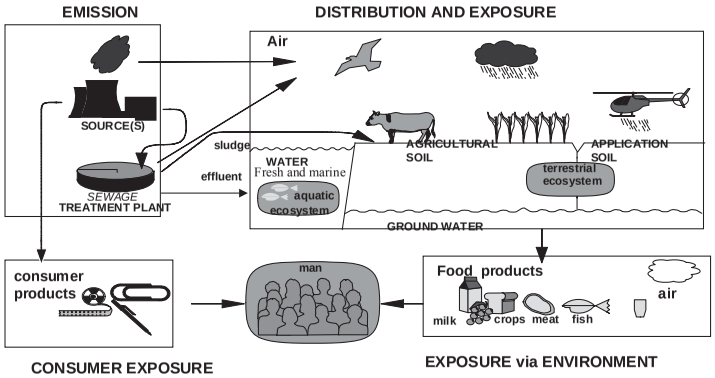

Figure 3: This figure is the summary of a non-compound specific conceptual model as used in the EU approach. The routes of exposure to the target organisms are visualized (see Table 1). Endpoints within these target organisms are defined as summarized in Table 2.

3.1.2.5 Integration of the Analysis Plan

In this step, the methods used to ensure the quality of the risk assessment are produced and discussed. This includes guidelines on how to select data, how to assess the quality of data, how to generate and analyze data, and how to cope with data incompleteness. The selection of acceptable computer models (if they are needed) is discussed along with a description of how results will be presented.

Potential Integration benefits

1. Enhanced efficiency and reduced cost since data for only one transport and fate model is needed. Emission data, physicochemical properties, fate and degradation data are only needed once. Ecological and human exposure models use the same data input. By integrating, decisions are based on more data and the available data is used more extensively.
2. Better identification of key research needs: (e.g., where do ecological and human health risk assessors lack information)? By using the same data on physicochemical properties, human and ecological health assessors can target shared research needs and transport of the stressor.
3. Ecological results and human health results adhere to the same data quality restrictions.
4. Ecological results and human health results are presented in the same terminology and if possible use the same method to express the risk and the uncertainty. This facilitates comparison between the ecological results and the human health results.
5. If the assessment will be iterated, an integrated approach might foster the development of parallel tiers, which use common data and models.

3.1.3 Integrated Risk Assessment

In the EU Risk Assessment framework for new and existing chemicals and biocides the stage of problem formulation is addressed, harmonized and laid down in advance of the preparation of Technical Guidance Documents (TGD) (EC, 2003). The level of integration therefore is determined largely by this general guidance and individual risk assessments for specific chemicals (such as the one for Nonylphenol) do not have an additional problem formulation stage. In some cases, the problem formulation stage results in a proposal for a more targeted risk assessment, but this has not been done for nonylphenol.

Risk assessment according to the EU-TGD is carried out in a stepwise procedure encompassing the following stages:

1. Exposure assessment: estimation of the concentrations/doses to which human populations or environmental compartments are or may be exposed.
2. Effects assessment, comprised of
   a. hazard identification: identification of the adverse effects which may be caused by the substance
   b. dose-response assessment: estimation of the relationship between the level of exposure to a substance (dose, concentration) and the incidence and severity of an effect.
3. Risk characterization: estimation of the incidence and severity of the adverse effects likely to occur in a human population or environmental compartment due to actual or predicted exposure to a substance.

At the risk characterization stage, this procedure will result in a quantitative comparison of the outcome of the exposure assessment and that of the effects assessment. For new and existing substances this will be a PEC/PNEC (i.e., Predicted Environmental Concentration versus a Predicted No-Effect Concentration) for environmental compartments, and a MOS (i.e., Margin of Safety), or the ratio of the estimated no-effect or effect level parameter to the estimated exposure level for human sub-populations. The risk characterization for biocides is performed by comparing the exposure to the AOEL (Acceptable Operator Exposure Level), a health based limit value. These PEC/PNEC and MOS ratios should be seen as surrogate parameters for risk characterization as they do not quantify the "incidence and severity" of adverse effects. The ratios are used as indicators for the likelihood of the occurrence of adverse effects, since a better method for a more quantitative risk characterization with general applicability is not available at the moment.

The human sub-populations and ecological systems and populations that are considered to be protection goals in the European Union System for the Evaluation of Substances (EUSES) are shown in Table 1. Examples of effects of the stressor on the health of the organisms are mentioned in Table 2.

The risk assessment for man aims at a level of protection, expressed in the MOS for new and existing substances or MOE and AOEL/exposure-ratio (biocides). These values indicate that the likelihood for adverse effects occurring is “of low concern”, taking into account the nature of the potentially exposed population (including sensitive groups); the nature and severity of the effect(s); and the uncertainties involved. In the environmental risk assessment it is assumed that ecosystem sensitivity depends on the most sensitive species and that protection of the ecosystem structure also protects community function. The PNEC derived for each ecosystem is regarded as a concentration below which an unacceptable effect will most likely not occur.

Risk assessment using the EUSES departs from a screening level approach in which so-called generic exposure scenarios are applied (see Figure 3). In the environmental risk assessment, it is assumed that substances are emitted in a standard environment with predefined environmental characteristics. No measured data are used at this level. The risk assessment covers the whole life cycle of substances as well as their fate in all environmental compartments. Four spatial scales (local, regional, continental, and global) and two time scales (acute, chronic) are distinguished. In the risk assessment for workers and consumers, again generic exposure models are applied initially, covering a wide range of applications. The resulting screening-level risk assessment is in principle valid for all EU countries, as required by the relevant EU regulations.

Table 1 ***Human target populations and ecological target systems and populations in EU-RA.***

Human populations:
- workers
- consumers
- non-professional users of biocides
- man exposed via the environment

Ecological systems and populations:
- micro-organisms in sewage treatment systems
- aquatic ecosystem*
- terrestrial ecosystem
- sediment ecosystem*
- (top) predators*

* Fresh and marine ecosystems

Table 2 ***Human endpoints and ecological endpoints in EU-RA.***

Human Endpoints:
- workers
- consumers
- non-professional users of biocides
- man exposed via the environment
- acute toxicity
- irritation
- corrosivity
- sensitization
- repeated dose toxicity
- mutagenicity
- carcinogenicity
- toxicity for reproduction

Ecological endpoints:
- survival
- toxicity for reproduction
- (cell) growth

The EU exposure assessment aims at a “reasonable worst-case” scenario by applying unfavorable, but not unrealistic, standard exposure scenarios and, as much as possible, mean, median or typical parameter values. If the outcome of the reasonable worst-case risk characterization indicates that the substance is “not of concern”, the risk assessment for that substance can be stopped with regard to the life cycle stage/effect/population considered. If, in contrast, the outcome is that the substance is “of concern”, the assessment must, if possible, be refined by adapting any default parameter value for which this is considered necessary. These may include the replacement of intermediate results by: a) the results of other models judged to be more suitable for the substance under investigation; and b) the use of more reliable and representative measured data.

In the case of the EU risk assessment for Nonylphenol, further integration in the problem formulation stage could have taken place with regard to recognition of the mode of action of the chemical as an estrogen.

Conclusions based on integration in the problem formulation phase

As pointed out above, integration in the problem formulation for nonylphenol in the EU risk assessment has already taken place to a certain extent with regard to:

1. assessment questions,
2. assessment endpoints,
3. conceptual models,
4. analysis plan.

The benefits of this integration have been pointed out in subsection 3.1.2. They mostly also apply to the risk characterization of nonylphenol. Further integration in the problem formulation for nonylphenol could have taken place with regard to the more explicit recognition of the mode of action of the chemical as an estrogen receptor agonist.

Without this integration the ecological and human health risk assessments may differ with regard to:

1. spatial and temporal scales considered,
2. the degree of conservatism,
3. the terminology used,
4. the scenarios for environmental exposure,
5. highlighting important effect endpoints,
6. the default values used,
7. the evaluation of the quality of the database.

3.2 Emission Sources, Environmental Concentrations and Exposure Estimates

3.2.2 Introduction

The scope of this section is the integration of exposure estimation, using external emission, fate and exposure models and measured concentrations in compartments and biota. External exposure can be converted to internal exposure if enough bio-kinetic information is present.

3.2.3 Potential benefits from integration of ERA and HHRA knowledge

1. Routes of emission, distribution and exposure (that were defined in the Conceptual Model Stage) are translated into model equations describing how the stressor reaches the organisms via diverse routes of exposure. Here human and ecological risk assessors can discuss which models and which input values are appropriate and choose a common approach.
2. The type of model (e.g., the fugacity transport and fate model) chosen in the conceptual model stage (which includes aspects such as advection and diffusion, partitioning, bioaccumulation and abiotic and biotic degradation) can be of the appropriate space- and time scales with regard to both the human and the environmental risk assessment.
3. Monitoring data for emissions, environmental compartments (such as air, soil surface water, groundwater and marine), biota, food, and drinking water can be shared.
4. The whole life cycle of the stressor and all possible sources of emission will be considered (such as production, processing, industrial/consumer use) to ascertain potential exposure of man and the environment.
5. Local sites with high concentrations of a chemical can cause potential adverse ecological effects with indirect effects on humans. These effects are not exemplified in an ERA. For example, this means that the effects of a massive fish extinction on human health or resources would not be estimated. Integration can solve this problem.
6. Coherent conclusions can be drawn with regard to additional analytical activities necessary for higher tier human and ecological risk assessment.
7. A common approach towards uncertainty analysis can be developed.
8. A common approach to the evaluation of data quality (completeness and relevance) will be developed.

3.2.4 Risk Assessment Data

3.2.4.1 EU-RAR: General Data

Source: EU-RAR

Nonylphenol is produced on four locations in the EU. The total production of these four locations in 1994 was 77,505 tons. This includes the NP in NP ethoxylates. The production was for 81% continuous production and 19% batch production. About 60% of the NP is processed into NP ethoxylates. NP ethoxylates are mostly used in industrial and institutional cleaning, emulsion polymerization and textile auxiliaries. Three percent of the NP is used in the metal extraction industry as phenolic oximes for the extraction of copper. The remaining 40% of the NP is mostly used for the production of resins, plastics, stabilizers etc.

3.2.4.2 EU-RAR: Environmental Concentration/ Data (Source EU-Risk Assessment Report, 2001)

In the EU, NP production and the production of its parent compounds take place at only four different sites. The air compartment does not receive meaningful amounts of NP. All remaining emission is either to the wastewater treatment plant or to the incinerator. From the wastewater treatment plant NPEO or NP goes to the surface water or as sludge to agricultural soil or authorized disposal sites. Effluent is always treated at the factories. In the waste water treatment plant model, it is assumed that 2.5% of the nonylphenol ethoxylate released to the waste water treatment plant would eventually be converted and released to surface waters as nonylphenol. Based on estimated emissions in the amount of nonylphenol released to surface water as a result of the use of nonylphenol ethoxylates is estimated as 2,690 kg/day in the continental model and 299 kg/day in the regional model.

Only a few studies have been done on the measurements of environmental concentrations in the compartments of air, soil and landfills. There are no reported measurements of nonylphenol in the atmosphere. Sludge was applied to the top 5 cm of grassland: the initial concentration of nonylphenol in the soil was 4.7 mg/kg, but this had dropped to 0.46 mg/kg dry weight after 322 days. The concentration of nonylphenol in grassland soil that had not been treated with sewage sludge was <0.02 mg/kg (dry weight). The study also looked at sludge-only landfill sites. The concentration of nonylphenol in the sludge samples ranged from 4-37 mg/kg (dry weight) for raw sewage sludge and 7-375 mg/kg (dry weight) for digested sludge. Measurements of NP in surface water are more readily available. The nonylphenol concentration in the river Main in Germany was monitored throughout the years 1989-1991. The nonylphenol concentration in the water of the Main (June 1991) was mostly 0.18 µg/L or less. More concentration data are available but concentrations in rivers in general do not exceed the 5 µg/l. In the English river Lea the total extracted amount of NP is 0.5 to 12 µg/l and the dissolved fraction of NP is 0.2 to 9.0 µg/l. Concentrations of NP in groundwater due to infiltration of river water are low. In seawater the concentration of NP only increased in estuaries that received water that carried effluent from industries. The highest concentrations were observed in the Tees estuary at 0.08 to 3.1 µg/l dissolved NP and 0.09 to 5.2 µg/l total extracted NP.

Conclusions about predicted environmental concentrations

Soil:

$PEC continental_{agri,\ soil}$	= 0.0271 mg/kg wet weight
$PEC continental_{nat,\ soil}$	= 2.39×10^{-6} mg/kg wet weight
$PEC continetal_{pore\ water}$	= 2.86×10^{-4} mg/kg wet weight
$PEC regional_{agri,\ soil}$	= 0.265 mg/kg wet weight
$PEC regional_{nat,\ soil}$	= 1.44×10^{-5} mg/kg wet weight
$PEC regional_{pore\ water}$	= 2.8×10^{-3} mg/kg wet weight

Air:

$PEC continental_{air}$	= 5.21×10^{-7} mg/m^3
$PEC regional_{air}$	= 3.14×10^{-6} mg/m^3

Surface water:

$PEC regional_{surface\ water}$	= 0.60 µg/l
$PEC continental_{surface\ water}$	= 0.066 µg/l
Sediment of freshwater:	
$PEC regional_{sediment}$	= 103 µg/kg wet weight
$PEC continental_{sediment}$	= 13.1 µg/kg wet weight

Water concentrations:

In top water the concentration of nonylphenol was between 1.7 to 3.02 µg/l, in middle waters the concentration was between 1.3 to 1.6 µg/l and in bottom waters between 0.54 to 1.2 µg/l. These measured levels will be used in the risk characterization section.

Surface water concentrations:

Based upon background data, concentrations of nonylphenol in surface waters would appear to be relatively low when compared to calculated levels (0.12 µg/L USA; 0.18 µg/L Glatt river; 0.01 µg/L Finnish lake water; 0.01 to 0.08 µg/L Bavarian rivers; <0.5 µg/L Hessian rivers). A background concentration of nonylphenol of 0.2 µg/L therefore appears to be a realistic level. The calculated predicted environmental regional (PECregional) based upon default releases is 0.6 µg/L which, although higher, is of the same magnitude. The recently measured data are typical of areas where the use of ethoxylates has been controlled to some extent, but may not be representative of areas where widespread use still occurs. Therefore the calculated PECregional will be used in the risk assessment, as this is taken as representing an area with widespread use of nonylphenol or nonylphenol ethoxylates. The estimated regional predicted environmental concentration (PEC) for surface water (0.6 µg/l) exceeds the aquatic (PNEC) of 0.33 µg/l.

Ground water

The groundwater levels reported should be used with care as they relate to river water infiltration into groundwater.

Sediment

A wide range of sediment concentrations is reported. As with the other data, the concentrations appear to vary widely depending upon the inputs to the receiving waters. The calculated levels were again similar to the measured levels.

Wastewater effluent

The measured levels downstream of wastewater treatment plants receiving industrial effluents are generally lower than the PEC local calculated for specific industries. This suggests that the PEC calculations are overestimating the concentrations in receiving waters. The measured data however are not comprehensive enough to have covered receiving waters from all the different industry types which use nonylphenol or nonylphenol ethoxylates. Therefore the calculated PECs will be used in the risk characterization section despite the concerns over the assumptions made in generating the data.

Soil with sludge

The Danish EPA reports that levels of nonylphenol in soil after sludge application are typically 0.3-1.0 mg/kg but that they can go up to 4.7 mg/kg. These measured levels are of the same order as a number of those calculated, but the PECs for some industries are much higher.

3.2.4.3 EU-RAR: Ecological Data (Source: EU-RAR, 2001)

Nonylphenol shows a high bioconcentration potential in aquatic organisms. A PNE Coral of 10 mg/kg food was derived for a secondary poisoning scenario. The concentration of nonylphenol in fish and earthworms for predators (mammals and birds) has been estimated. There are 12 lifecycle stages of NP containing products that can cause potentially harm to fish-eating or earthworm-eating organisms.

3.2.4.4 EU-RAR: Human Health Data (Source: EU-RAR, 2001)

The highest estimate for exposure of man *via* the environment (not in the vicinity of a nonylphenol plant) is provided by the regional model at 5.31×10^{-3} mg/kg/day. The maximum combined local intake, taking account of exposure via air, drinking water and food is 4.42 mg/kg/day (from the textile industry). The highest exposure an individual is likely to experience would occur if they apply specialty paints (2 mg/kg/day), use a pesticide product (0.35 µg/kg/day), use cosmetics (0.1 µg/kg/day) and are exposed via food packaging materials (0.2 µg/kg/day) while living in the locality of a textile factory (4.42 mg/kg/day). The maximum combined daily total exposure for an individual is approximately 6.4 mg/kg/day from the estimates provided in the EU report. However, there is considerable uncertainty in the estimated human daily intake figures; consequently the accuracy of the predictions is difficult to determine. The first cause of uncertainty results from the lack of reliable data on the quantities of nonylphenol released into the environment from actual production and various uses. Releases and hence concentrations from actual production and use sites are likely to be much lower than

the figures used here. The second cause of uncertainty concerns the assumption made in the local calculations that all of the water, air and food comes from close to a point source of release. The largest contributor to the human exposure is the intake of fish. This accounts for around 70-80% of the daily dose. The other significant contributor is the intake of plant roots (1-29%). The figures are based on predicted environmental concentrations in a local scale scenario. The calculations may be overestimates but the degree of overestimation is uncertain. A number of emission scenarios in the model are based upon default estimations. This may result in significant variations between predicted concentrations and actual environmental concentrations.

3.2.4.5 Other Data (Source: Environment Canada, 2000)

A steady-state, non-equilibrium model (EQC Level III fugacity model) was run using the methods developed by Mackay (1991) and Mackay and Paterson (1991). The results of this modeling predicts that when NP is released in water, most of it is present in water (49–59%) and, to a lesser extent, sediment (41–50%), with a negligible proportion (<1%) in air and soil. When emissions are released to the soil, most of the NP would remain in the soil. When emissions are released to the air then most of the NP would be in the air. Emission to surface water is also a very realistic emission scenario. Sludge application to land is considered in the human health assessment. Soil (e.g. attached. to vegetables) eaten by humans is considered non-degraded sludge mixed with soil.

Data on human exposure in the Canadian assessment are summarized below:

Route Of Exposure	Dose Per Route (mg/kg-bw/day)
air	0.000016
surface water	0.00039
food packaging	0.017
meat	0.017
sludge-amended soil	0.0000025
LOEL of 12 mg/kg-bw/day for rats, (based on an oral dose for 3 generations long)	12

Human exposure was calculated based on limited data on measured human concentrations in combination with consumption information. Due to worst-case scenarios and lack of actual exposure data the calculated human exposure dose is quite uncertain. By combing data for each route of exposure, the total human exposure dose adds up to 27 mg/kg-bw/day. This is a worst case scenario using limited environmental sampling measurements. Although, the EU assessment used a model and the Canadian assessment used scenarios to calculated human exposure, the calculated worst-case exposures were in the same order of magnitude.

3.2.5 Conclusions on benefits of integration

Integration benefits already present in EU-RAR

In the EU-RAR, the exposure estimates are already performed in an integrated manner and the following benefits of integration can be identified:

1. A common modeling approach is applied to the exposure estimation of nonylphenol for ecological receptors and humans leading to a coherent assessment and avoiding duplication of work. For example, the same estimated emission and background levels are used in the exposure estimation for environmental organisms and for human beings. The estimation of exposure of man via fish intake is estimated from the surface water concentration. The same concentrations also determine the risks for aquatic organisms.
2. This approach uses common space and time scales. The risk assessment for ecosystems and humans exposed via the environment is done at a local scale (around a point source) as well as at a regional level (considering all point sources together). Short-term exposure levels during emission periods are estimated as well as annual averages for long-term exposures.
3. The available monitoring data for (concentrations in environmental compartments, biota, food and feed and drinking water) are shared. This avoids the use of different data of different quality in independent assessments. It results in a common approach towards the analysis of the accuracy, specificity and relevance of these data.
4. The whole life cycle of nonylphenol and all possible sources of emission are considered in both the environmental and the human health risk assessment, stimulating a holistic view and a coherent development of risk reduction options.
5. The nonylphenol assessment shows a common approach to the evaluation of data quality, completeness, and relevance as outlined in the TGD (EC, 2003).
   Coherent conclusions can be drawn with regard to additional analytical activities necessary for higher tier human and ecological risk assessment. This will promote the best use of the available resources and an integrated sampling strategy. For example, when a lack of data is identified then default worst-case or reasonable worst-case scenarios are used to make an estimate. When the PEC/PNEC ratio is close to or higher than one, the risk assessment is refined via an iteration of collection of new and/or more precise data until either the ratio is reasonably smaller or it becomes apparent that the new data confirm a higher risk estimate and risk reductive measurements are needed. Guidelines on which type of data to refine first are available in the TGD. Parameters that need refinement are selected based on sensitivity analysis. The execution of an actual monitoring program is one of the last options to gain more reliable environmental concentrations.

Additional benefits of integration

No additional benefits are identified above those already present in EU-RAR.

3.3 Toxicokinetics

3.3.1 Introduction

Toxicokinetics represent the fate of a chemical within the organism. This includes (1) the uptake of NP after exposure; (2) the biotransformation of NP; (3) the tissue distribution of NP and its metabolites, and (4) the elimination of NP and its metabolites. Accumulation is a result of the complex toxicokinetics behavior in the food chain. Accumulation can lead to increased exposure at higher trophic levels.

3.3.2. Potential benefits by integration ERA and HHRA knowledge

Potential benefits of linking ERA in relation to toxicokinetics are:

1. ADME (Absorption, Distribution, Metabolism and Excretion) data and toxicokinetic models for laboratory animals and man may be extrapolated to wildlife.
2. Development and improvement of Physiologically Based Pharmacokinetic (PBPK) modeling by combining data sets of different species could improve interspecies extrapolation.
3. Identification of metabolic pathways observed in environmental biota, in laboratory mammals or humans may strengthen each other.
4. Information about elimination rates in environmental biota, mammalian test organisms or in humans lead to better predictions on the bioaccumulative potential.
5. Information about accumulation in specific biota may point to relevant uptake routes for humans (for example: if a particular chemical has limited accumulation in a certain food product there will be no need to take this route of exposure into account in the human health risk assessment. In the opposite case: chemical accumulation might occur in an unexpected manner).
6. Biomarkers developed for one species may be useful for exposure/effect assessment in other species. Biomarkers (e.g., DNA-adduct formation or the occurrence of certain metabolites in urine) could be used to demonstrate the presence of the stressor and help quantify exposure.

3.3.3 Risk Assessment Data (Source: EU-RAR, 2001)

3.3.3.1 Environmental Data

It is clear from the available data that nonylphenol bioconcentrates to a significant extent in aquatic species, with bioconcentration factors (BCFs) (on a fresh weight basis) of up to 1,300 in fish. However, this value may overestimate the BCF; more reliable values with a mean of 741 have been measured, which are of a similar order of magnitude. Bioconcentration factors of around 2000-3000 have been measured in mussels. The BCF calculated from the log Kow of 4.48, using the TGD equation, is 1,280, which agrees well with the measured values. The calculated value of 1,280 will be used in the risk assessment. Nonylphenol was detected in the

following tissues of experimental fish in descending order of concentration: bile, liver, kidney, fat, gill, heart, muscle.

3.3.3.2 EU-RAR: Human Health Data

Most of the information on the toxicokinetics of nonylphenol concerns oral exposure and is based on a small number of limited rat and human studies. This is supported by data on octylphenol (an alkylphenol with a close structural relationship to NP). The available data, though sparse, does provide the basis for a general understanding of the main features of the toxicokinetic profile. Absorption from the gastrointestinal tract is initially rapid, and probably extensive. The major metabolic pathways are likely to involve glucuronide and sulphate conjugation, and there is evidence of extensive first pass metabolism of nonylphenol absorbed through the gastrointestinal tract. Because of first pass metabolism, the bioavailability of unconjugated nonylphenol is probably limited following oral exposure (at no more that 10-20% of the administered dose). Nonylphenol is distributed widely throughout the body, with the highest concentration in fat. Available data on bioaccumulation potential from both animal and human studies are inconsistent and do not allow for conclusions on the bioaccumulation potential of NP. The major routes of excretion of NP are via the faeces and urine. There are no data on the toxicokinetics of nonylphenol following inhalation exposure, but on the basis of the oral absorption data and high partition coefficient, it would be prudent to assume that significant absorption via the inhalation route can occur. Because first pass metabolism will not take place following exposure by this route, the systemic bioavailability is likely to be substantially greater than is associated with the oral route. Concerning the dermal route, *in vitro* data indicate that nonylphenol is poorly absorbed across skin, although there is some limited skin penetration.

3.3.3.3 Other Data

(Source: CAN-EPA, 2001)

Nonylphenol accumulates in several species of plants and is metabolized to hydroxylated and conjugated derivatives.

(Source: US-EPA, 2003)

Nonylphenol is metabolized by cytochrome P450 enzymes in the rainbow trout. Bile was found to be the major route of excretion for both waterborne and dietary exposure of the fish.

(Source: US-EPA, 2003)

Nonylphenol bioaccumulates in aquatic organisms to low levels. In freshwater fish, lipid normalized bioconcentration factors ranged from 39 to 209. Bioaccumulation was apparently greater in saltwater organisms, where bioconcentration factors ranging from 78.75 to 2,168 were measured.

Conclusions on benefits of integration

Integration benefits already present in EU-RAR: None.

Additional benefits of integration

Table 3 summarizes the available information on the toxicokinetics of nonylphenol. The only additional insight gained here is that the metabolism of nonylphenol proceeds through similar pathways across species, including humans. Overall the data are rather limited for integration.

3.4 Estrogenic Effects

3.4.1 Introduction

One of the reasons for a risk assessment on nonylphenol (NP) for both the EU and Canada was the demonstrated estrogenic effects of NP and its parent compounds on fish and mammals. Since direct human health data are not available, the available data on estrogenic effects in experimental animals are used to extrapolate to humans. Various endpoints have been used to measure the estrogenic effects of NP and other estrogenic chemicals (Damstra et al., 2002). For example, increased vitellogenin production can be used as an endpoint in fish to measure exposure to a high nonylphenol concentration (or another estrogenic compound). Endpoints can indicate the effect of the stressor on an ecosystem, a population or a single organism.

3.4.2 Potential benefits by integration ERA and HHRA knowledge

Benefits on the understanding of mechanism of action and endpoints:

1. Mechanisms of action can be confirmed by looking across the species barriers. Estrogen/steroid modes of action in fish and mammals can be the same, as estrogen receptors are often highly conserved in structure.
2. Opportunity to detect (common) critical pathways from target site to endpoint across species may be identified.
3. Knowledge on links between molecular events and endpoints will be improved.
4. Effect found in wildlife populations might identify new endpoints, and could assist in identifying emerging new risks for humans. This also reduces the chances of overlooking critical effects.

Table 3: Toxicokinetics

Knowledge in this area of integration	Additional conclusions *(based on integration)*
Accumulation in plants seems negligible. Accumulation in fish is of a low to moderate level.	The uptake of NP into plants seems negligible, thus concentrations in plants will be negligible. So exposure via plants is not expected to be an important route of exposure for humans. However, the data sets that support the low uptake of plants are rather limited.
Metabolism by cytochrome P450 enzymes and subsequent glucuronidation is the major pathway of NP in fish, laboratory animals and humans.	The metabolization of NP is based on the same mechanism in diverse taxa.
A major route of excretion of NP in fish was via bile. This route was not investigated in laboratory animals and humans. In laboratory animals, though, excretion of radiolabel occurred mainly via faeces, while in humans most excretion occurred via urine.	As faeces contain bile, the routes of excretion of NP in fish and laboratory animals are similar. The route of excretion via urine in humans is different.
Although several studies on toxicokinetics and metabolism are performed with mammals and major metabolites are identified, no PBPK models are applied to these toxicokinetic studies.	A comparison of kinetics in mammals and environmental biota is impossible.

Benefits for dose-effect relations:

5. Integration strengthens association of exposure-effects in one species if the same exposure-effect relation is also observed in other species.

Benefits for extrapolation from human health data to wildlife data:

6. Improved cross-species extrapolation might reduce or validate extrapolation factor values.
7. In the absence of toxicity data for predators (for example fish-eating birds, fish-eating mammals and organisms feeding on earthworms in the ecological risk assessment), toxicity data for rats or mice (generated in the framework of the human health risk assessment) can be used to evaluate the hazard to predators.
8. Effects found in wildlife populations might serve as a warning for low dose-effect in human populations. In the same reasoning: one sensitive species may serve as "early warning" for other organisms, including humans.

3.4.3 Risk Assessment Data

3.4.3.1 EU-RAR: (Source: EU-RAR, 2002)

In vitro ***data on ecological endocrine effects***

Vitellogenin production by isolated hepatocytes from rainbow trout has been used as an *in vitro* test system for estrogenic activity of nonylphenol and several nonylphenol ethoxylates. Vitellogenin is a yolk protein normally produced in response to estrogen in female trout. The relative potency of nonylphenol to estradiol -17β was 0.0000090. The mean EC_{50} for the test was measured at 16.15 µM nonylphenol (3.56 mg/l). Studies have reported that nonylphenol can stimulate vitellogenin secretion, *in vitro*, at concentrations of 10^{-6} M (0.2 mg/l) and above in hepatocytes from rainbow trout. Nonylphenol showed competitive displacement of estrogen from its receptor site in rainbow trout.

In vivo ***data on ecological endocrine effects***

A summary of in vivo data is provided in Appendix 1.

Summary of ecological endocrine effects

The estrogenic effect of nonylphenol on fish and Daphnids has been studied by a number of authors. Generally the work shows that nonylphenol and nonylphenol ethoxylates do exhibit estrogenic activity. For nonylphenol ethoxylates the activity was found to increase with decreasing chain length, with nonylphenol showing the greatest activity. Most of the tests indicate that estrogenic effects may start to occur at around 10-20 µg/L.

3.4.3.2 EU-RAR: Human Health Data (Source: EU-RAR, 2002)[*]

In vitro ***data on human endocrine effects***

4-Nonylphenol was one of a number of alkyl phenols tested in a yeast assay in a study which looked at the structural features important for estrogenic activity in this chemical group (Routledge and Sumpter, 1997). The assay uses a recombinant strain of yeast (*Saccharomyces cerevisiae*) which contains an estrogen-inducible expression system. In the presence of estrogens a reporter gene (Lac-Z) encoding for the enzyme ß-galactosidase is expressed, which can be monitored by measuring a colour change reaction in the culture medium. The estrogenic activity of the test substances was expressed as a potency relative to 17ß-estradiol by comparing the molar concentrations required to produce the same response. 17ß-estradiol was found to be about 30,000 times more potent than nonylphenol. Tamoxifen, an estrogen antagonist known to act via the estrogen receptor, was shown to inhibit the activity of the alkyl phenols, demonstrating that the assay response was due to interaction with the estrogen receptor. The estrogenic activity of nonylphenol has also been assessed in an *in vitro* assay involving estrogen sensitive human

[*] Individual references are listed in the EU-RAR.

breast tumor MCF-7 cells containing human ERα (Soto *et al.,* 1991). The cells are cultured in the presence of charcoal-stripped (to remove endogenous estrogens) human serum so cell proliferation is inhibited. Substances with estrogenic activity can then overcome this inhibition. The MCF-7 cells were cultured in the presence of 17ß-estradiol or nonylphenol at several concentrations in triplicate in multi well plates. Cell proliferation was assessed after a six-day exposure period by counting nuclei from lysed cells. Nonylphenol at a concentration of 10 µM elicited a similar proliferative response to estradiol at a concentration of 30 pM; thus, on a molar basis the estrogenic potency of estradiol, as measured in this assay, is 3.0E6 times greater than that of nonylphenol. At concentrations of 1 and 0.1 µM the proliferative response produced by nonylphenol was similar to that observed in vehicle treated control cultures.

In another similar *in vitro* assay, MCF-7 and ZR-75 human breast cancer cell lines were used (White *et al.,* 1994). Cells were cultured in quadruplicate in the presence of nonylphenol at concentrations ranging from 0.1 nM to 10 µM or 17ß-estradiol at 10 nM. No estrogenic activity was detected at nonylphenol concentration of 100 nM and less. At 1 and 10 µM nonylphenol elicited a proliferative response which at the higher concentration was similar to that produced by estradiol. Thus, 17ß-estradiol was 1000 times more potent than nonylphenol in this assay. In a further investigation, the ability of nonylphenol to stimulate transcriptional activity was determined in MCF-7 and chicken cell fibroblasts (CEFs) transfected with reporter gene pEREBLCAT and a mouse estrogen receptor. Nonylphenol stimulated transcription at culture concentrations of 1 and 10 µM.

To summarise the *in vitro* estrogenic data, there is evidence that nonylphenol has estrogenic activity, of 3-6 orders of magnitude less potent than estradiol.

In vivo *data on human endocrine effects – EU-RAR*

A summary of data on in vivo effects is provided in Appendix 2.

Summary *of human endocrine effects – EU-RAR*

No human data are available. Nonylphenol has been shown to have estrogenic activity in a number of *in vitro* (yeast, MCF-7 cells, ZR-75 cells) and *in vivo* assays (with rats and mice). The potency of this estrogenic activity in these assays ranged from 3 to 6 orders of magnitude less than that of estradiol. The effects of nonylphenol on fertility and reproductive performance have been investigated in a dietary administration in a multigeneration study in the rat. This study provided evidence that nonylphenol exposure over several generations can cause minor perturbations in the reproductive system of offspring, namely slight changes in the oestrous cycle length, the timing of vaginal opening and possibly also in ovarian weight and sperm/spermatid count. Functional changes in reproduction were not induced at the dose levels tested. The NOAEL for these changes was 15 mg/kg/day. The observed perturbations in offspring are compatible with the predictable or hypothesized effects of exogenous estrogenic activity. Evidence of testicular toxicity, seen as seminiferous tubule vacuolation, cell necrosis and a reduction in tubule diameter, was reported at exposure levels which also cause mortality in a repeated dose gavage study in rats. The LOAEL for testicular toxicity was 100 mg/kg/day. The toxicity of nonylphenol appears to be enhanced by gavage administration in comparison to

dietary administration, presumably because higher peak blood concentrations of nonylphenol are achieved by gavage.

A standard oral developmental toxicity study in the rat showed no developmental toxicity of NP. Maternal and foetal NOAELs were 75 and 300 mg/kg/day, respectively. In contrast, in a gavage study involving *in utero*, lactational and direct post-weaning exposure, there was a reduction in sperm count at 250 mg/kg/day (although it is not possible to state whether this is a developmental effect or a result of direct exposure after weaning). In an intraperitoneal study designed to investigate the effects of nonylphenol on male reproductive tract development of neonatal rats, evidence of impaired development was observed. However, this study was difficult to interpret, so that these results carry minimal weight in the overall assessment of the available data.

Overall, the results of estrogenic activity in the *in vitro* and *in vivo* assays showed minor perturbations in the reproductive system of offspring in the multigeneration study, and testicular changes in gavage studies collectively raise concerns for reproductive toxicity, possibly mediated through action on the estrogen receptor. These concerns for reproductive toxicity are addressed in the risk characterization, although there are uncertainties. The estrogenic activity assays are merely screening tests. The effects on reproduction-related parameters in the multigeneration study were marginal and there was no evidence of functional changes in reproduction; furthermore any changes that were seen occurred at exposure levels in excess of the LOAEL for repeated dose toxicity (LOAEL for renal toxicity is 15 mg/kg/day, NOAEL for reproductive changes is 15 mg/kg/day). Evidence of testicular toxicity was reported in two repeated exposure studies designed specifically to investigate the effects on this organ, but only at doses which also caused mortality. No evidence of testicular toxicity was seen in standard repeated dose studies involving dietary administration. Development was not affected in a standard rat oral developmental toxicity study. With respect to the effects on the reproductive system, a NOAEL of 15 mg/kg/day has been established in a multigeneration study and this value is used in the risk characterization.

3.4.3.3 Other Data (Source: Environment Canada, 2000)**

In vitro data on ecological endocrine effects

Limited data on *in vitro* test results were available and are provided in the summary.

The relative potency of NP was $8.9E^{-5}$ to $2.0E^{-4}$ compared to estradiol; the relative binding affinity to E_2 receptor was (Kd) $5.0E^{-5}$ M, binding to estrogen receptor in trout was $2.54E^{-4}$.

** Individual references are listed in the Environment Canada report (2000).

Summary of ecological endocrine effects

Alkyl phenols (APs) and alkyl phenol ethoxylates (APEs) have been reported to cause a number of estrogenic responses in a variety of aquatic organisms. These responses occur at concentrations similar to those at which chronic effects are reported in aquatic biota. Experiments in several different in vitro systems have indicated similar relative potencies among NPEs. NP was found to be ~1.0E5 times less potent than estradiol (E_2). NP_2EO and NP_1EC were only slightly less potent than NP in inducing vitellogenin in trout hepatocytes. Addition of EO units to NPEs reduced the potency, such that NP9EO was an order of magnitude less potent *in vitro*. APEs bind to the estrogen receptor, resulting in the expression of several responses, including the induction of vitellogenin in both *in vitro* and *in vivo* systems. One of the functions of endogenous estrogens in fish is to stimulate the liver to produce vitellogenin , a large phospholipoprotein. It is released into the bloodstream and sequestered by developing oocytes for production of egg yolk. In maturing female fish, vitellogenin is a major constituent of blood proteins; in male fish, it is not normally present in appreciable amounts. If male fish are exposed to estrogens, however, vitellogenin can be produced at similar levels to those found in maturing females. Although the implications of the induction of vitellogenin for the reproductive function of fish are not fully understood, it has been used as a very sensitive indicator of exposure of fish to exogenous estrogens. Jobling *et al.* (1996) determined the potency of NP2EO and NP1EC to be only slightly less than that of NP in rainbow trout. Jobling *et al.* (1996) also demonstrated that NP2EO and NP1EC had similar potency for *in vivo* induction of vitellogenin in rainbow trout. The threshold for vitellogenin induction in fish is 10 µg/L for NP in the water (Jobling *et al*., 1996). The induction of mRNA coding for vitellogenin in rainbow trout was recently reported at 1 µg NP/L (Fent *et al*., 1999). The estrogenic responses of NP and NPEs appear to be at least additive (Soto *et al*., 1994; Sumpter and Jobling, 1995) and should, therefore, be considered as a group. The threshold for expression of intersex (ova-testes) in killifish was <50 µg NP/L (Gray and Metcalfe, 1997). APEs also affect the growth of testes in fish, alter normal steroid metabolism and disrupt smoltification (Fairchild et al., 1999). There is currently considerable debate resulting from the inconsistency in relative potency reported for estradiol receptor binding, yeast estrogen screen (YES) assay and vitellogenin induction in trout hepatocytes. Additional research is required to fully understand the potential estrogenic effects of APs and APEs on the environment. The significance of estrogenic responses to the individual or population is also not known.

In vitro *data on human endocrine effects*

In *in vitro* studies, NP activated the estrogen receptor with a potency 5000–7000 times less than that of 17ß-estradiol (Routledge and Sumpter, 1996; Gaido *et al*., 1997; Odum *et al*., 1997). In MCF-7 human breast cancer cells, cell proliferation was stimulated by NP at concentrations between 0.1 and 10 µM (22 and 2203 mg/L) (White *et al*., 1994; Villalobos *et al*., 1995; Blom *et al*., 1998).

Summary *of human endocrine effects*

In a multigeneration study in which rats were exposed to NP in the diet, the LOEL was 200 ppm in diet (equivalent to a mean dose of approximately 12-18 mg/kg-bw per day in males,

16–21 mg/kg-bw per day in non-lactating females or 27-30 mg/kg-bw per day in lactating females), based on an increase in renal medullar tubular dilation and cyst formation in males in all generations (F0–F3) and in F3 females. There were also increases in gestation length and in percent abnormal sperm morphology observed in the F2 generation at this dietary level, as well as at the 650 ppm and at 2000 ppm, but these were probably not treatment-related. In both cases, the increase was small, not clearly dose-related, and within the range of control values from other generations and from historical controls. As well, these effects were not observed in other generations and the F2 control values were unusually low. No developmental effects were reported at any dietary level; however, a range of effects on endocrine-regulated endpoints, including delayed vaginal opening, was observed at 650 and 2000 ppm. In reproductive toxicity studies, histological changes in the seminiferous vesicles of the testes of rats were observed following oral exposure to 100 mg NP/kg body weight per day for 10 days. This was accompanied by compound-related mortality at doses that did not cause deaths in several other studies. Reductions in relative testis, epididymis, seminal vesicle and prostate weights were reported in rat pups exposed to 0.8 mg NP/kg-bw per day intraperitoneally in the first 15 days after birth. However, this information is not considered directly relevant to the margin of exposure, in view of the lesser relevance of this route of administration.

In a number of *in vivo* and *in vitro* studies, NP has been weakly estrogenic. NP increased uterine weight in immature or ovariectomized rats and in mice following oral administration of 50 mg/kg body weight per day and above following subcutaneous or intraperitoneal. Several other effects indicative of estrogenic activity have been observed in rats following the subcutaneous administration of NP *in vivo*, including endometrial proliferative response, and stimulation of uterine vascular permeability. An increase in cell proliferation in the mammary gland of rats exposed to 0.01 m g NP/day by subcutaneous minipump has also been reported; however, this effect was not reproducible in two subsequent studies. NP was 1000–100 000 times less potent than estradiol in stimulating estrogenic activity. In *in vitro* studies, NP activated the estrogen receptor with a potency 5000–7000 times less than that of 17ß-estradiol. In MCF-7 human breast cancer cells, cell proliferation was stimulated by NP at concentrations between 0.1 and 10 µM (22 and 2203 mg/L).

The potential estrogenicity of NP and NPEs has been investigated in a number of studies. NP and NP2EO activated the estrogen receptor and had some estrogenic activity *in vitro*. NP was uterotrophic or induced other effects indicative of estrogenic activity in several studies *in vivo*. However, these compounds were between 3 and 5 orders of magnitude less active in this regard than estradiol. In addition, NP was estrogenic only at relatively high dose levels; for example, effects on renal histopathology were observed at 3 times lower doses of NP than those in estrogen responsive tissues in the multigeneration study in rats (i.e., 12 vs. 50 mg/kg-bw). In addition, NPEs of longer chain lengths (4, 9 and 12) were not uterotrophic in vivo, and NP12EO was not estrogenic in a recombinant yeast screen assay.

Hence, while it is clear that NP and some short chain NPEs have estrogenic potential, the evidence that this is a critical effect of these substances is considered inadequate at this time. However, NP and NPEs are likely early candidates for additional investigation when more sensitive methods for testing and assessment of endocrine-disrupting substances are developed.

Upon completion of such testing, evaluation of the potential endocrine-mediated adverse health effects of NP and NPEs should be considered a priority.

3.4.4 Conclusions on benefits of integration

Conclusions on benefits already present in EU-RAR

None.

Additional benefits of integration

1. Integration strengthens the association of exposure-effects relationships in one species if the same exposure-effect relation is also observed in other species. For example, mechanisms of action in one fish species were confirmed with other fish species. Trout, salmon and killifish all respond to NP by making vitellogenin. Mechanisms of action in one rodent species were also confirmed with other rodent species (e.g., mice and rats responded similarly when exposed to NP).
2. Endpoints could be the same between species. However, data concerning an endpoint in one species are often not comparable or extensive enough (or not relevant enough) to make a useful comparison possible with the same endpoint of another species.
3. Mechanisms of action are confirmed by looking across the species barrier. It is even possible to integrate ecological data and human health data. Table 4 and Table 5 summarize the available *in vivo* and *in vitro* data. These tables support the findings that a) NP displaces estradiol and binds to the ER in both fish and mammals; and b) that NP influences reproductive organs in fish and mammals.

Conclusions missed by not integrating

The aim of an integrated risk assessment is to detect and identify adverse effects on humans and the ecosystem. There are enough data to set maximal safe concentrations of NP in water for fish and daphnia. For amphibians no estrogenic data are presented in either the EU and Environment Canada risk assessment reports. There is also enough experimental data from rats to set a maximal safe dose of NP for humans. There is sufficient information on reported adverse effects on mammals to be concerned about the potential estrogenic effects of NP on humans. This means that the risk assessments on the subject of estrogenic effects are fulfilling their purpose of identifying risk to men and ecosystems. As it is, there is a lot of information on dose-effect relations (on endocrine effects) for human health and for ecological assessments on NP. This reduces the need to look over species boundaries and between areas of expertise and specialization. It appears as if the separate risk assessments are quite complete on the subject of estrogenic effects for the purpose of establishing no-effect concentrations for fish and mammals. Limited data is available in the risk assessments on mechanisms of action of NP in various species.

Table 4 summarizes some of the *in vitro* and *in vivo* data on the ecological effects of NP. An attempt is made to combine ecological data with human health data to confirm known information or to find new insights. Cited references are listed in the EU-RAR.

		Table 4: Ecological Test Data (Source: EU-RAR, 2002)
Ecological Test Data	*In Vivo*	White *et al.* (1994) found that nonylphenol showed competitive displacement of estrogen from its receptor site in rainbow trout (Oncorhynchus mykiss).
		Concentration of 50 µg/L in water induces the expression of intersex-alterations in killifish.
		Jobling *et al.* (1996) found statistically significant reductions in testis size, expressed as gonadosomatic index (GSI). Histological examination of the testes showed that control fish had actively developed testes with a predominance of spermatocytes type A. The fish exposed to nonylphenol had a significantly higher proportion of spermatogonia type A than controls. A second experiment conducted, when the testes were more developed, examined a dose-response relationship for the two effects using nonylphenol. A significant stimulation of blood vitellogenin levels was seen after exposure to 20.3 µg/l but not at 5.02 µg/l, which was the NOEC for this effect. A significant reduction in GSI relative to controls was seen at 54.3 µg/l but not at 20.3 µg/l which was the NOEC for testicular growth.
		Concentration of 1 µg/L in water induces vitellogenin mRNA production in rainbow trout (Fent *et al*., 1999).
		Elevated levels of blood vitellogenin in rainbow trout *in vivo* exposed to NP for 3 weeks, ranged 0.24-54.3 µg/L. The levels of blood vitellogenin were found to be significantly elevated at concentrations of 20.3 µg/L (1 µg vitellogenin /ml; a tenfold increase over controls) and 54.3 µg/L (100 µg vitellogenin /ml; a 1000-fold increase over controls) (Harries *et al*., 1995).
		Concentration of 10 µg/L in water induces vitellogenin production in rainbow trout (Jobling *et al*., 1996).

		Table 4: Ecological Test Data (Source: EU-RAR, 2002)
		Arukwe *et al.* (1997) found that NP treatment caused an increase in the 6β-, 16α- and 17α-hydroxylase activities in salmon liver microsomes. There was an apparent dose-related decrease in the hydroxylase activities of liver microsomes. Reductions of activities were seen in the 7-ethoxyresorufin-O-deethylase (EROD) activity and the UDP-glucuronosyl-transferase activities. Immunochemical analysis of CYP1A, CYP2K-like and CYP3A-like proteins showed reductions in enzyme-linked immunosorbent assay absorbance levels. Plasma levels of estradiol-17β were found to be lowered.
		No relationships have been demonstrated between water quality characteristics (such as hardness and pH) and toxicity of NP.
		It was concluded that nonylphenol is capable of significantly perturbing components of androgen metabolism in daphnids at concentrations of ≤ 25 µg/L (Baldwin *et al.*, 1997).
		Gray and Metcalfe (1997) found that a LOEC for incidence of testis-ova in the Japanese Medaka was 50 µg/L.
		Nimrod and Benson (1996) investigated the induction of serum vitellogenin in Channel Catfish. The mean serum vitellogenin levels were only significantly different ($p<0.05$) from controls in the high dose (237 mg nonylphenol/kg) fish. NP exposure was by intraperitoneal injection. After seven days, the serum vitellogenin level was determined.
		Christensen *et al.* (1995) dosed male flounders (Platichthys flesus) with nonylphenol by four intraperitoneal injections over a period of two weeks. Vitellogenin was detected in plasma of fish dosed with 10 mg/kg wet weight. Effects were also seen on plasma lipids (increase), protein (increase) and ninhydrin positive substances (decrease). Toxic effects (cell damage), as indicated by increased activity of the plasma enzyme GPT were also found.
		Ashfield *et al.* (1998) found that the ovosomatic index of female juvenile rainbow trout was found to be significantly ($\rho<0.05$) elevated in the 30 µg/L NP group.
	In Vitro	White *et al.* (1994) reported that nonylphenol can stimulate vitellogenin secretion, *in vitro*, at concentrations of 10^{-6} M (220 µg/L) and above in hepatocytes from rainbow trout.

Table 5 summarizes some of the *in vitro* and *in vivo* data on the human health effects of NP. Cited references are listed in the EU-RAR.

		Table 5: Human Health Tests Data (Source: EU-RAR, 2002)
Human Health Tests Data	*In Vivo*	NP and NP2EO activated the estrogen receptor and had some estrogenic activity *in vitro*. NP was uterotrophic or induced other effects indicative of estrogenic activity in several studies *in vivo*. However, these compounds were between three and five orders of magnitude less active in this regard than estradiol. In addition, NP was estrogenic only at relatively high dose levels; for example, other effects (on renal histopathology) were observed at three times lower doses of NP than those in estrogen responsive tissues in the multigeneration study in rats (i.e., 12 vs. 50 mg/kg-bw).
		The influence of nonylphenol on growth and cell proliferation and of the mammary gland has been investigated in rats in two studies using non-standard methods. In the group receiving the highest dose of nonylphenol there was a 1.5-fold increase in the number of mammary structures and a fourfold increase in the number of cells/16 mm^2 area, compared with the vehicle control group (Colerangle and Roy, 1996).
		No developmental effects were reported at any dietary level; however, a range of effects on endocrine-regulated endpoints, including delayed vaginal opening, were observed at 650 and 2000 ppm. LOEL: 12–18 mg/kg-bw per day in males, 16–21 mg/kg-bw per day in non-lactating females or 27–30 mg/kg-bw per day in lactating females (NTP, 1997; Chapin *et al.*, 1999).
		NP is weakly estrogenic. NP increased uterine weight in immature or ovariectomized rats and in mice following oral administration of 50 mg/kg-bw per day and above and following subcutaneous and intraperitoneal administration (Lee and Lee, 1996; Shelby *et al.*, 1996; CMA, 1997; Coldham *et al.*, 1997; Laws and Carey, 1997; Odum *et al.*, 1997).
		Absorption from the gastrointestinal tract is initially rapid, and probably extensive. The major metabolic pathways are likely to involve glucuronide and sulphate conjugation, and there is evidence of extensive first pass metabolism of nonylphenol absorbed through the gastrointestinal tract. Because of first pass metabolism, the bioavailability of unconjugated nonylphenol is probably limited following oral exposure, at no more that 10-20% of the administered dose. Nonylphenol is distributed widely throughout the body, with the highest concentration in fat.
	In Vitro	In MCF-7 human breast cancer cells, cell proliferation was stimulated by NP at concentrations between 0.1 and 10 µM (22 and 2203 µg/L) (White *et al.*, 1994; Villalobos *et al.*, 1995; Blom *et al.*, 1998).
		In a proliferation test with MCF-7 and ZR-75 cells, from 10 µM/L in the medium the cells accelerated their growth.
		In *in vitro* studies, NP activated the estrogen receptor with a potency 5000–7000 times less than that of 17ß-estradiol (Routledge and Sumpter, 1996; Gaido *et al.*, 1997; Odum *et al.*, 1997).

3.5 Risk Assessment for wildlife

3.5.1 Introduction

There is a lack of measured exposure data and data on NOECs for wildlife. Both exposure and NOECs are needed to be able to quantify the risks for wildlife.

3.5.1.1 Measuring NOECs for wildlife

Direct measures of NOECs for most wildlife species are unavailable. NOECs are difficult to derive indirectly via measurements of concentrations in cadavers or unhatched eggs of birds of prey. Establishing a relation between concentrations in prey and predator population size and health is unlikely to succeed because cause and effect are difficult to prove.

3.5.1.2 Extrapolating rat NOAELs to NOAEL for humans

A rat LOAEL of 15 mg/kg/day (repeated dose for 20 weeks) based on histo-pathological changes in the kidneys and a rat NOAEL of 15 mg/kg/day based on minor perturbations in the reproductive system of offspring have been reported. In the case of NP, it is assumed that man and rat are equally sensitive and direct extrapolation from rat to human is allowable, reaching a N(L)OAEL of 15 mg/kg/day for oral exposure. In the risk characterization the Margin Of Safety will be used, taking into account uncertainties due to inter- and intraspecies differences as well as differences in dosing schemes compared to real-life situations.

3.5.1.3 Extrapolating rat NOAEL to NOECs for wildlife

A lot of data are available from rodent lab testing. Based on the $NOAEL_{oral}$ of the rat using $NOECs_{oral}$ for predators, oral exposure can be calculated as shown in Figure 5.

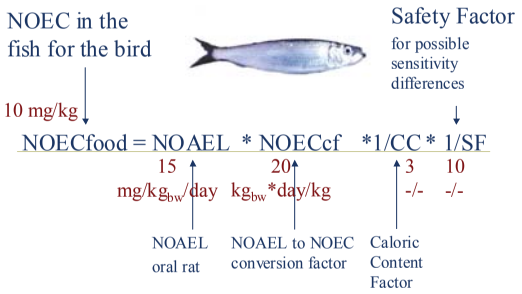

Figure 5: The $NOAEL_{oral}$ of the rat is based on reproductive effects. A safety factor of 10 is applied in case birds are intrinsically more sensitive to nonylphenol than rats. It is assumed that the feed of laboratory animals is three times more caloric than the feed eaten by wild animals. The calculated concentration of 10 mg/kg in prey fish is the expected concentration that will cause no detrimental effects in the bird of prey on the long term.

Due to the uncertainties in extrapolation factors, safety factors are necessary, and therefore, low avian and mammalian NOECs are derived. Additional safety Factors could also be applied for differences (e.g. hibernation, migration, or other periods of higher or lower metabolic activity) in caloric content of the food between species, and in route of exposure.

3.5.2 Potential benefits by integration ERA and HHRA knowledge

1. Derivation of NOECs for untested organisms from mammalian toxicity data.
2. Estimates of exposure in wildlife species.

3.5.3 Risk Assessment Data (Source: EU-RAR, 2002)

3.5.3.1 Environmental Data

Only toxicity studies reporting on dietary and oral exposure are relevant. Secondary poisoning effects on bird and mammal populations rarely become manifested in short-term studies. Therefore, results from long-term studies are strongly preferred (such as NOECs for mortality, reproduction or growth). But, if no adequate toxicity data for mammals or birds are available, an assessment of secondary poisoning cannot be made. Nonylphenol has been shown to bioconcentrate in aquatic species. No toxicity data are available on avian species; thus a PNEC is derived from laboratory mammal data. A NOAEL of 15 mg/kg body weight was found for reproductive effects. Using appropriate conversion factors to allow for the fact that the caloric content of a laboratory diet is higher than that of the diet of fish-eating mammals and birds, this NOAEL is equivalent to a daily dose of 100 mg/kg food. Using an additional safety factor for reproductive effects, $PNEC_{oral}$ has been calculated as 10 mg/kg food.

3.5.3.2 Human Health Data

The calculations of human intake from air, water and food assume absorptions of 75% by inhalation and 100% from the oral route. Exposure via the air makes little contribution to the overall dose. The oral uptake may be an overestimate but the amount taken up is compared directly with the rat oral LOAEL for repeat dose-effects and NOAEL for reproductive toxicity affect (both of 15 mg/kg/day) which represents the dose given rather than the amount taken up. Based on these estimates, an human NOEL of 15 mg/kg/bw have been calculated.

3.5.4 Conclusions on benefits of integration

Conclusions on benefits already present in EU-RAR

1. NOECs for predators (although uncertain) are derived using human-toxicological data.
2. Uncertainty in the extrapolation from species to species is acknowledged.
3. Approaches using safety assessment factors are possible.
4. Exposure of fish-eating birds/mammals and earthworm-eating birds/mammals can be estimated or determined through monitoring based on the model as used in the EU-RAR conceptual.

Additional benefits of integration
None can be derived for the data available.

Differences between conclusions of the EU and Canada

- The Canadian-EPA does not consider secondary poisoning an issue, due to the low bio-accumulative potential of NP. The EU-RAR, however, mentions the risk of secondary poisoning at local sites.

Opportunities missed in the EU-RAR

- Higher tropic levels of fish-eating fish are not considered.
- The current guideline for extrapolation is focused on earthworm-eating birds and fish-eating birds. Extrapolation should also include small wild predators such as badgers, foxes, ferrets, owls and hawks and terrestrial prey such as mice, rabbits and squirrels. Larger relevant organisms such as deer and wild ranging animals should also be included.

4. CONCLUSIONS

4.1 Advantages of Integration

The advantages of integration for nonylphenol are summarized per area of integration in Table 6. The partly integrated EU nonylphenol risk assessment was taken as the basis for this integrated risk assessment. Some benefits of integration might have been stronger if one separate ecological and one separate human health risk assessment had been available and merged into one integrated risk assessment. The problem formulation and the execution of the risk assessment were already standardized in the EU approach. This made it difficult to specific benefits of integration in these phases.

Table 6: Benefits of Integration for Nonylphenol (Per Area of Integration)

EXPECTED BENEFITS This column contains the expected benefits of risk assessment per phase of the assessment.	**IDENTIFIED BENEFITS** This column contains the identified benefits of risk assessment. Empty cells mean that the expected benefits were not found.
Problem formulation	
Assessment questions	
• Issues that are critical for both humans and the environment are more easily identified. A deeper, daily, working integration would greatly increase the chance of serendipitous recognition of problems for which evidence in any one sector is limited, but when all data are considered together, cause for concern may become evident. • Risks to humans are adequately considered through evaluation of risks to other organisms that influence human health and welfare. • Consistency in the spatial and temporal scope, e.g. with regard to the information and processes used, is established. • Data and knowledge gaps are identified at an early stage.	Without integrating, the ecological and human health risk assessments may have differed with regard to spatial and temporal scales considered, the degree of conservatism, the terminology used, the exposure scenarios for environmental exposure and the default values used. In addition the evaluation of the quality of the database may have differed.

Table 6: Benefits of Integration for Nonylphenol (Per Area of Integration)	
Impetus for the assessment	Not relevant, since the stressor, nonylphenol, had been specified.
Assessment endpoints	
• Susceptible endpoints in animals or ecosystems could indicate unidentified endpoints in humans	
• Knowledge on the fate of the compound and the target organisms or organs(s) can predict potential effects in ecosystems or organs, respectively.	
• Ecologists and human health assessors can discuss the relevance of all chosen endpoints.	
Conceptual model	
• Both human and ecological risk assessors scrutinize the quality of the common pathways to humans and ecology from the sources of the stressor.	
• Consensus between ecologists and human health assessors on the fate of the stressor is established.	
• Indirect exposure pathways via the environment to the humans are more likely to be identified, as humans are modeled as just one more receiving species in the web of exposure pathways.	
• When relevant and possible, multiple sources of exposure such as consumer products, emissions, and natural emissions are incorporated.	
• Only one conceptual model is produced; the ecological conceptual model and the human health conceptual model are one and based on the same assumptions and data.	
Analysis plan	
• Enhanced efficiency and reduced costs as only data for one transport and fate model are needed. Emission data, physico-chemical properties, fate and degradation data are only needed once.	Emission data, physico-chemical properties, fate and degradation data are searched for, evaluated and used only one time. Measured data are also searched for and evaluated once.

Table 6: Benefits of Integration for Nonylphenol (Per Area of Integration)	
Ecological and human exposure models use the same input, that is, the results of one transport and fate model. By integrating, decisions are based on more data and the available data are used more extensively.	
• It helps identify targeted research needs (e.g., where do ecological and human health risk assessors lack information).	This benefit is not verified but very likely.
• Ecological results and human health results adhere to the same quality restrictions.	The quality of the IRA is ensured with one analysis plan. Conclusions for ecological or human health are equally strong and equally reliable: questioning the quality of the ecological conclusions means questioning the quality of the human health conclusions. One cannot selectively use data in the integrated assessment.
• Ecological results and human health results are presented using the same terminology and if possible use the same method to express the risk and the uncertainty. This facilitates comparison between the ecological results and the human health results.	Use of the same risk representations (e.g., MOS) facilitates comparison between the ecological results and the human health results.
• If the assessment will be iterated, an integrated approach might foster the development of parallel ties, which use common data and models.	
Emission Sources, Environmental Concentrations, and Exposure Estimates	
• Routes of emission, distribution and exposure pathways are translated into model equations describing how the stressor reaches the organisms via diverse routes of exposure. Human and ecological risk assessors can discuss which models and which input values are appropriate and choose a common approach.	A common modeling approach is applied to the exposure estimation of nonylphenol for ecological receptors and humans leading to a coherent assessment and avoiding duplication of work. For instance, the same estimated emission and background levels are used in the exposure estimation for environmental organisms and for human beings. The estimation of exposure of man via fish is estimated from the surface water concentration. The same concentrations also determine the risks for

Table 6: Benefits of Integration for Nonylphenol (Per Area of Integration)	
	aquatic organisms.
• The type of model can be of the appropriate space- and time scales with regard to both the human and the environmental risk assessment.	An integrated exposure model is used.
• Monitoring data for emissions, environmental compartments, biota, food, feed and drinking water can be shared.	The available monitoring data are shared. This avoids the use of other data of different quality in independent assessments. It results in a common approach towards the analysis of the accuracy, specificity and relevance of these data.
• The whole life cycle of the stressor and all possible sources of emission will be considered.	Emissions to the environment from all potential sources are considered.
• Local sites with high concentrations of a chemical can cause potential adverse ecological effects with indirect effects on humans. These effects are not exemplified in an ERA. This means that such effects of (e.g., a massive fish extinction) are not estimated. Integration can solve this problem.	The EU approach predicts concentrations on different spatial scales. This helps to identify potential local high concentrations in the environment of man and animals living near a source of NP. The EU approach helps to identify problems due to high background exposure on a continental scale. By integrating several spatial scales, more information is generated than by only using one scale of space.
• Coherent conclusions can be drawn with regard to additional analytical activities necessary for higher tier human and ecological risk assessment.	This promotes the best use of the available resources and an integrated sampling strategy.
• A common approach towards uncertainty analysis can be developed.	The exposures of humans or the environment are uncertain due to emission uncertainties. In this case, integration does not help against a lack of data.
• A common approach to the evaluation of data quality, completeness, and relevance is developed.	In the case of the EU approach, guidelines on when to accept and when to decline data have been formulated.
Toxicokinetics	
• ADME (Absorption, Distribution, Metabolism, and Excretion) data and toxicokinetic models for laboratory animals and man may be extrapolated to wildlife and vice versa.	Based on the available information for nonylphenol, the combination of data from the ERA and HHRA does not result in additional insights or remarkable benefits on the topic of toxicokinetics.

Table 6: Benefits of Integration for Nonylphenol (Per Area of Integration)	
• Development and improvement of Physiologically Based Pharmacokinetic (PB/PK) modeling by combining data sets of different species could increase interspecies extrapolation.	
• Identification of metabolic pathways observed in environmental biota (ERA) and in laboratory mammals (HHRA) may strengthen each other.	
• Information about elimination rates in environmental biota or in mammalian test organisms may point to the expectation that a chemical may have a short or long half-life in organisms.	
• Information about accumulation in specific biota may point to relevant uptake routes for humans. For example: if a particular chemical hardly accumulates in a certain food product there will be no need to take this route of exposure into account in the human health risk assessment. In the opposite case, chemical accumulation might occur in an unexpected manner. Such information could be used both to find relevant routes of exposure for humans and to find biota that is likely to be more at risk.	
• Biomarkers developed for one species may be useful for exposure/effect assessment in other species. Biomarkers such as DNA-adduct formation or the occurrence of certain metabolites in urine could be used to demonstrate the presence of the stressor and quantify exposure.	

Table 6: Benefits of Integration for Nonylphenol (Per Area of Integration)	
Estrogenic Effects	
Understanding of mechanism of action and endpoints	
• Mechanisms of action can be confirmed by looking across the species barrier. Estrogen/steroid modes of action in fishes and mammals can be the same, as estrogen receptors are often highly conserved in structure.	Mechanisms of action are confirmed by looking across the species barrier. It is even possible to integrate ecological data and human health data. • NP displaces estradiol and binds to the ER in both fish and mammals. • NP influences reproductive organs in fish and mammals.
• Detection of critical pathways from target site to endpoint across species may be possible.	
• Knowledge on links between molecular events and endpoints is improved.	Endpoints could be the same between species; but data concerning an endpoint in one species are often not comparable, relevant, or extensive enough to make a useful comparison with the same endpoint of another species.
• Effect found in wildlife populations might identify new endpoints. This could assist in identifying emerging new risks for humans. This also reduces the changes of overlooking critical effects.	
Dose-effect relationships	
• Integration strengthens associations of exposure-effects in one species if the same exposure-effect relation is also observed in other species.	
Extrapolation from human health data to wildlife data	
• Improved cross-species extrapolation might reduce or validate extrapolation factor values.	
• In the absence of toxicity data for predators in the ecological risk assessment, the toxicity data for rodents (generated in the framework of the human health risk assessment) can be used to evaluate the hazard to predators.	See Risk Assessment of Wildlife below.

Table 6: Benefits of Integration for Nonylphenol (Per Area of Integration)	
• Effects found in wildlife populations might warn for low dose-effect in human populations. One sensitive species may serve as "early warnings" for other organisms, including humans.	Comparing human and ecological dose-effect data has identified no new endpoints.
Risk Assessment of Wildlife	
• NOECs for untested organisms, such as wildlife from mammalian toxicity data, are derived.	• NOECs for predators, although uncertain, are derived using exposure data from human health assessments. • Extrapolation problems from species to species are acknowledged but not solved. • Secondary poisoning in fish-eating birds and earthworm-eating birds would be detected or predicted.
• The exposure of wildlife can be calculated.	

4.2 Evaluation of the Scientific Benefits and Drawbacks of this Nonylphenol IRA

The expected benefits of integration would involve enhanced coherent expression of assessment results, enhanced interdependence of the results, identification of sentinel organisms, enhanced scientific quality of the assessment results and an increased efficiency in using and generating data (HERA, 2003).

Coherent expression of assessment results

Human and ecological results are expressed in risk characterizations ratios: PEC/PNECs for environmental species and margins of safeties (MOS) for humans. Throughout the assessment the same type of risk characterization terms, such as PNEC, are used. The final conclusions of the risk assessment reports in the EU (concern and risk reduction measures needed, no concern, more data required) are based on decision rules with these risk characterization ratios as points of departures. Such a coherent expression is easier to communicate.

Interdependence of the results

The conceptual model in the EU risk assessment is already partly integrated. This approach means that where overlaps in exposure routes and the calculation and measurements of environmental concentrations occur, human and ecological exposures are calculated with the same tools and data. Results are harmonized with regard to concentrations, contact media and routes of exposures. With regard to the estrogenic effects of nonylphenol, the mechanism of action is confirmed by looking across species barriers and integrating the ecological data with

human data. Additionally, effects data on mammals are shared for the determination of no-effect levels on humans and in wildlife.

Identification of sentinel organisms

Although no new sentinel organisms were identified, the integrated risk assessment does lead to an enhanced understanding of the impact of nonylphenol as an endocrine disruptor on different species, including humans. When bioaccumulation takes place, NP concentrations become higher in the predatory fish (resulting in increased vitellogenin production in male fish). Elevation of vitellogenin levels can thus possibly serve a sentinel process.

Enhanced scientific quality of the assessment result

- Concentrations in humans and organisms in the environment are harmonized by using the same measured or modeled concentrations in the environmental compartments. Human and environmental exposure pathways are combined in one conceptual model. Human and top predator exposures are integrated via calculation of the concentrations of NP products in the same species. The EU approach integrates direct and indirect exposure. Humans and ecosystem are both included in the model, with common sources and the same fate and transport model.
- Integration does not increase the quality of the dose-effect characterization in the risk assessment for humans. The environmental risk assessment can gain from the human health risk assessment by extrapolations from rat data to other mammals.
- Integrating in the area of toxicokinetics is unlikely to yield benefits given the minimal amount of available data. Integration via internal dose modeling, for example, is not feasible due to a lack of data. The only additional insight gained here is that the metabolism of nonylphenol proceeds through similar pathways across species, including humans. Overall the data are rather limited for integration.
- Only the most general overlap in mechanism of action of nonylphenol has been found, using data from the available risk assessments.

In summary, because no new data were used and the EU-RAR is already partly integrated, the conclusions of the EU-RAR have not changed in this report. The benefits of integration apparent in the EU-RAR have been highlighted. The ecological and human assessment results are made interdependent and use the same data as much as possible.

Efficiency in using and generating data

The integrated approach means that where overlaps in exposure routes, and in calculation and measurements of environmental concentrations occur, human and ecological exposure is calculated with the same tools and data. Available measured concentrations and emission data are used for both the human and ecological exposure assessments. Data searches and the evaluation of the quality of these data occur only once. Data requirements for the ecological and human risk assessments could be further harmonized (e.g., with regard to further elucidation of the mechanism of action, dose-effect relationships and inter- and intraspecies variation of the estrogenic effect).

Drawbacks

No drawbacks were identified. Integration does increase the need for ecologists and human health assessors to meet and spend time in discussion, to generate a common vision. Based on these decisions, risk assessments can be made more efficient and complete.

4.3 Costs and Benefits in Economics Terms

It was impossible to quantitatively estimate the differences in costs and benefits in economic terms between independent ERA and HHRA assessments of nonylphenol and the integrated risk assessment in this exercise. Therefore a more qualitative approach was followed. The IPCS framework for integrated risk assessment (see Table 7) can be used as a checklist of the steps to conduct a solid integrated risk assessment. Almost all the steps taken to make an ERA are also done when making a HHRA. The assumption is made that the more steps the ERA and HHRA have in common, the greater the reduction in costs will be in making an IRA. The benefits gained and costs saved are thus proportional to the measure of similarity per phase or step. This measure of similarity between ERA and HHRA is quantitatively expressed using ratings from 0 to 3 (taking the assessment of nonylphenol as example). Zero means no similarity; 1 means some similarity in terminology and types of decisions to be taken; 2 means multiple commonalities in terminology, types of decisions to be taken, and data requirements and type of experts and knowledge needed; and, 3 stands for a high degree of similarity.

From Table 7 it can be concluded that a high gain in benefits and reduction of costs can be expected on approximately 50% of the steps taken. Nevertheless, some caution is needed because:

1. This is a limited analysis.
2. If animal testing and data collection on environmental concentrations consume the bulk of the budget then a relatively high reduction in the budget for the other steps is only a small reduction in absolute numbers on the total budget.
3. Before any testing and measurements are done, data searches are done to find available data. If a HHRA is done before an ERA, then the available data from that risk assessment will be used in the ERA. This reduces the costs of the ERA and is a sensible practice.

Table 7[†]: Steps or Data Needed per Phase

Based on the IPCS-Framework (HERA 2003)

Problem formulation	**Ecological**	**Human**	**IRA**	**Similarity**
planning dialog	X	X	X	2
management goals	X	X	X	2
purpose and scope	X	X	X	2
available resources	X	X	X	?
identification of the effects caused by the stressor	X	X	X	3
preliminary identification of endpoints	X	X	X	3
Characterization of exposure				
data completeness	X	X	X	3
stressor characteristics	X	X	X	3
sources and emissions	X	X	X	3
industrial use	X	X	X	3
consumer usages	O	X	X	0
distribution pathways	X	X	X	3
quantitative / computer model	X	X	X	3
environmental transport and fate, degradation	X	X	X	3
external exposure model	X	X	X	2
internal exposure model	?	?	?	?
phrasing of uncertainties	X	X	X	3
choice of hyper-conservative or realistic scenario	X	X	X	3
Characterization of effects				
identification of mode of action	X	X	X	3
exposure-response analysis:				
plants	X	X[#]	X	3
fish	X	X[#]	X	3
mammals	X	X[#]	X	3
birds	X	X[#]	X	3
humans via rats	O	X	X	0
evaluation of data	X	X	X	3
evaluation of time scales of effect	X	X	X	2
extrapolation factors	X	X	X	2

[†] This table is meant to be completed in a general manner. X means this step is needed in the RA. O means this step is not needed in the RA. ? means this step could be useful if enough data are present. # means food and resource insurance for humans. See text for explanation of numbers.

Table 7[†]: Steps or Data Needed per Phase

Based on the IPCS-Framework (HERA 2003)

Risk characterization				
combine exposure and dose-effect data	X	X	X	3
uncertainty estimation	X	X	X	3
'translate' results and conclusions for risk managers and stakeholders	X	X	X	3
Risk management				
selection of feasible management measurements	X	X	X	1
consideration of consequences of management measurements	X	X	X	1
Stakeholder participation				
Stakeholders discuss endpoints and review assessment results.	X	X	X	2
Risk communication				
explanation of legal, policy, time and resource constrains to stakeholders	X	X	X	3
expression of type of risks and explanation of uncertainties to stakeholders	X	X	X	3

4.4 Evaluation of the IPCS Framework

Since the EU ecological and human risk assessments of nonylphenol are already partly integrated and fully reviewed by EU-experts, the IPCS Framework could not be tested to its full extent. An important element of the framework (i.e., the interaction between ecological and human risk assessors with risk managers and stakeholders) was not investigated.

The Framework provided guidance since it helped to generate a list of steps needed to perform an IRA and can be used as a starting point to derive areas of integration. For example, the problem formulation phase is well-explained and divided into smaller well ordered steps, such as assessment questions, impetus for the assessment and assessment endpoints. Each step of the Framework was checked in this report for the possibility to improve the EU assessment. Overall, the Framework appears to give a complete discussion of all essential elements. The Framework is written as a general guidance. It would benefit from giving more detailed guidance on several issues (such as calculations, assumptions, decisions, and data selection per topic and per stressor). A list of references and examples illustrating the various steps in an integrated risk assessment would be useful. Overall, the Framework provides good guidance for the harmonization of risk assessments worldwide.

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6. APPENDICES

6.1 Appendix 1: *In vivo* data on ecological endocrine effects (Source: EU-RAR, 2002)

Individual references are listed in the EU-RAR.

Jobling *et al.* (1996) exposed two-year-old male rainbow trout (*Oncorhynchus mykiss*) to nonylphenol at 30 µg/l (nominal concentration) in a flow through system for three weeks. Measured concentrations of nonylphenol were 36.81± 2.4 µg/l throughout the experiment. Exposure was conducted in May, when growth of the testes was at an early stage. Blood samples were taken at the beginning and end of the exposure period. After three weeks, the fish were killed and testicular weight measured. Nonylphenol was found to stimulate production of vitellogenin , by a factor of 100 to 1000 times compared to controls. Statistically significant reductions in testis size, expressed as gonadosomatic index (GSI) were also noted. Histological examination of the testes showed that control fish had actively developed testes with a predominance of spermatocytes type A. The fish exposed to nonylphenol had a significantly higher proportion of spermatogonia type A than controls. A second experiment conducted when the testes were more developed, examined the dose-response for the two effects. A significant stimulation of blood vitellogenin levels was seen after exposure to 20.3 µg/l but not at 5.02 µg/l, which was the NOEC for this effect. A significant reduction in GSI relative to controls was seen at 54.3 µg/l but not at 20.3 µg/l which was the NOEC for testicular growth.

Baldwin *et al.* (1997) investigated the effects of exposure of *Daphnia magna* to nonylphenol in a three-week assay designed to look at the effects on the metabolism of the steroid hormone testosterone and any resulting effects on reproduction. Both acute and long-term exposures were used in the test. In acute tests, adult (ten-day-old) female daphnids were exposed to nonylphenol (25, 50 or 100 µg/L) for 48 hours. After the acute exposure, the daphnids were exposed to [^{14}C] testosterone for a further sixteen hours and analysed for total radioactivity. The presence of radiolabelled metabolites in the water was also determined. Effects of exposure to nonylphenol on reproduction were investigated in a three-week static renewal toxicity test. Again, after the three-week exposure, the daphnids were exposed to [^{14}C] testosterone for a further sixteen hours to investigate the effects on steroid hormone metabolism. After 48 hours of exposure to nonylphenol at 100 µg/L, a significant increase ($p=0.01$) over the controls was seen in the accumulation of [^{14}C] testosterone and/or its metabolites in the daphnids. No significant effect was seen at nonylphenol concentrations of 25 or 50 µg/L. More detailed investigation of the metabolic elimination products indicated that the increased accumulation of androgens in the daphnids was a result of a decrease in the production of the major testosterone elimination product (testosterone-glucose) and an increase in the production of reduced/hydrogenated metabolites that are preferentially retained in the daphnids. These effects were seen at all exposure concentrations and were concentration-related (although the effects were not always statistically significant at nonylphenol concentrations of 25 µg/L). It was concluded that nonylphenol is capable of significantly perturbing components of androgen metabolism in daphnids at concentrations of ≤ 25 µg/L. In the three-week reproduction assay, nonylphenol concentrations of up to 100 µg/L had no effect on survival of parental daphnids. The number of off-spring produced was reduced on exposure to 50 or 100 µg/L, but this reduction was only statistically significant ($p=0.05$) at 100 µg/L. The reproductive chronic value derived from these data was 71 µg/L (geometric mean of the NOEC and LOEC for reproduction) and this

concentration was estimated to reduce the elimination of testosterone by approximately 50%. The results indicate that nonylphenol can cause effects on steroid hormone metabolism that may contribute to its reproductive toxicity (Baldwin *et al.*, 1997).

The effects of nonylphenol exposure on both the asexual and sexual reproduction of *Daphnia galeata mandotae* has been studied over 30 days of exposure (Shurin and Dodson, 1997). Four parameters (averaged over a female's lifetime) were examined: a) number of female offspring; b) number of male offspring; c) number of ephippia and d) number of developmentally abnormal male and female offspring. The laboratory conditions used induced the production of all three types of offspring (males, females and ephippia) and the exposure media were renewed every 48 hours. The nonylphenol concentrations used were 10, 50 and 100 µg/L. The results from the test were complicated due to the fact that different responses were seen in the solvent control (acetone at 80 µg/L) and the medium control. The daily production of female offspring/adult was found to increase over that seen in the medium control at the high concentrations (50 and 100 µg/L) of nonylphenol, but a similar increase was seen in the solvent control. No effects were seen on the daily production of male offspring/adult at any concentration and a slight decrease in the number of ephippia/adult was seen at high doses of nonylphenol. This latter effect was thought to be a result of increased adult mortality at the high nonylphenol concentrations. The daily production of deformed live offspring/adult was found to be related to nonylphenol exposure as a clear dose-response curve was seen and no such deformed offspring were seen in the two controls. The deformed offspring were of similar size to normal offspring but had forward curled tail spines and lacked, or had severely reduced, terminal setae on their second antennae, which reduced the swimming ability of the organism. This deformity was seen in 11% of live young at a nonylphenol concentration of 10 µg/L, and only animals that were prenatally exposed to nonylphenol exhibited this deformity.

Gray and Metcalfe (1997) investigated the sexual development of male and female Japanese Medaka (*Oryzias latipes*) exposed to nonylphenol from hatching to three months of age. The test used was a static renewal system (renewal every 72 hours for first month and then every 48 hours), using 30 fish per exposure concentration. Exposure was initiated one or two days post hatch. The nominal concentrations used were 10, 50 and 100 µg/L, but analysis indicated that these concentrations fell over the 48-hour or 72-hour renewal period and the mean measured concentration over the renewal period was around 55% of the nominal for 72-hour renewal and 66% for 48-hour renewal. Between 18 and 20 of the original 30 fish in each treatment and control survived to the end of the three-month exposure period. A statistically significant increase in mean body weight and length was found for the fish in the 10 and 50 µg/L groups when compared with controls. This was not apparent in the 100 µg/L treatment group. Histological examination indicated that males in the 50 and 100 µg/L had developed testis-ova, characterized by the presence of both testicular and ovarian tissue in the gonad. The incidence of this was six out of twelve males (50%) in the 50 µg/L treatment and six out of seven males (86%) in the 100 µg/L treatment. No incidence of testis-ova was found in the control group (twelve males) or the 10 µg/L treatment (ten males). The LOEC for this effect was therefore 50 µg/L. At 100 µg/L the authors suggested that sex reversal (male to female) may also be occurring as the ratio of males to females was different to that seen in controls or the 10 and 50 µg/L treatments. However this could also be due to different mortality patterns in the various treatments (i.e. greater mortality in male fish at 100 µg/L). It was also noted that the Japanese

Medaka have a relatively unique process of gonadal differentiation and development and it is not clear how these results relate to possible effects in other fish species.

Nimrod and Benson (1996) investigated the induction of serum vitellogenin in Channel catfish (*ictalurus punctatus*) by 17β-estradiol, several synthetic estrogens and several suspected xenestrogens including nonylphenol. Juvenile fish (65-95 g) were exposed to each substance by intraperitoneal injection. After seven days, the serum vitellogenin level was determined. Fish exposed to nonylphenol at doses of 79 mg/kg and 237 mg/kg showed elevated serum vitellogenin levels when compared to controls. The response of individual fish was found to be very variable and the mean serum vitellogenin levels found in control, low dose and high dose groups were 0.3±0.4 mg/ml, 3.6±3.4 mg/ml and 9.5±5.7 mg/ml respectively, however, this was only significantly different ($p<0.05$) from controls in the high dose (237 mg nonylphenol/kg) fish. The response from nonylphenol was much lower than that found with 17β-estradiol by a factor of around 5000 (i.e. a 500 times higher dose of nonylphenol resulted in a ten times lower serum vitellogenin level compared with that seen with 17β-estradiol).

Christensen *et al.* (1995) dosed male flounders (*Platichthys flesus*) with nonylphenol by four intraperitoneal injections over a period of two weeks. Vitellogenin was detected in plasma of fish dosed with 10 mg/kg wet weight. Effects were also seen on plasma lipids (increase), protein (increase) and ninhydrin positive substances (decrease). Toxic effects (cell damage), as indicated by increased activity of the plasma enzyme GPT, was also found.

Elevated levels of blood vitellogenin have been found in rainbow trout (*oncorhynchus mykiss*) exposed *in vivo* to nonylphenol for three weeks. The nonylphenol concentrations used were in the range 0.24-54.3 µg/L. The levels of blood vitellogenin were found to be significantly elevated at concentrations of 20.3 µg/L (1 µg vitellogenin /ml; a tenfold increase over controls) and 54.3 µg/L (100 µg vitellogenin /ml; a 1000-fold increase over controls) (Harries *et al.*, 1995).

The effects of nonylphenol on steroid metabolizing enzymes from the liver have been studied using Atlantic Salmon (*Salmo salar*) (Arukwe *et al.*, 1997). Groups of six fish (approximately one year old and between 75 and 120 g in weight) were injected intraperitoneally with either 1, 5, 25 or 125 mg/kg bodyweight of nonylphenol (consisting of 85% para-isomers, and around 8-13% phenol, 1% tripropylene and 1% dinonylphenol) and then maintained at 10°C and 34‰ salinity for two weeks. Similar groups of fish were dosed with 5 mg/kg body weight of estradiol-17β as positive control and the carrier solvent (vehicle control group). After the two-week period, various assays were carried out using liver microsomes collected from the exposed and control fish. The nonylphenol treatments caused an increase in the 6β-, 16α- and 17α-hydroxylase activities in liver microsomes from the 1 mg/kg body weight groups (the increase was only statistically significant ($\rho<0.05$) compared with vehicle controls for the 6β-activity). With increasing dose of nonylphenol, there was an apparent dose-related decrease in the hydroxylase activities of liver microsomes compared to vehicle controls. This decrease was statistically significant for 6β-hydroxylase in the 25 mg nonylphenol/kg body weight group and for all activities in the 125 mg nonylphenol/kg body weight group. Reductions compared with vehicle controls were also seen in the 7-ethoxyresorufin-O-deethylase (EROD) activity (23-70% reductions were seen but they were only statistically significant in the 125 mg nonylphenol/kg

body weight groups) and the UDP-glucuronosyltransferase activities (decrease was not statistically significant). Immunochemical analysis of CYP1A, CYP2K-like and CYP3A-like proteins showed statistically significant 18%, 47% and 30% reductions in enzyme-linked immunosorbent assay absorbance levels respectively compared with vehicle controls in the 125 mg nonylphenol/kg body weight group. Plasma levels of estradiol-17β were found to be lowered by 24-43% compared with vehicle controls, but this decrease was only statistically significant in the 1 and 5 mg nonylphenol/kg body weight treated groups. The report concluded that nonylphenol may increase the activity of steroid-metabolising enzymes at low concentrations but decrease the activity of these enzymes at high concentrations.

Ashfield *et al.* (1998) investigated the effects of prolonged exposure to nonylphenol on growth and the gonado(ovo)somatic index of female juvenile rainbow trout (*oncorhynchus mykiss*). Groups of 200 fish were exposed to three concentrations of 4-nonylphenol using a flow-through system from hatch to early sexual maturity (approximately one month after hatch). Two series of experiments were conducted. In the first series, exposure to nonylphenol (nominal concentrations 1, 10 and 50 µg/L) was for 22 days from hatch, and monitoring of the fish was continued for a further 86 days. In the second series, exposure to nonylphenol (nominal concentrations 1, 10 and 30 µg/L) was for 35 days from hatch, with monitoring of fish continuing for a further 431 days. In all tests, the water had a pH of 6.5, a hardness of 12.5 mg/l as $CaCO_3$, a temperature of 7-13°C and was continuously aerated to maintain the dissolved oxygen level. The stock nonylphenol solutions were made up in methanol/water mixture and each exposure solution had around 0.0005% methanol present (the same amount of methanol was added to the control). In the tests no significant difference was seen in total mortality between controls and treated fish. At the end of the first series of tests, fish that had been exposed to 1 and 50 µg/L showed a statistically significant ($\rho<0.001$ and $\rho<0.01$ at the two concentrations respectively) lower body weight relative to controls (the 10 µg/L group was not significantly different from the control group). In the second series of experiments, by day 55 the mean weights and lengths of fish exposed to 30 µg/L were significantly lower ($\rho<0.05$ for weight, $\rho<0.01$ for length) than in the control group. The 10 µg/L group showed no significant effect on weight at this time, but the length was significantly reduced ($\rho<0.05$) compared with controls. These differences in weight and length became more pronounced at day 84, with significantly lower weights in the 10 µg/L ($\rho<0.001$) and 30 µg/L ($\rho<0.01$) groups. The significantly reduced body weight seen in the 30 µg/L group continued up until the experiment ended on day 466, but the fish exposed to 10 µg/L showed a significantly elevated bodyweight ($\rho<0.05$) compared with controls from day 300 onwards. The fish body weight in the 1 µg/L group was not significantly different from controls at any time during the experiment. At the end of the experiment, the ovosomatic index (OSI = (100×gonad weight/[bodyweight-gonad weight]) was determined, and this was found to be significantly elevated ($\rho<0.05$) in the 30 µg/L group. The paper concluded that significant effects on growth of the fish had occurred during the test, although the mechanism by which nonylphenol caused these effects was unclear.

6.2 Appendix 2: *In vivo* data on human endocrine effects (Source: EU-RAR, 2002)

Individual references are listed in the EU-RAR.

Only data from animals or *in vitro* test systems were available.

Studies investigating estrogenic activity:

The estrogenic activity of nonylphenol has been investigated in a number of studies using either recombinant yeast, estrogen sensitive MCF-7 cells or a rodent uterotrophic assay response. None of these assays have been validated as an internationally accepted toxicity test method, although the MCF-7 and uterotrophic assays have been established for a number of years as standard assays for estrogenic activity. It should be noted that the significance to human health of estrogenic activity detected in these assays has yet to be established.

In vivo systems

The estrogenic activity of nonylphenol has been assessed in several studies using an assay based upon the uterotrophic response in the rat. In the first study, five groups of immature (aged 20-22 days) female rats (six in each group) of a Wistar-derived strain received single oral gavage doses of nonylphenol in corn oil on three consecutive days (ICI, 1996). The dose levels ranged from 9.5 to 285 mg/kg/day. Vehicle and positive (estradiol benzoate 8 µg/kg, by subcutaneous route) groups were included. One day after the final dose the females were killed and the uterus was removed from each animal and weighed. Absolute uterus weight and bodyweight-related uterus weight were statistically significantly increased, in a dose-dependent manner, at levels of 47.5 mg/kg/day and above. The NOAEL was 9.5 mg/kg/day. The uterine response seen in the positive control group was much greater than that of the nonylphenol groups, although a direct comparison of potency is not possible given the differing exposure routes. Similar data from the same laboratory have also been presented in peer-review literature (Odum *et al*., 1997). This latter report also included oral positive control groups (17ß-estradiol, 10-400 µg/kg), which indicated that estradiol was about 1000 times more potent in this assay than nonylphenol.

In a similar assay, groups of ten ovariectomised female Sprague-Dawley rats were dosed once daily for three consecutive days by the oral route with ethanol/oil suspensions of nonylphenol at levels of 0 (vehicle control), 30, 100 and 300 mg/kg/day (Chemical Manufacturers Association 1997b). Positive control groups received ethynylestradiol in ethanol at levels of 10, 30 and 80 µg/kg/day according to the same dosing regimen. One day after the final dose the females were killed and the uterus was removed from each animal and weighed. Uterus weights at 300 mg/kg/day were significantly increased (1.5-fold) in comparison with the vehicle control group. A slightly greater response (a twofold increase) was seen in the 30 and 80 µg/kg/day positive control groups.

In an other uterotrophic assay, groups of three immature (aged 20-21 days) Sprague-Dawley rats each received a single intraperitoneal injection of nonylphenol at dose levels of 0, 1, 2 or 4 mg/animal (approximately 25, 50 or 100 mg/kg) (Lee and Lee, 1996). Estradiol,

administered by the same route, served as a positive control. The animals were killed 24 hours later and each uterus was removed, weighed and analysed for protein and DNA content and peroxidase (thought to be a uterotrophic marker enzyme) activity. There was a dose-dependent and statistically significantly increase in uterine weight at all levels, with associated increases in uterine protein and DNA content and uterine peroxidase activity. In further experiments, the uterotrophic activity of nonylphenol was found to be blocked by the co-administration of ICI 182,780, an estrogen antagonist, providing evidence that the effect of nonylphenol is mediated through the estrogen receptor. Also, the potency was compared with estradiol; in this assay estradiol was found to be about 1000-2000 times more potent than nonylphenol.

Overall, these *in vitro* and *in vivo* studies show that nonylphenol has estrogenic activity of a potency between three to six orders of magnitude less than that of estradiol.

Effects on fertility

The effects of nonylphenol on fertility and reproductive performance have been investigated in a multigeneration study. The testicular toxicity of nonylphenol has been studied in a repeated exposure study.

The multigeneration study was comprehensive and was conducted in compliance with GLP (NTP 1997). The overall study design was based on the OECD two-generation reproduction toxicity study guideline, with an extension to include the production of an F_3 generation. Groups of thirty male and thirty female Sprague-Dawley rats were exposed to nonylphenol via incorporation in the diet at concentrations of 0 (control) 200, 650 or 2000 ppm over three generations. Calculated nonylphenol intakes were, respectively, about 0, 15, 50 and 160 mg/kg/day during non-reproductive phases and rising to around 0, 30, 100 and 300 mg/kg/day during lactation. Nonylphenol exposure commenced for the F_0 generation at about seven weeks of age and continued until study termination when the F_3 generations were about eight weeks old. F_0 animals were mated (one male with one female) within each dose group to produce the F_1 generation. Selected F_1 animals were similarly mated to produce the F_2 generation and selected F_2 animals were mated to produce the F_3 generation. For the F_0 generation and retained F_1, F_2 and F_3 animals, clinical signs of toxicity, bodyweight and food consumption were reported. Oestrous cycles were monitored prior to mating. At the necropsy of adult animals, sperm samples were taken (but not from the F_3 generation) for analysis of density, motility (using a computer-assisted sperm motion analysis system) from control and high dose group males, morphology, organ weights, and selected organs were sampled for histopathology. Additionally, testicular spermatid counts were made. Parameters assessed in the young offspring included litter size, bodyweight, survival, gross appearance, ano-genital distance, sexual development and, for animals killed at weaning, gross appearance of organs at necropsy and reproductive organ weights.

There was evidence of general toxicity in adults of all generations, seen as a reduction in bodyweight gain at 50 and 160 mg/kg/day and histopathological changes in the kidneys at all dose levels. These aspects are described in greater detail in section 4.1.2.6.1.

Considering the reproduction-related parameters, there were no adverse effects on fertility or mating performance. However, several other parameters were affected. Oestrous cycle length was increased by about 15% in the F_1 and F_2 females at 160 mg/kg/day, in comparison with controls. The timing of vaginal opening was accelerated by 1.5-seven days at 50 mg/kg/day and by three to six days at 160 mg/kg/day in females of the F_1, F_2 and F_3 generations. Also, absolute ovarian weights were decreased at 50 mg/kg/day in the F_2 generation and at 160 mg/kg/day in the F_1, F_2 and F_3 generations; however, no effect on ovarian weight was apparent in the F_1 and F_3 generations when analysed as an organ-to-bodyweight ratio. In males, changes in sperm endpoints were seen only in the F_2 generation; epididymal sperm density was decreased by about 10% at 50 and 160 mg/kg/day and spermatid count was decreased by a similar amount at 160 mg/kg/day. However, there may have been methodological problems with the epididymal sperm density measurements, because the density in all F_2 generation groups, including controls, was considerably greater (by about 25-40%) than reported for the F_0 and F_1 generation males; the age of each generation was similar at necropsy, so major differences in the sperm density would not be expected. To summarise the reproductive aspects of this study, fertility and mating performance were not adversely affected by nonylphenol treatment. However, there were changes, albeit relatively slight, in the oestrous cycle length, timing of vaginal opening, ovarian weight and sperm/spermatid count. The effects on the oestrous cycle were seen in both the F_1 and F_2 generations (not assessed in F_3 females) and the timing of vaginal opening was influenced in all three generations. This consistency provides firm evidence of a relationship with the treatment. These effects were possibly related to the estrogenicity of nonylphenol. There is some uncertainty about the relationship to nonylphenol treatment with respect to the ovarian weight reduction, because this effect was apparent after adjusting for bodyweight in only one generation and did not correlate with any histopathological changes. Nevertheless, it is compatible with the anticipated direct effects of exogenous estrogenic activity. Also, there is uncertainty regarding the cause of the apparent reduced sperm/spermatid numbers in the F_2 generation. It has been hypothesised that such changes could result from foetal or neonatal exposure to exogenous estrogenic activity (Sharpe and Skakkebaek, 1993), but if the hypothesised mechanism was operating, semen/testicular changes should also have occurred in the F_1 generation. Furthermore, the possibility of methodological problems adds to the difficulty in interpreting the sperm/spermatid count data. However, the observation of impaired male reproductive tract development in an intraperitoneal study provides supporting evidence in favour of the sperm/spermatid count changes being causally related to nonylphenol treatment. Furthermore, the intraperitoneal study indicates that a critical window of exposure for this effect is likely to be the neonatal period. Overall, this study provided evidence that nonylphenol exposure over several generations can cause minor perturbations in the reproductive system of offspring, which are compatible with the predictable or hypothesised effects of exogenous estrogenic activity. These perturbations did not cause functional changes in reproductive capacity of the rat at the dose levels tested. A clear NOAEL for these changes of 15 mg/kg/day was identified.

The testicular toxicity of nonylphenol was investigated in Sprague Dawley rats in a repeated dose study (de Jager *et al.,* 1999a). Groups of 20 male rats were dosed once daily by the oral (gavage) route at doses levels of 0 (vehicle control, cotton seed oil), 100, 250 or 400 mg/kg/day for a period of ten weeks, from the age of twelve weeks. The animals were killed at the end of the dosing period and a detailed evaluation of the reproductive organs was conducted. Testes and epididymal weight were recorded. The total l epididymal sperm numbers were

determined. The testes were stored in Bouin's fixative and processed for histological examination, which included the identification of the stages of spermatogenesis present and the measurement of the seminiferous tubule diameter, lumen diameter and epithelial thickness. Three, fifteen and eighteen animals from the 100, 250 and 400 mg/kg/day groups, respectively, died during the dosing period; no further information on these deaths was presented. Clinical signs of toxicity were not reported. The bodyweight gain of surviving animals was not affected by treatment, although bodyweight gain was reduced among the decedents. In comparison with the control group, lower testicular and epididymal weight, tubule and lumen diameter and seminiferous epithelial diameter were seen in surviving animals at 250 and 400 mg/kg/day and the sperm count was reduced at 400 mg/kg/day. However, because of the very small group sizes due to mortality, little toxicological significance can be accorded to these findings. At 100 mg/kg/day, testes and epididymal weight were not affected, but tubule and lumen diameter and seminiferous epithelial diameter were statistically significantly lower than in the control group; the mean tubule diameter was reduced by 10%, but data for the other two parameters were not presented. Testicular abnormalities were identified by histopathology at both 250 and 400 mg/kg/day. In one animal at 250 mg/kg/day vacuolization and cell necrosis with sloughing of the epithelium was seen in about 40% of tubules. Both surviving animals at 400 mg/kg/day had tubular vacuolization, cell necrosis and derangement, with very few secondary spermatocytes and sperm being present.

This study provides evidence of nonylphenol-related testicular toxicity at exposure levels which also cause mortality. A LOAEL for testicular toxicity of 100 mg/kg/day can be designated. The observation of mortality at 100, 250 and 400 mg/kg/day in this gavage study contrasts with the findings of studies involving dietary administration summarised in the Repeated Dose Toxicity section (Hüls, 1989; Chemical Manufacturers Association, 1997a; NTP, 1997). This difference can probably be accounted for by the method of administration; gavage dosing is likely to produce higher peak concentrations of nonylphenol in the blood than dietary administration.

Developmental toxicity

One oral rat developmental toxicity study was evaluated, as well as two studies looking specifically at the potential effects of NP on the developing male reproductive tract, one using the intraperitoneal route and one using the oral route.

The standard rat developmental toxicity study was conducted according to OECD guideline 414 and in compliance with GLP standards. Groups of timed-mated females of the Wistar strain were administered by oral gavage corn oil solutions of nonylphenol from days 6 to 15 of pregnancy at dose levels of 0, 75, 150 and 300 mg/kg/day. A further group receiving 600 mg/kg/day was terminated prematurely because many females died during the first few days of treatment. Sufficient females were allocated to the study to produce at least 21 pregnant females in each group. Surviving females were killed on day 20 of pregnancy and the foetuses were subjected to routine external, visceral and skeletal examinations.

There was clear evidence of maternal toxicity at 300 mg/kg/day, manifested as a reduction in bodyweight gain and food consumption, mortality of two females and macroscopic organ changes in the kidney (pale or irregular shape in seven mothers) or spleen (reduced size in two mothers). Similar macroscopic changes were seen occasionally at 150 mg/kg/day and at a high

incidence in females from the prematurely terminated 600 mg/kg/day group. No maternal toxicity was seen at 75 mg/kg/day. Post-implantation loss, litter size, foetal weights and incidence of both major and minor foetal abnormalities was not affected by treatment. This study provided no evidence of developmental toxicity in the rat at exposure levels which are toxic to the mother. The maternal NOAEL was 75 mg/kg/day and the foetal NOAEL was 300 mg/kg/day.

In the intraperitoneal study, the effects of nonylphenol on male reproductive tract development were investigated in neonatal Sprague-Dawley rats (Lee, 1998; additional information was obtained by personal communication with the author). Age-matched male pups were randomly allocated to either the control or treated groups. Daily doses of nonylphenol were administered by the intraperitoneal route at a dose volume of 5-10 µg/injection, for varying schedules between the day of birth (day 0) and 30 days of age. Control animals received the vehicle (dimethylsulfoxide) only, by the same route. The pups were killed at 31 days of age; terminal observations included external appearance of genital area, ano-genital distance, the presence of undescended testes, and reproductive organ weights (which were reported as bodyweight-related values). In the initial experiment, groups of at least three pups were dosed at 0, 0.08, 0.8 and 8 mg/kg/day, from birth to fifteen days of age. At 0.8 and 8 mg/kg/day there was a statistically significant, dose-dependent reduction in testes, epididymis, seminal vesicle and prostate weight; typically weights were about 15 to 25% less than found in the control group. Additionally, ano-genital distance was reduced at 8 mg/kg/day, only. Reproductive organ weights were not affected at 0.08 mg/kg/day. Next, groups of three or four pups received nonylphenol at 0 or 8 mg/kg/day, either from days 1 to 18 of age, days 6 to 24 or days 13 to 30, to see if there is a vulnerable phase of development. Reproductive organ weights were significantly reduced in the groups for which dosing commenced on day 1 or 6, but not in the group dosed from day 13. In a third experiment, the influence of the estrogen receptor antagonist, ICI 182,780, on nonylphenol-impaired reproductive organ weight development was investigated in groups of six or seven pups dosed with nonylphenol at 8 mg/kg/day from days 1 to 5 of age. The antagonist was administered by the intraperitoneal route at a dose of 0.5 mg/kg and dose volume of 5-10 µg/injection, ten minutes after the nonylphenol dose. It was found that ICI 182,780 blocked the effects of nonylphenol on organ weights. Administration of ICI 182,780 alone had no effect on reproductive organ weight. The incidence of undescended testes was reported in groups of between six and 34 pups dosed with nonylphenol at 8 mg/kg/day, days 1 to 5, days 1 to 10 or days 1 to 18; this was 33%, 55% and 62%, respectively. Undescended testes were not observed in vehicle control pups, in pups receiving a single dose of nonylphenol on day 1, or when ICI 182,780 was administered concurrently with nonylphenol.

In another study, eight male pups, selected from two litters, were dosed by the intraperitoneal route from days 1 to 15 of age with nonylphenol at 8 mg/kg/day and then reared to sexual maturity. Their fertility was assessed by serial pairing with either six or twenty untreated female rats and recording the number of females which became pregnant. Vehicle control male pups, selected from the same two litters, were used for comparison. Among the controls, pregnancies resulted from almost all pairings. In contrast, in the nonylphenol-treated group, two males were completely infertile, failing to impregnate any females; three were initially fertile, but failed to impregnate females in later pairings; two showed comparable fertility to the controls; the remaining male died near the start of the fertility trial. Necropsy findings were reported for five of the nonylphenol-treated males; all were observed with

undescended testes and/or either slight or marked testicular atrophy. There are a number of design weaknesses to this study: the group sizes were generally very small; the pups were apparently not weight-matched at the start of treatment; and the intraperitoneal route of administration, which could result in unrealistically high exposure of the reproductive organs, is of questionable relevance to the human risk assessment. Nevertheless, the consistent observation throughout the series of experiments of reduced reproductive organ weight or undescended testes, supported by observations of reduced ano-genital distance and, in animals reared to sexual maturity, reduced fertility, provides evidence that nonylphenol-exposure during the neonatal period impairs male reproductive tract development in the rat. The period of maximum vulnerability to this effect appears to be prior to the age of thirteen days. The blocking influence of the estrogen receptor antagonist ICI 182,780 suggests that the effect of nonylphenol on the male reproductive tract may be mediated through action on the estrogen receptor. However, in view of corrosive properties of nonylphenol and use of the intraperitoneal route of administration, it is possible that non-specific irritation of the undescended testes may have contributed to the observed effects. The author has stated that about 50% of the nonylphenol-treated pups had peritoneal cavity adhesions, while none were seen in control animals, which supports this hypothesis. Although adhesions were seen, there were no treatment-related clinical signs of toxicity or increased mortality. The blocking influence of ICI 182,780 may possibly have resulted from dilution of the injected nonylphenol (this alternative explanation was not tested as the study did not include a control group receiving nonylphenol followed by a vehicle-only injection). It should be noted that precise information on clinical signs, mortality and general macroscopic necropsy findings were not available from the author. No effects were seen in pups dosed at 0.08 mg/kg/day but, because of the very small numbers of animals receiving doses other than 8 mg/kg/day, information on the NOAEL and dose-response relationship can be gained from this study. Overall, because of the design weaknesses and the possibility that non-specific irritation may have contributed to the observed effects on the male reproductive tract, it is not possible to draw any firm conclusions from this study with respect to specific reproductive toxicity of relevance to humans.

In another study, the effects of nonylphenol exposure from the *in utero* period to sexual maturity were investigated in an oral (gavage) study (de Jager *et al*., 1999b). Groups of ten mated females were dosed once daily with nonylphenol at levels of 0 (vehicle control, cotton seed oil), 100, 250 and 400 mg/kg/day from day 7 of pregnancy to weaning of their litters. Twenty F_1 generation males were randomly selected from each group for dosing as for the mother until ten weeks of age. The selected F_1 males were then killed. Testes and epididymal weight were recorded. The total l epididymal sperm numbers were determined. The testes were stored in Bouin's fixative and processed for histological examination, which included the identification of the stages of spermatogenesis present and the measurement of the seminiferous tubule diameter, lumen diameter and epithelial thickness. No information was presented on maternal bodyweight, but it was observed that no females showed any physical or behavioural abnormalities. No offspring were born from the mothers receiving 400 mg/kg/day; it is not clear from the report if this was because of maternal deaths or embryonic/foetal resorption. `There were no malformations or still births among the F_1 offspring. No physical or behavioural abnormalities were seen among the selected F_1 males. This contrasts with the De Jager (1999a) study conducted in adult males in which fifteen out of twenty animals died at 250 mg/kg/day. F_1 bodyweight gain over the course of the study was significantly reduced at both 100 and 250

mg/kg/day (by 11 and 20%, respectively), relative to the control group. F_1 absolute testicular and epididymal weights were less than the controls at both 100 and 250 mg/kg/day, but this effect was not evident when organ weights were expressed relative to bodyweight; the differences in absolute organ weight are thought likely to be related to the intergroup bodyweight differences. Total epididymal sperm count was reduced at 250 mg/kg/day (by 36%, relative to controls), but at 100 mg/kg/day sperm counts were similar to those of the control group. Seminiferous tubule diameter was slightly lower in both nonylphenol-treated groups (by about 10%); surprisingly, these slight differences were declared to be highly statistically significantly different from the control group. The authors also stated that the tubule lumen diameter and seminiferous epithelium thickness were highly statistically significantly less than the control group in both nonylphenol groups, but the data were not presented. Although these quantitative tubular changes were consistent with those of the De Jager (1999a) study, in the present study these may be related to the fact that testicular weight was lower in these groups. Histopathology revealed pathological changes in the testes of one F_1 male from the 100 mg/kg/day group; in the tubules, cell necrosis, vacuolation and sloughing of the germinal epithelium were described. However, no such histopathological abnormalities were seen at 250 mg/kg/day, so the changes outlined above cannot be attributed to nonylphenol treatment.

This study provides evidence of a reduction in sperm count at 250 mg/kg/day, a dose level which may have caused mortality, although it is not possible to state whether this is a developmental effect or a result of direct exposure of the males after weaning. It is not clear if the changes in the tubular measurements represent specific reproductive toxicity or non-specific secondary consequences of the reduction in bodyweight gain.

Risk Assessment Case Study (11/07/2012)

Questions and Answers:

1. Is nonylphenol typically used in products in the public domain?

Yes, nonylphenol (NP) is used primarily as a building block for the monomers used in the production of resins and polymers. Sixty percent of the NP is used for the production of nonylphenol ethoxylate which is used in end-use products including non-agricultural pesticides, cosmetics, cleaning products and office products such as correction fluids and inks.

2. What is the primary source or pathway of nonylphenol emissions into the environment?

Small emissions of NP may occur during production, and escape to air or surface water. Most of the NP are released from NP containing compounds which are first passed through a wastewater treatment plant, aerobically degraded by bacteria into shorter nonylphenol ethoxylates or NP. In the wastewater treatment plant, half of the NP absorbs on particles which then stay in the wastewater treatment plant as sludge or are emitted into the aquatic phase and settle on the sediment.

3. Is nonylphenol likely to be widely distributed among air, water, and soil? Why or why not?

Majority of the emissions of NP end up in the water compartment and are relatively restricted and partition to the sediment and biota because NP is poorly soluble and unlikely to evaporate from the water.

4. Are nonylphenol concentrations in surface water likely to be about the same everywhere?

No. Background concentrations on average in rivers in Germany in 1989 measured 0.038 µg/L, with peaks up to 1.3 µg/L, while in the River Aire in England in 1995, downstream of the emission sites of textile processing industry, locally high concentrations of NP were found; up to 53 µg/L freely dissolved nonylphenol and up to 180 µg/L when including particles. Thus, as one would expect, concentrations are generally greatest near points of discharge into water bodies and lower elsewhere.

5. Is nonylphenol likely to present as much of a risk to people as to ecological receptors?

Nonylphenol is mostly an environmental health issue for aquatic organisms: in the EU risk assessment report, a NOEC of 0.33 µ /L was derived, while in the River Aire in England in 1995, locally high concentrations of NP were found, up to 53 µg/L freely dissolved NP; the Tees estuary in England contained up to 3.1 µg.L freely dissolved NP. The exposure of humans to nonylphenol from background concentrations (5.13×10^{-3} mg/kg/d) is of limited concern, compared to NOAEL of 15 mg/kg/d. Only a local high exposure could affect human health.

6. Discuss the scope of the chemical(s) considered in the risk assessment by Fenner et al. 2002. Do they consider only the ‘parent’ compounds? Why or why not?

They investigate the still widely used nonylphenol ethoxylates (NPnEO) and their transformation products, including short-chain NPEOs, nonylphenoxy carboxylic acids, and nonylphenol. Because many chemicals are transformed to structurally related transformation products in the environment before they are mineralized and each of these transformation products displays its own toxicity and persistence. It could be seen from table 5 that RQ^x vary among NPnEO and transformation products using their own PNEC and estimated degradation rates.

7. What is the temporal scope of the assessment: acute or chronic exposures and effects?

Chronic.

8. Do Fenner et al. rely on a model or measurements for their assessment of exposure?

They used a four-compartment model.

9. What form of exposure does Fenner et al. consider (concentration, dose, absorbed dose, etc.?)

They used predicted environmental concentrations, expressed in units of μg/L.

10. Where are the exposure assessment results presented in the paper?

In table 4.

11. Did Fenner et al. do any analysis to evaluate the validity of their exposure assessment results?

Yes. They compared the water concentrations obtained from the model with measured concentrations for five locations in Swiss rivers. They found that the predicted concentrations tended to underestimate the value which might be due to the fact that the calculations represent averages of all Swiss waters, while the measurements were conducted in rivers with characteristically high anthropogenic loads.

12. Describe the toxicity values from which Fenner et al. derived guideline values

They used lowest acute lethal concentrations (LC_{50}) for every single substance from a database that was compiled from reference 9, 12, 21, 22.

13. What uncertainty or extrapolation factors, if any, were applied to derive guideline values?

For all substances, PNEC values in water were deduced from acute toxicity data by applying an EF of 1000 which accounts for acute-to-chronic ratio, sublethal effects and species differences.

14. Rank the various chemical forms of nonylphenol considered in this paper in order of highest to lowest toxicity based on the PNEC.

Toxicity from highest to lowest: NP>NP2EO=NP1EO>NPnEO>NP2EC>NP1EC.

15. Describe the method by which the risk of the individual nonylphenol-related compounds was characterized

For a single compound x, the risk to the organisms living in a given environmental compartment is expressed as risk quotient (RQ^x), which compared the concentration c^x of the compound x in that compartment to some measure of its toxicity. In this paper, ——.

16. Describe how the risk of adverse effects from the mixture of nonylphenol-related compounds was characterized

Risk quotient of mixture is derived by adding risk quotients for single compounds together, assuming that there is no interaction between different components of a chemical mixture and the mixture components have the same mode of action and the same slope of their dose-effect curves so that, at each concentration level, one component can be substituted by an equi-effective amount of another component. The formula is .

17. Fenner et al. describe the uncertainty associated with their risk charcterization. Identify and describe the “two conservative” and “one non-conservative” assumption they mention in the second full paragraph of the final page of the paper.

The first conservative assumption is using TGD standard which has a lower PNEC and higher extrapolation factor. The second is assumption of concentration addition which may overestimate the toxicity by maximally a factor of 10 according to Fenner et al. The non-conservative assumption is that possible estrogenic effects are excluded from the evaluation of the mixture toxicity at all.

18. Compare the Fenner et al. predicted environmental concentrations (PEC) of nonylphenol to the values described in the WHO nonylphenol report. Discuss whether or not the Fenner et al. PECs are conservative.

    The PEC of NP by Fenner et al. was 0.012 μg/L. WHO NP report showed that in the water in Main in Germany was mostly 0.18 μg/L. In English river Lea, the total extracted amount of NP is 0.5 to 12 μg/L and dissolved fraction of NP was 0.2 to 9.0 μg/L. In the Tees estuary, the highest concentrations were 0.08 to 3.1 μg/L dissolved NP and 0.09 to 5.2 μg/L total extracted NP. So we could see that the predicted environmental concentration of NP is lower than the observational concentration, especially failed to capture the upper bound. That is to say, Fenner et al. PECs are not conservative. This tendency toward under prediction might be due to the fact that the calculations represent averages of all Swiss waters, while the measurements were conducted in revers with characteristically high anthropogenic loads.

Risk Assessment Case Studies

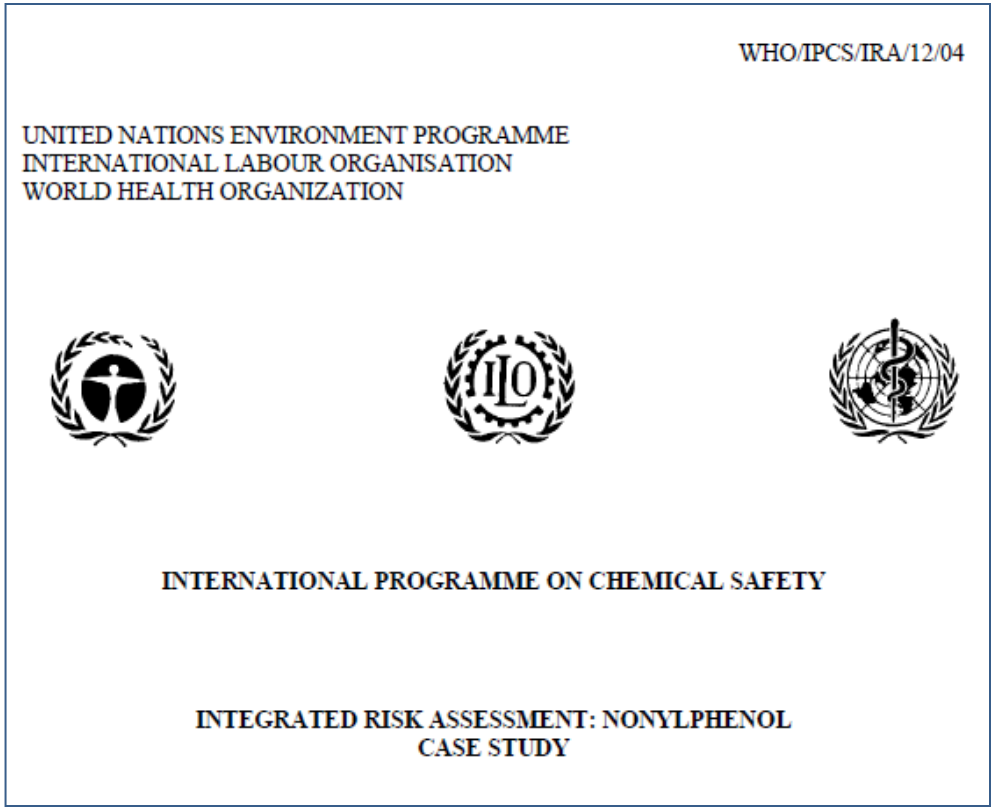
Slides to guide discussion of answers

Learning Objectives

- To learn more about key concepts of risk assessment through examples
- To practice using the roadmaps provided in the WHO Toolkit for Human Health Risk Assessment: Chemical Hazards
- To share experiences with other workshop participants

Nonylphenol Case: Background

Take 5 minutes to review background information on nonylphenol presented in pp. 9-11 of the WHO integrated risk assessment case study. Emphasize the highlighted portions of the document.



WHO/IPCS/IRA/12/04

UNITED NATIONS ENVIRONMENT PROGRAMME
INTERNATIONAL LABOUR ORGANISATION
WORLD HEALTH ORGANIZATION

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

INTEGRATED RISK ASSESSMENT: NONYLPHENOL
CASE STUDY

Charge Questions: Nonylphenol Background

- Is nonylphenol typically used in products in the public domain?
- What is the primary source or pathway of nonylphenol emissions into the environment?
- Is nonylphenol likely to be widely distributed among air, water, and soil? Why or why not?
- Are nonylphenol concentrations in surface water likely to be about the same everywhere?
- Is nonylphenol likely to present as much of a risk to people as to ecological receptors?

Nonylphenol Case: Risk Assessment

Take 15 minutes to review the risk assessment for nonylphenol ethoxylate usage described by Fenner et al. (2002). Emphasize the highlighted portions of the document.

Environ. Sci. Technol. **2002**, *36*, 1147−1154

Including Transformation Products into the Risk Assessment for Chemicals: The Case of Nonylphenol Ethoxylate Usage in Switzerland

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(iii) the group of chemicals forms a complex mixture that is difficult to assess, and (iv) toxicity data for transformation products is often lacking. (For pesticides, the regulatory requirements in Europe are more stringent than for other industrial chemicals in that the identification, analysis, and risk assessment of all relevant metabolites is mandatory for their registration (*2*, *3*).) All of these tasks pose methodological problems and increase the time and effort required for the assessment. Accordingly, there are only a limited number of studies dealing with the risk assessment of transformation products of industrial chemicals (e.g., refs *2* and *4*−*8*).

One approach to include transformation products into the risk assessment of their parent compounds is to identify important transformation products, such as DDE formed out of DDT or nonylphenol stemming from nonylphenol ethoxylates, and to perform a risk assessment for these

Charge Questions: Nonylphenol Problem Formulation

- Discuss the scope of the chemical(s) considered in the risk assessment by Fenner et al. 2002. Do they consider only the 'parent' compounds? Why or why not?

- What is the temporal scope of the assessment: acute or chronic exposures and effects?

Charge Questions: Nonylphenol Exposure

- Do Fenner et al. rely on a model or measurements for their assessment of exposure?
- What form of exposure does Fenner et al. consider (concentration, dose, absorbed dose, etc.?)
- Where are the exposure assessment results presented in the paper?
- Did Fenner et al. do any analysis to evaluate the validity of their exposure assessment results?

Nonylphenol Case: Exposure

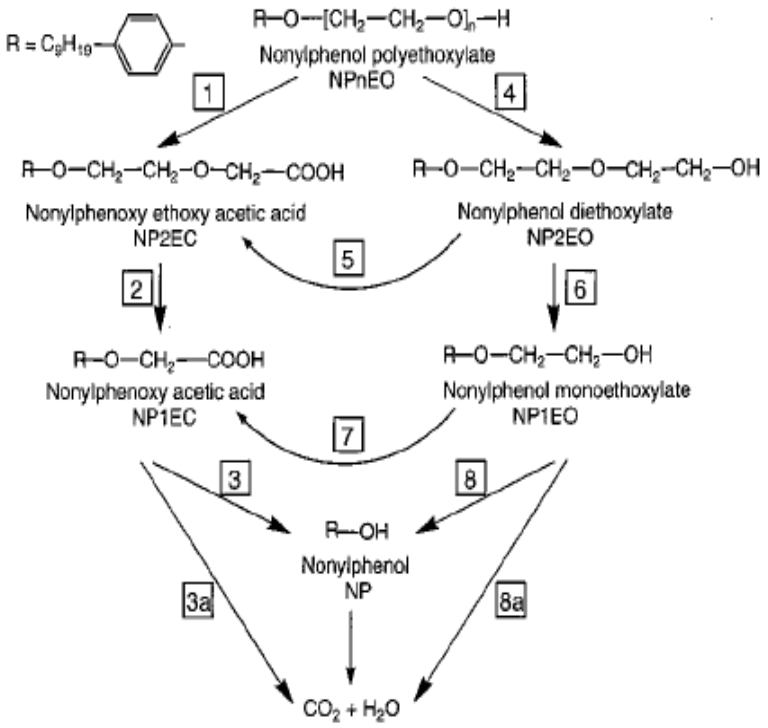


FIGURE 2. Simplified transformation scheme of NPnEO in waste-water treatment plants and in natural environments according to refs *12* and *34*. Numbers of reactions are used in Table 2.

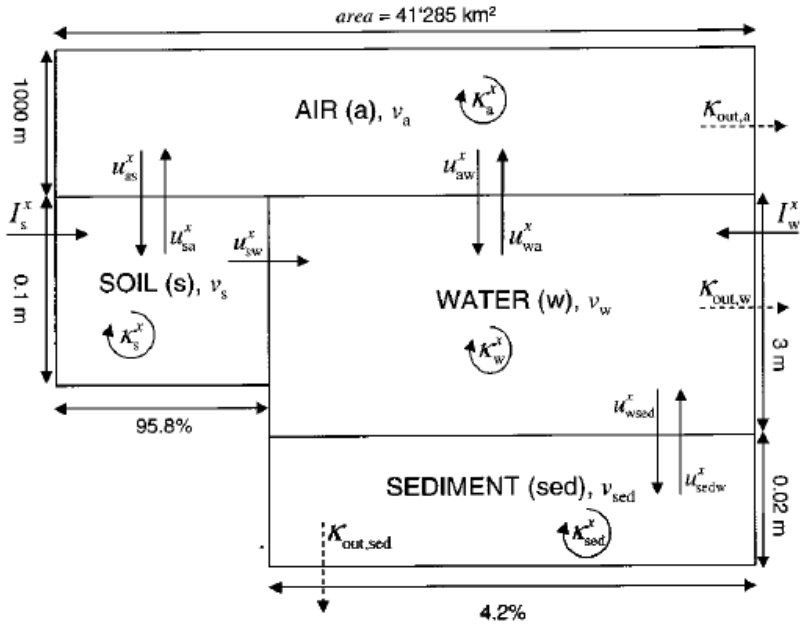


FIGURE 1. Open four-compartment model for Switzerland. In each compartment (soil (s), water (w), air (a), and sediment (sed)), all chemicals *x* undergo first-order degradation (k_i^x) and transformation ($k_i^{xy} = \theta_i^{xy} k_i^x$), advective and diffusive transfer processes between the compartments (u_{ik}^x), and advective transport out of the system ($k_{out,i}$). Substances are emitted into the model system as secondary effluents into water (I_w^x) and, adsorbed to sewage sludge, into soil (I_s^x).

Degradation of nonylphenol ethoxylates to nonylphenol

Transport and Fate Model

Nonylphenol Case: Exposure

TABLE 4. Comparison of Calculated Steady-State Concentrations c_w^x, and Measured Concentrations of NPE in the River Glatt (Switzerland) and Other Swiss Rivers (*27*)

	c^{NPnEO}	c^{NP2EC}	c^{NP1EC}	c^{NP2EO}	c^{NP1EO}	c^{NP}
calculated concentrations [μg/L]	0.21	0.30	0.19	0.04	0.07	0.012
measured concentrations in the river Glatt [μg/L]		0.60	0.70	0.095	0.06	0.06
measured concentrations at five locations in Swiss rivers over the period 1997−1998 (μg/L)[a]				nd−0.31 (2.55)[b]	nd−0.35	nd−0.48

[a] nd: below detection limit of 0.03 μg/L. [b] Exceedingly high value, measured in small river with high loads of NPE.

Charge Questions: Nonylphenol Hazard Characterization

- Describe the toxicity values from which Fenner et al. derived guideline values

- What uncertainty or extrapolation factors, if any, were applied to derive guideline values?

- Rank the various chemical forms of nonylphenol considered in this paper in order of highest to lowest toxicity based on the

Nonylphenol Hazard Characterization

TABLE 3. Selected Toxicity Values of NPnEO and Its Transformation Products[a]

	NPnEO[b]	NP2EC	NP1EC	NP2EO	NP1EO	NP[c]
endpoint	LC_{50}	LC_{50}	LC_{50}	LC_{50}	LC_{50}	LC_{50}
test duration [h]	96	48	96	48	48	96
concentration [μg/L]	900	990	2000	110	110	20.7
ref	39	40	Williams, J. B. et al., 1996 in ref *21*	39	39	Brooke, L. T., 1993a, in ref *21*
extrapolation factor (EF)	1000	1000	1000	1000	1000	1000
PNEC in water (μg/L)	0.90	0.99	2.00	0.11	0.11	0.021
PNEC in sediment (μg/kg)	83.3	3.43	6.93	86.0	79.8	27.0

[a] Lowest acute lethal concentrations (LC_{50}) were taken from a database that was compiled from refs *9*, *12*, *21*, and *22*. [b] Values for NP9EO and NP15EO were used. [c] CAS Registry Number: 84852−15−3.

Charge Questions: Nonylphenol Risk Characterization

- Describe the method by which the risk of the individual nonylphenol-related compounds was characterized
- Describe how the risk of adverse effects from the mixture of nonylphenol-related compounds was characterized
- Fenner et al. describe the uncertainty associated with their risk charcterization. Identify and describe the “two conservative” and “one non-conservative” assumption they mention in the second full paragraph of the final page of the paper.
- Compare the Fenner et al. predicted environmental considerations (PEC) of nonylphenol to the values described in the WHO nonylphenol report. Discuss whether or not the Fenner et al. PECs are conservative.

Nonylphenol Risk Characterization

Risk Quotient for a Mixture of Parent Compound and Transformation Products. For a single compound *x*, the risk to the organisms living in a given environmental compartment is commonly expressed as risk quotient (RQ^x), which compares the concentration c^x of the compound *x* in that compartment to some measure of its toxicity (e.g., EC_I^x (EC = effect concentration, *I* = effect level in percent of affected organisms)).

or different receptor systems. The second is concentration addition (CA), which means that the mixture components have the same mode of action and the same slope of their dose−effect curves so that, at each concentration level, one component can be substituted by an equi-effective amount of another component.

Given CA, the concentrations of all of the components of a mixture can be transformed into an equivalent concentration c_{EQ}^{ref} of a reference compound by summing up the concentration of each component multiplied by its relative potency RP^x. The relative potency RP^x is defined as the ratio of the toxic potency of the reference compound (EC_I^{ref}) divided by that of the compound *x* (EC_I^x). The total risk of the mixture can then be assessed by comparing the equivalent concentration c_{EQ}^{ref} with a given toxicity threshold of the reference compound (eq 1).

$$RQ_{mix} = \frac{c_{EQ}^{ref}}{EC_I^{ref}} = \frac{\sum_x c^x RP^x}{EC_I^{ref}} = \frac{\sum_x c^x \frac{EC_I^{ref}}{EC_I^x}}{EC_I^{ref}} = \sum_x \frac{c^x}{EC_I^x} = \sum_x RQ^x \quad (1)$$

Calculated RQ^x Values in Water of Single Components *x* and RQ_{mix} of the NPE Mixture[a]

r	scenario description	RQ^{NPnEO}	RQ^{NP2EC}	RQ^{NP1EC}	RQ^{NP2EO}	RQ^{NP1EO}	RQ^{NP}	RQ_{mix}
	Standard	0.229	0.304	0.094	0.323	0.645	0.568	2.16

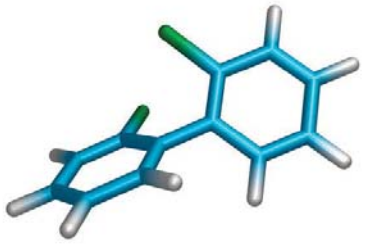
PCBs Case Study - Background Information

Presentation by: Dr. David MacIntosh
APEC risk assessment and risk management workshop
November 7-8, 2013
Bangkok, Thailand

Polychlorinated biphenyls (PCBs)

1

- A group of 209 chemicals that was first manufactured in 1929
- Accumulation of PCBs in people is associated with negative health effects
  - Cancer and reproductive effects in adults
  - Learning deficits in children
  - Hormone disruption
- New uses and most existing uses of PCBs in many economies were banned in and around 1980

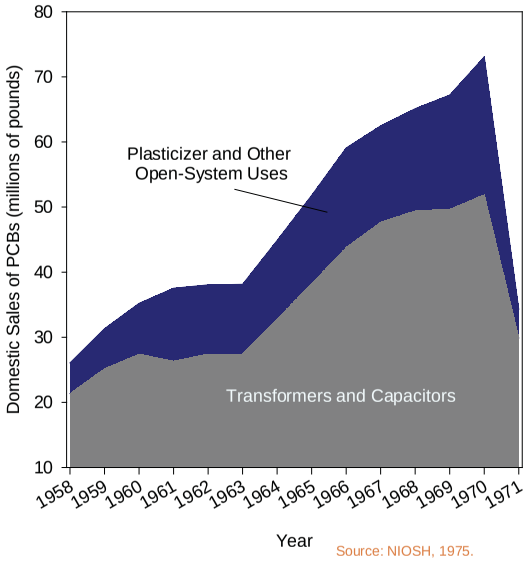


Source: SciencePhoto.com

PCB Properties and Former Uses

2

- Inert, non-conductive, high heat capacity, non-reactive, low volatility
- Major use was to absorb heat in transformers, capacitors and other closed systems
- Secondary use was a plasticizer in open systems such as caulk, adhesives, and sealants
- Over 160 million pounds of PCBs were sold for open system use in the U.S. from ~1958 to 1971

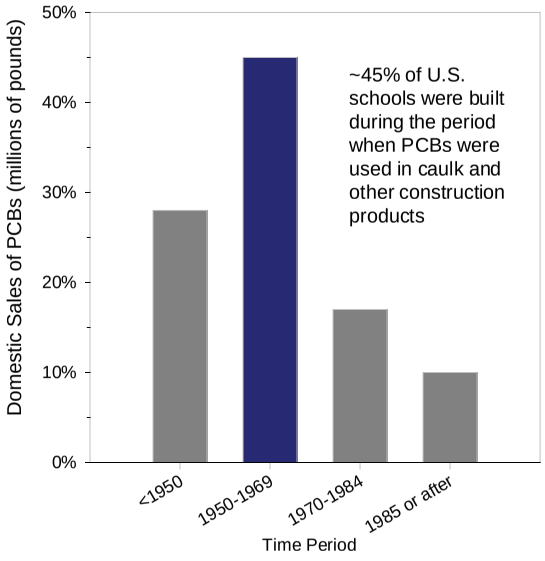


Source: NIOSH, 1975.

Estimates of US School Stock at Risk

3

- About 40% of U.S. schools were built during the time that PCBs were sold for use in caulk and other open system applications
- There is little variation among U.S. regions. The percentage of schools built from 1950 – 1969 is:
  - Northeast – 49%
  - Southeast – 43%
  - Central – 46%
  - West – 44%



Source:
[1] National Center for Education Statistics, 1999.

PCBs in Building Materials

Examples

4

Products Manufactured with PCBs

- Caulk
- Mastic
- Paint
- Ceiling tiles
- Glazing
- Light balllast
- Wiring insulation

Materials Near Primary Sources

- Brick and mortar
- Concrete block
- Backer rods
- Vapor barriers
- Insulation
- Paint and sealants
- Ceiling tiles
- Debris
- Foam
- Others

Costs for Remediation of Primary and Secondary Sources

5

Building Type	Costs ($/ft²)	Size (Square feet)	Costs ($000,000)	Work Schedule
University Academic	$18 ($47)	80,000	$1.4M ($3.7M total)	Vacated due to occupant concerns
Commercial Office	$13	260,000	$3.4M	Occupied
University Office	$9	155,000	$1.4M	Unoccupied
University Academic	$12	197,000	$2.4M	Occupied
Elementary School	$9	70,000	$0.6M	Occupied; containment

Elementary School (Grades K-5)

6

PCB Disposition

7

PCB Disposition

8

PCB Disposition

9

PCBs in Building Materials: Risk-Related Questions

10

- Questions we would like to answer in a situation like this:
  - Could students and staff be exposed?
  - How much exposure is occurring?
  - What should we expect the consequences of exposure to be?
  - Can the exposures be controlled? (i.e., is it possible to modify exposure?)
  - What is the most effective means of controlling exposure?
    - How much will the controls lower exposure?
    - How long will it take to complete?
    - What will it cost?
  - Should the exposures be controlled? (i.e., What are risks to health? Are the risks meaningful?)

Vapor Pressure and Temperature

11

- Vapor pressure is a strong function of temperature
- The relationship is given by the Clausius-Clapeyron equation

$$\ln P = -\frac{\Delta H_{vap}}{RT} + C$$

where

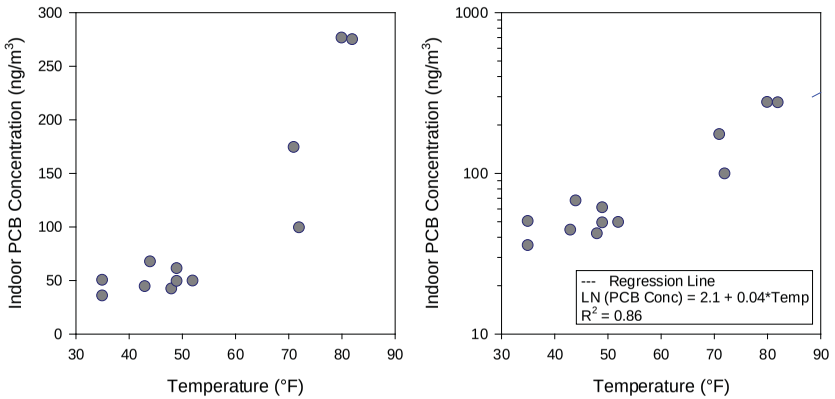
P = vapor pressure

H_{vap} is the compound's heat of vaporization

R is the gas constant (8.3 J deg^{-1} mol^{-1}), T is the temperature of the system (in Kelvin), and C is a constant that depends on the compound – Wikipedia entry for the gas constant

C is a compound-specific constant

PCBs in Indoor Air



School-wide average PCB concentration versus ambient temperature

PCBs Case Study - Exercise

Presentation by: Dr. David MacIntosh
APEC risk assessment and risk management workshop
November 7-8, 2013
Bangkok, Thailand

APEC Workshop on Risk Assessment and Risk Management

Case Study – Day 2

An elementary school in your economy was constructed with PCB-containing caulk. Measurements of PCBs in indoor air were made in 7 of the 15 classrooms two weeks before the start of the school year. The school-wide average concentration was 650 nanograms per cubic meter of air (ng/m^3). Concentrations in individual classrooms ranged from 300 to 1,800 ng/m^3. You are responsible for Environmental Health & Safety of the schools in your province.

Reporting Group: F

1. Your first action is to determine if the current levels of PCBs in indoor air of the school are acceptable for occupancy by children. From a search of the literature, you determine that non-cancer risks will be a more sensitive conservative benchmark than cancer risk for your analysis. Following your organization's normal practice, you decide to rely on the Reference Dose (chronic RfD) for PCBs recommended by the U.S. Environmental Protection Agency for a health protective guideline value for PCBs in indoor air at school. Answer the following questions about the challenges you encounter in deriving an acceptable concentration of PCBs in indoor air of the school.
    a. You quickly realize that USEPA established a RfD for two different mixtures of PCBS: Aroclor 1016 and Aroclor 1254. Which RfD do you choose to work with? What is your rationale for that choice? What is the RfD in units of nanograms per kilogram body weight per day (ng/kg/d)?
    b. From your experience, you understand that PCBs are highly persistent and present in food, soil, and biota near the top of their food web around the globe. Your research reveals that a reasonable estimate of dietary intake of PCBs from food for children in your economy is 5 nanograms per kilogram per day. Assuming no other pathways of exposure than diet and indoor air at school, what is the remaining amount of the RfD that is "available" for in-school inhalation exposure? Your answer should be in units of ng/kg/d.
    c. So far, so good, but you are not finished yet. You want to know a concentration of PCBs in indoor that will be acceptable; in other words, a guideline value for airborne concentrations at the school. You recognize from prior training that guideline values are related to guidance values (exposure rate or dose) by exposure factors. Assume that health risks of PCBs are independent of route of exposure. Assume that a typical child in the school inhales 0.5 cubic meters of air per hour on average and weigh 20 kilograms. School is in session for 7 hours per day, 180 days per year. Also assume that the duration of exposure represented by the chronic RfD is one year. Derive a guideline value for PCBs in indoor air of the school for children based on this information.

2. Assume that derive the guideline value from the oral RfD for Aroclor 1254 and that the resulting guideline value for the annual average concentration of PCBs indoor air of the school is 175 ng/m^3.
    a. Calculate the Hazard Quotient for PCBs, using the school-wide average concentration in indoor air based upon the measurements reported above.
    b. Return to the Oral RfD Summary for Aroclor 1254 then identify the Critical Effect upon which the RfD is based and the corresponding uncertainty factor applied by EPA to derive the RfD. Prepare a brief statement that you will use to inform the Director of the relevance and meaning of the RfD for potential risks at the school.
    c. Look ahead to the immediate future when school is scheduled to open for the year. Will you attempt to reduce the exposure concentrations? Will you inform other school officials of the situation? What recommendation will you give to the Director of the School System regarding information to share with parents of children who attend the school? What about the teachers and other staff of the school? Why? Prepare written answers to these questions.

Reporting Group: G

3. Assume that you and your colleagues decide to take action to reduce the indoor air PCB concentrations. You retain engineering and hazardous material experts who inform you that removal of the PCB-containing caulk would cost approximately 4 million US dollars. The experts also tell you that an alternative remedy would be to lower emissions to indoor by encapsulating the PCB-containing caulk with silicone sealant, foam board insulation, and gypsum wall board. Based on experience and an indoor air quality model, they are confident that school-wide average concentrations of PCB indoor air can be reduced to 50 ng/m^3. The work could be done at night and on weekends (allowing the school to stay open), would be complete by the 30th day of the school year, and would cost US $200,000.
    a. Will this level of mitigation result in an exposure concentration that is below the guideline value for indoor air of 175 ng/m^3 derived above?
    b. Will you recommend that the Director to keep school in session during the remediation work? List at least 5 factors that you will evaluate when developing your recommendation for the Director. Summarize your recommendation and supporting rationale in a paragraph; state any assumptions that you make.

4. Review the following abstracts of papers published in the scientific literature then respond to the d below.
    a. Review the abstracts below and answer the following question
        i. PCBs: routes of exposure and human health (review paper) http://www.ncbi.nlm.nih.gov/pubmed/16700427
        ii. Prenatal exposure to PCBs and intelligence in children - http://www.ncbi.nlm.nih.gov/pubmed/18941588

iii. Discuss the extent to which the RfD for Aroclor 1254 provides protection against the risk of PCB exposure in the school having an adverse effect on the intelligence or cognitive functioning of students in the school?

b. Review the abstracts and table below then answer the following questions
   i. PCBs in serum and indoor air - http://www.ncbi.nlm.nih.gov/pubmed/21724230
   ii. PCBs in serum of school students - http://www.ncbi.nlm.nih.gov/pubmed/15471095
   iii. Table 4-5 in this document
   iv. What is the relationship between the congeners that comprise Aroclor 1254 (item iii) and the PCB congeners reported in items (i) and (ii)?
   v. Describe how this could information affect your recommendations for communicating information on potential health risks to the community?

APPENDIX X. EXAMPLES BY ECONOMIES (PRESENTATIONS)

Sound Management of Chemicals: Elements for Decision Making

Marianne Heinrich, BP
APEC Risk Assessment Workshop
November 2012
Bangkok, Thailand

Sound Management of Chemicals: Elements for Decision Making

- Definitions and Key Concepts of Risk Assessment
- Overall Process of Decision Making
  - *Hazard Assessment*
  - *Exposure Assessment*
  - *Risk Characterization*
  - *Risk Management*

What is there that is not poison?
All things are poison and nothing without poison
Only the dose determines that an agent is not a poison
Paracelsus, 1538

How Do We Determine "Safe"?

What harm can occur? → Hazard

How much causes an effect? → Dose-Response

How much do we encounter? → Exposure

Is it safe? → Risk Assessment

Risk Assessment Process

- Tool to enable us to make appropriate risk management decisions to ensure adequate protection to people and the environment
  - *Real objective of any new chemical notification scheme*
- To be effective, the risk assessment process needs to be
  - Tiered
  - Iterative
  - Flexible
  - Based on Sound Science

Key Thoughts About Assessments

- Objective: to establish that the expected exposure will not equal or exceed the amount that can cause harm
- Exposure and hazard assessments frequently proceed in parallel
- Assessment is an iterative process –
  - Consideration is made first using the most readily available, least accurate information
  - If a conclusion about safety can be reached, no further work is needed
  - If a conclusion about safety cannot be reached, increasingly more sophisticated estimates are used until an acceptable degree of certainty is achieved
- Not every hazard must be measured and not every measurement needs the same precision/accuracy.

Foundational Principles

- Information gathered should be
  - Sufficient to support decision making regarding risks to people and the environment
  - Does not need to be comprehensive
- Testing on animals should be conducted only as a last resort
  - All other reasonable means including models and surrogate data (read across) to characterize the hazards should be exhausted means Results from animal tests of acceptable quality to support decision making should be utilized and considered sufficient
    - *Such tests should not be repeated regardless of where the tests were conducted*

General Approach

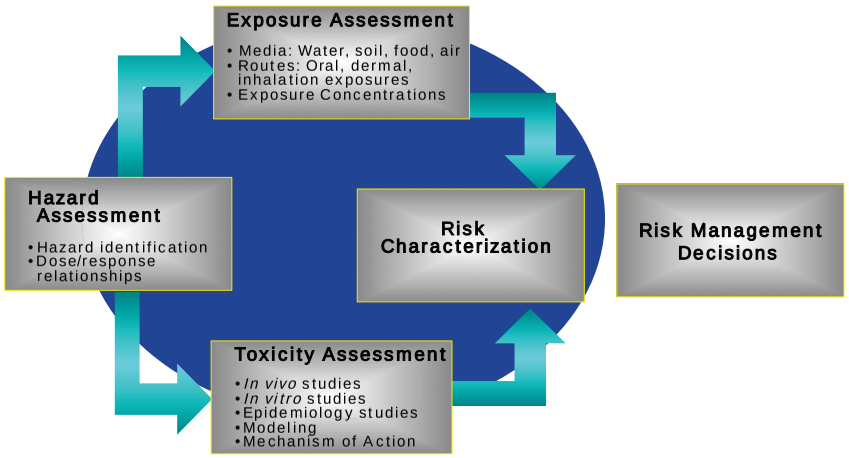
- Identify likely routes and evaluate magnitude of exposure associated with commercialization
  - Identity of the substance
  - How the substance will flow through commerce (use pattern, life cycle)
  - Something about its behavior (phys/chem properties and environmental fate)
- Identify adverse effects that could occur via the identified routes of exposures and the doses at which they would occur
- Determine whether or not exposure will exceed the dose at which an adverse effect will result
  - Take into account any related uncertainties
  - Evaluate in the context of any risk management steps (e.g., PPE, engineering controls, labeling, etc.) that will be implemented

How Do We Define Risk?

$$Risk = \{([Exposure\ Conc.], [Exposure\ Factors], [Toxicity^{*}\ Info.])\}$$

- Acute vs. Chronic
- Tiered Risk Assessment
- Forward / Backward Risk Assessment
- Additive and Cumulative
- Carcinogen vs. Non-Carcinogen

Risk Assessment Overview



Hazard Assessment

- Establishes toxicity of a chemical *and*
- Identifies the set of inherent properties that makes it capable of causing adverse effects

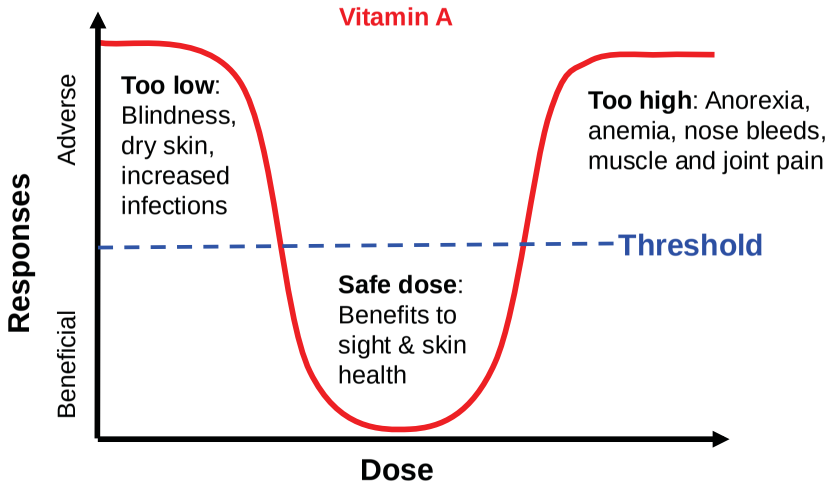
- Hazard assessment step identifies
  - Type of hazard that might occur given the appropriate circumstances
    - *Important to consider route of administration*
  - Defines dose/response and/or concentration/response relationships

Toxicity Assessment

- Access data from approved toxicological databases (hierarchical)
- References available for toxicology of carcinogens and non-carcinogens
- Rapidly emerging field (IRIS updated monthly)
- Sources of toxicity information:
  - e.g. IRIS (US EPA), IARC, US ATSDR, WHO/IPCS
- Use of models (QSARs) when data gap analysis is appropriate

How Much Causes An Effect?

Some chemicals have both therapeutic and toxic effects



Physical and Chemical Information-
what it can tell you about a chemical

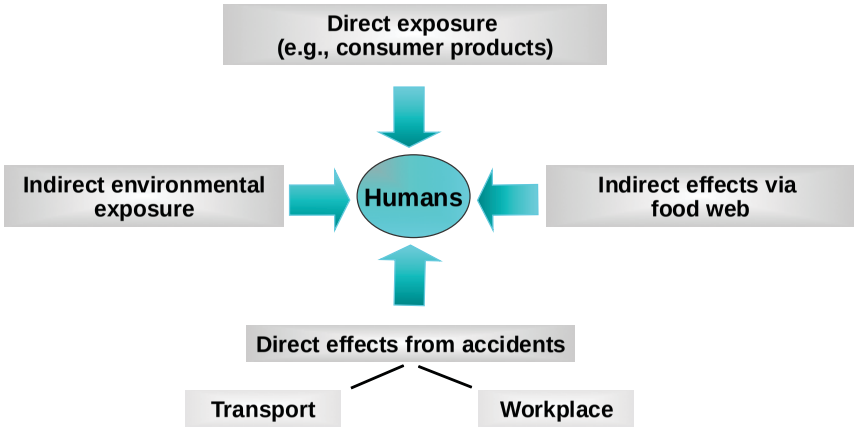
Test	Method	Result/Information	Comments
Vapour Pressure	EC A4 = OECD 104	Low Vapour Pressure High Vapour Pressure	Low concentration in air and therefore exposure to the chemical as a gas is negligible Greater inhalation exposure potential
Explosive Properties	EC A14	Negative	Relates to health and safety information
Boiling Point	EC A2 = OECD 103	 Low Boiling Point	Relates to potential routes of exposure Indicates substance will be a gas at room temperature
Water Solubility	EC A6 = OECD 105	Provides information on quantity of a substance by with it will dissolve in water at room temperature	Provides information on the ability to cross cell membranes (for organic molecules) Also provides information on potential for bioaccumulation
Octanol/Water Partition Coefficient	EC A8 = OECD 107	Low or High log of octanol/water partition coefficient (Log K_{ow}) Log Kow < 1 5< Log Kow < 7 Log Kow >7	Movement of substances across the dermal and gastric membranes is greatly reduced. Thus contact via dermal or oral routes would result in negligible exposure. • Substance is water soluble • Indicates potential for bioaccumulation • Substance is not water soluble
Octanol/ Water Partition Coefficient	EC A8 = OECD 107	High log of octanol/water partition coefficient Log of >5	Movement of substances across the dermal and gastric membranes is greatly reduced. Thus contact via dermal or oral routes would result in negligible exposure
pH	EPA OPPTS 830.7000 CIPAC MT75.3	Strong acids pH≤ 2 Strong alkalis pH ≥ 11.5	Indicative of skin, eye or gastrointestinal tract irritation potential

Exposure Assessment

- Purpose of an Exposure Assessment is to:
  - Identify the magnitude of exposure to a particular chemical
  - Determine the frequency and duration of that exposure
  - Determine all of the routes by which exposure occurs over the chemical life cycle

Estimating Exposure -
Considerations Including but not limited to….

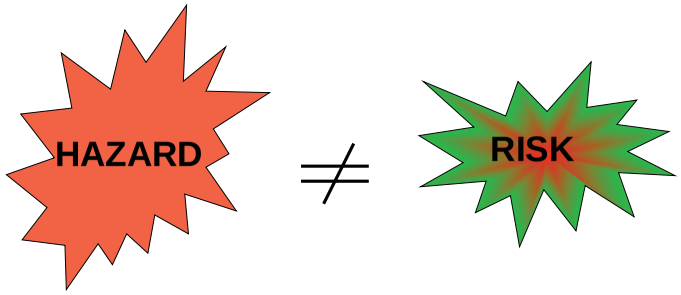
What targets ? **What type of exposure ?**



Risk Characterization

- Process of interpreting and integrating the information on hazard and exposure to provide a practical estimate of risk
  - Complex process
  - Defines how a risk should be managed
- Provides information on defining the conditions of use under which we may *safely* use chemicals
- Conditions under which the use of a particular chemical should be *avoided, minimized or eliminated*

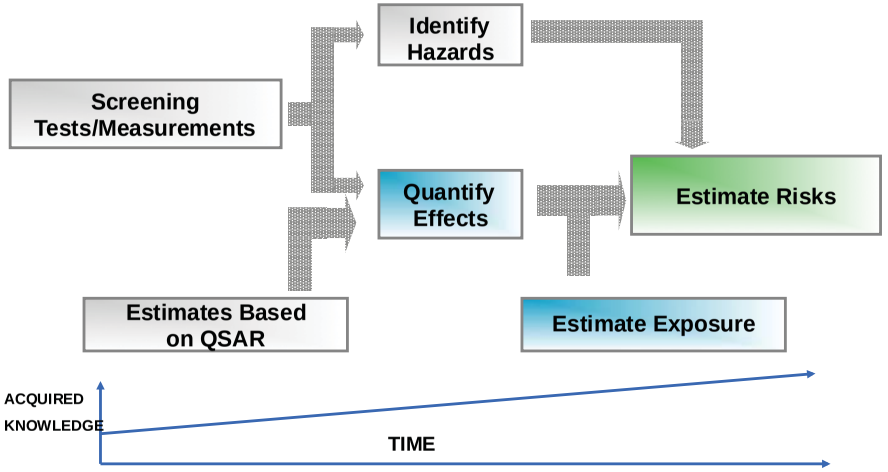
Identifying Hazards and Assessing Risks



Property of a chemical

Likelihood of that property being expressed

Assessment Continuum : *Hazard Screening to Risk Assessment*



Risk Management Decisions

- When risk characterization shows that risks of new chemical substance **are acceptable**,
  - Risk control measures are **not necessary**
- When risk characterization shows that risks of new chemical substances are **not acceptable**
  - Risk control measures **may be warranted**

Decision Making – How to Interpret Endpoints

- **Flash point (FP) and boiling point (BP)**

FP < 0°C, BP ≤ 35°C → ***extremely flammable***

→ **Labeling, handling precautions**

but…..

Not a risk to workers if handled accordingly

Sound Management of Chemicals

- Key objective of new chemical legislation is to provide a national system of notification and assessment of industrial chemicals for the purpose of protection of people and the environment
  - By finding out the **risks** to occupational health and safety
  - By finding out the **risks** to public health
  - By finding out the **risks** to the environment
    - That could be associated with the importation, manufacture, distribution, use and disposal of the chemicals

*These are the Elements of **Risk** Based Regulatory System*

Foundational Principles

- Objectives of an NSN review
  - Assess (ultimately enable management of) risks associated with commercialization of the new substance
  - Respect and balance equally valid purposes:
    - Protect people and the environment from harm
    - Not unduly impede innovation
  - Objective is not to increase basic scientific knowledge
- Underlying legislation should permit discretion by the authority to include only information elements that achieve the objective in the least burdensome fashion
- All evaluation techniques involve uncertainty
  - Unnecessary, wasteful and realistically impossible to completely eliminate uncertainty
  - Critical to ensure role for expert judgment regarding managing uncertainty

Information Needs
Summary

- Objective of an NSN review is to assess the risks associated with the commercialization of the new substance
  - Process to achieve this should be effective, efficient and flexible
  - Protect health & environment while enabling innovation
- All evaluations involve uncertainty
  - Process must be tiered and iterative
  - Enable evaluator to consider then set aside concern when supported by available information
  - Standardized lists of required tests are an obstacle
- Pre-notice consultations between notifiers and authorities can importantly enhance the process

Questions??

RISK ASSESSMENT and MANAGEMENT IN CHEMICAL INDUSTRY IN VIET NAM

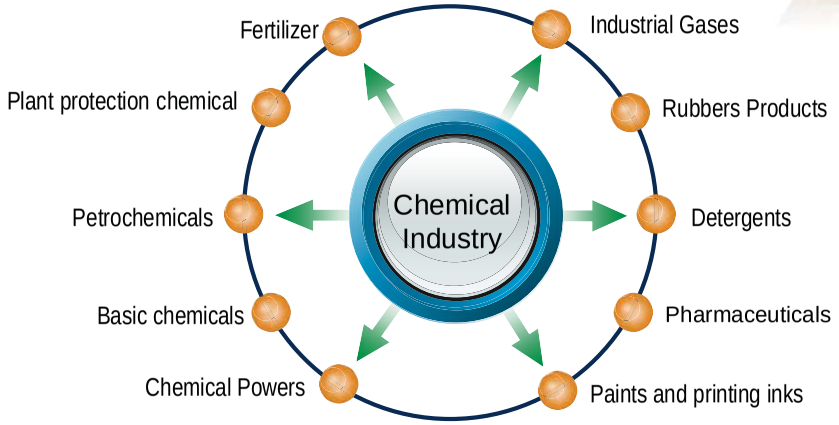
Nguyen Xuan Sinh
Viet Nam Chemicals Agency
Ministry of Industry and Trade of Viet Nam

Bangkok, November, 2012

Contents

Overview of Viet Nam chemical industry

Overview of Viet Nam Chemical Industry



Overview of Viet Nam Chemical Industry

No	Product Group	Enterprises	Total capacity	To meet the demand
1	Fertilizer	69	7.590.000ton/year	78%
2	Plant protection chemical	93	60.000 ton/year	15%
3	Petrochemicals	11	1.013.000 ton/year	raw materials imports to 90%
4	Basic chemicals	25	1.836.000 ton/year	import 100% of soda, sulfur
5	Chemical Powers	26	20.000.000kWh	
6	Industrial Gases	41	68.000 m^3/h	acetylene and rare gases are still imported
7	Rubbers Products	154	895.000 ton/year	70-75%
8	Detergents	103	800.000 ton/year	meet the demand in the domestic market
9	Paints and printing inks	143	300.000 ton/year	70%
10	Pharmaceutical chemicals	6	500 ton/year	> 90% is imported
	Total (to the end of 2010)	**671**		

Overview of Viet Nam Chemical Industry

	Up to 2012	Up to 2020
Average Annual Growth Rate	14%	15 – 16%
Sector Contribution	- Around 10% Industrial Production Value - 10% Industrial Labor Force	10.8% Industrial Production Value
Priority sub-sectors		- Agrochemicals (fertilizers, Pesticides) - Petrochemicals

www.cuchoachat.gov.vn

Viet Namese Law on Chemicals

Viet Namese Law on Chemicals

Date of issue: the law was passed on November 21, 2007, by the XII National Assembly of the Socialist Republic of Viet Nam at it 2nd session.

- **Composition : 10 Chapters, 71 Articles**
- **Special Attentions**

  - Chapter I: General provisions;
  - Chapters II –VII: Specific provisions stipulating chemicals activities & chemical - related activities;
  - Chapter IX: State administration on chemical activities and others

www.cuchoachat.gov.vn

Viet Namese Law on Chemicals

Content of Chapters

I

1. Applicable Legislation;
2. Definitions of Terminology;
3. Governing Principles;
4. Government policy on chemical activities;
5. Prohibited activities.

II - VII

1. Development planning;
2. Production and trade of chemicals;
3. Classification, labeling, packaging and MSDS of chemicals;
4. Use of chemicals;
5. Prevention and mitigation of chemical accidents;
6. Declaration, registration and notification of chemicals, in particular.

VIII &IX

1. Environment protection and community safety;
2. State administration on chemical activities;
3. State Agency;
4. Specialized inspection on chemical activities;
5. Penalization of violations under the law;
6. Settlement of disputes;
7. Implementation of the Law.

Chemical management and implementation of Chemical Law in Viet Nam

Chemical Management and implementation of Chemicals Law in Viet Nam

❖ CHEMICAL CONTROL LEGISLATION *(National Level)*:

Environmental Protection Law
Health Care Law
Safety Code for production, use, storage and transportation of dangerous chemicals
Narcotics (drug, heroin) Prevention Law
Radiation Safety Law
Ordinance on Plant Protection
Prime Minister's Decision on Controlling Petrol, oil and LPG
Food Safety Law.

Chemical Management and implementation of Chemicals Law in Viet Nam

Chemical Law (Vinachemia)

Decree from the Government

- ❖**Decree No. 108/2008/ND-CP** dated October 2008 on "Detailed regulation and guideline of implementation of several articles in Law of chemicals"
- **Decree No.90/2009/ND-CP** dated October 20th, 2009 on administrative punishment of chemical activity.
- ❖**Decree No.26/2011/ND-CP** dated April, 8 th, 2011 on "Repair some articles of Degree No.108/NĐ-CP on guideline of implementation of several articles in Law of chemicals"
- ❖**Decree No.26/2011/ND-CP** dated April, 8 th, 2011 on "Repair some articles of Degree No.108/NĐ-CP on guideline of implementation of several articles in Law of chemicals"
- ❖**Decree No. 104/2009/NĐ-CP** dated 2009 on Transportation of Chemicals.

Circular from the MOIT

- ❖ **Circular 28/2010/TT-BCT** dated June 28th, 2010 guiding on implementation of Chemical Law and Decree 108/2008/ND-CP dated 07/10/2008;
- ❖ **Circular 30/2011/TT-BCT** dated August 10th, 2011 stipulating temporarily the permissible content limitation of some hazardous chemicals in the electronic, electrical products.
- ❖ **Circular 40/2011/TT-BCT** dated November 14th, 2011 guiding on chemical declaration.
- ❖ **Circular 04/2012/TT-BCT** dated February 13th, 2012 guiding on chemical category and labeling.

❖ **Chemical Management Activities in Viet Nam:**

- Master Plan for chemical industry development to 2020, vision to 2030;
- Chemical register;
- Establish the Center for Chemical database and Support for Chemical accident response;
- Chemical inspection;
- Information for chemicals management in national level on the website: www.cuchoachat.gov.vn;
- First stage for implementing GHS;
- International cooperation for chemicals management.

❖ **Chemical management activities in cooperation with SAICM, APEC, AMEICC; KEMI (Sweden); METI (Japan) and KOICA (Korea)**

- Chemical management project with UNDP)/SAICM;
- Project «Survey of Mercury Management in Viet Nam» with UNEP;
- Chemical Management Forum for Indochina countries with KEMI;
- Information Center for REACH and ROSH with UNIDO;
- Chemical management projects with METI, Japan under MOC between MOIT and METI

❖ **Chemical management in accordance with international conventions:** Kyoto Protocol;Stockholm Convention (POP convention);Chemical Weapon Convention;Vine Convention & Montreal Protocol on ODS; Rotterdam Convention

❖ **CHALLENGES**

- Lack of technical guideline: although there has been Government Decree of chemical safety and that comes into force already, but because still lacking guidelines for implementing the certain items.
- Overlap of activities: because of a lot of stakeholders (ministries) involved in the chemical management and chemical safety in a not clear mechanism of duty or responsibilities allocation, the response ways of the relevant bodies to the management requirements could be quite passive, not active.
- Lack of coordination and cooperation;
- Information exchange;

❖ **CHALLENGES**

- The legal provisions are not enough strict. Chemical inspection: have not been given due attention
- Awareness of the business on the chemical safety remains low
- Coping skills of workers is not good
- Equipment and manpower to response for chemical accident: not good.
- Chemical breakdown of the chemical industry of Viet Nam occurred more

Risk Assessement and Management in chemical industry in Viet Nam

- ❖ Regulation on RA in chemicals: not available.
- ❖ Study on RA: Until now, there are some case study on RA in the few chemical factory. Example: Application of risk assessment methods in Fertilizer; Assessment of chemical risk and hazardous waste management and some initial results of research on methods of assessment chemical risk for human health.
- ❖ In 2011 & 2012: Japan support some training course on RA & RM for Viet Nam Chemical Agency

Cont.

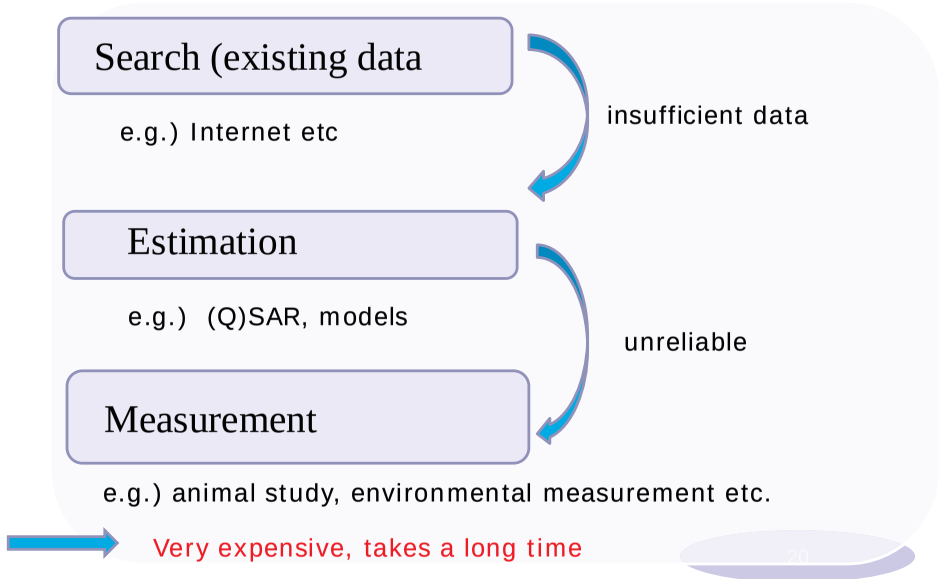
- This team will apply the theory into pratice to reduce the toxic effect caused by use of chemicals to human health and our environment and also to strengthen education to raise awareness about safety risks of chemicals in the community to the individual to the individual stakeholers.
- The demand for human resources needs to be seen as the key in the implementation of the purpose of education and implementation of requirement for safety management of chemical risks.
- Most of chemicals are toxic and potentially affected the environment and human health. But awareness of chemicals risks and the preventive measures are limited.

Need to training of safe management of chemical risk

- Demand for chemical in increasing in Viet Nam, raising awareness of safety – management of chemical risk to communities, businesses and for people exposed to chemicals in general, the toxic chemical in particular is a important work.
- People will be more aware of action consistent with the actual situation and mitigate the negative impact cause by chemical triggers.
- To achieve these objectives should have a team equipped with the knowledge of safety management – risk chemicals.

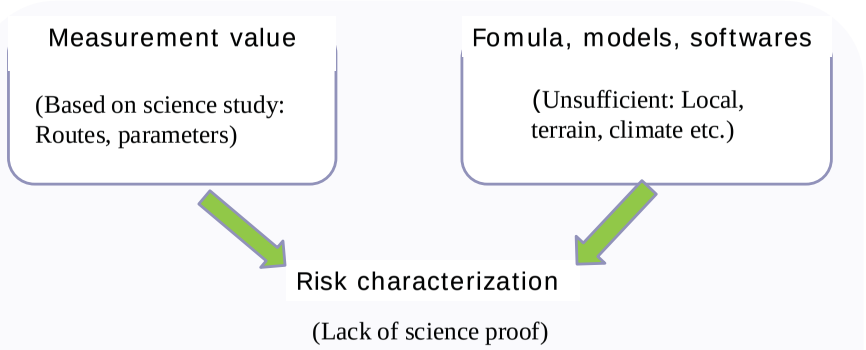
Challenge for Risk Management

❖ Gathering Data



Challenge for Risk Management

❖ Analysis Data



Proposals in RA & RM in Viet Nam

- Legal solution: Promote the implementation and monitoring closely the implementation of legal document on chemical safety, assessement and chemical risk management in an industrial chemical and chemical protection plants.
- Technical solution: need to improve production techniques and related toxic chemical to reduce damage caused by use chemicals to human helth and env.
- Measures for education training: Human resources firm from the traning of young scientists and intellectual capacity.
- Investment in facilities for basic reaseach areas of chemical risk assessement.

Trends of RA in Viet Nam

- Methodology of RA: Develop long term cooperation program with the developed as Japan, USA;
- To exchange experiences with foreign expert to raise the level of scientists in Viet Nam.
- Establish a legal document in RA

VINACHEMIA Vietnam Chemicals Agency

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Thank You for Your Attention!

"Chemical Risk Assessment and Management among Institutions of the Environment Sector"

Ministry of Environment in Mexico (SEMARNAT)

Maria Teresa Gómez Osorio

National Institute of Ecology and Climate Change

Leonor A. Cedillo

Outline

-Legal framework related to Chemical Risk in Mexico.

-Applications related to Chemical Risk at the Ministry of Environment

Chemical risk

Legal framework

Principles related to Chemical Risks:

-integral management of wastes to avoid health **risks**

- undertake immediate actions to remediate contaminated sites, to prevent or reduce health and environmental **risks**.

Definitions related to chemical risks:

-**Risk**: Likelihood of the occurrence of adverse health effects in humans and other organisms, as well as effects in water, air, soil, and ecosystems caused by the management , release to the environment and exposure to a material or waste

-**Environmental Risk Assessment**: process to determine the likelihood of adverse affects caused by the exposure to substances contained in hazardous wastes.

Chemical risk

Legal framework

- Hazardous wastes
- Contaminated sites

General Law for Prevention and Integral Management of Wastes (2003, updated May 2012)

- Highly risky activities
- Pesticides, plant nutrients, substances and toxic or dangerous materials

General Law for Ecological Equilibrium and Environmental Protection (1988, updated June 2012)

Chemical risk

Legal framework

Hazardous wastes — General Law for Prevention and Integral Management of Wastes (2003, updated May 2012)

Classified according to the following characteristics:

Corrosive,
Reactive,
Explosive, Toxic,
Flammable
or containing infectious agents;
as well as **risk to the environment**.

Chemical risk

Legal framework

Contaminated sites — General Law for Prevention and Integral Management of Wastes (2003, updated May 2012)

Application at the Ministry of Environment

Site Remediation

1. - Site characterization.
2.- Environmental Risk Assessment.
3.- Remediation proposal.

Human health risk — Ministry of Health

Chemical risk

Legal framework

Highly risky activities — General Law for Ecological Equilibrium and Environmental Protection (1988, updated June 2012)

Application at the Ministry of Environment

Environmental Risk Assessment for highly risky activities

Facilities that manage toxic substances

Facilities that manage flammable and explosive substances

Risk assessment focuses on release during production, processes, transport, storage, use and final disposal

Chemical risk

Legal framework

Pesticides, plant nutrients, substances and toxic or dangerous materials — General Law for Ecological Equilibrium and Environmental Protection (1988, updated June 2012)

Application at the Ministry of Environment

Import

Registration

Health risk assessment and environmental risk assessment

Ministry of Health and Ministry of Agriculture

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Y CAMBIO CLIMÁTICO

How we have used the risk assessment approach?

- **To support the proposed environmental regulations**
- **To determine whether we need further research**

Leonor A. Cedillo, Sc D.
November 2012

Air pollution Impacts to Public Health and Ecosystems Advances supported by Impacts Evaluation (examples)

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A. Local significance:

1. Five measures to control emissions from the metropolitan Area of Mexico City 2002-2010:

   - Subway expansion,
   - Introduction of hybrid buses,
   - LPG leakage control,
   - Renewal of the taxi fleet and
   - Co-generation.

2. Evaluating measures to control pollution in the city of Mexicali:

We identified control measures that offered the greatest benefits and elements were to reinforce the paving program implemented by local authorities

Advances supported by Impacts Evaluation (examples)

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Y CAMBIO CLIMÁTICO

B. Nationwide :

Update of the fuel quality regulation *:*

- ✓ The benefits of reduced sulfur content in fuel cost exceeds at least 2.3 times.
- ✓ This results were an important decision to submit budget request to Congress

Standard on carbon dioxide emissions (CO2) and fuel efficiency for new light duty vehicles

- ✓ The target to 2016 requires an increase on fuel economy of 21% for the entire fleet.
- ✓ The benefits of such effort outweigh the costs by 3.5
  - ✓ Fuel savings
  - ✓ CO2 emission reductions
  - ✓ Conventional pollutant emission reductions and corresponding health benefits (morbidity, mortality and productivity indicators)

Future Challenges on the Impacts of pollution on public health and ecosystems?

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Y CAMBIO CLIMÁTICO

- Strengthen partnerships with academia and other government agencies (federal, state and municipal), in areas such as health, energy, economy and environment.
- Strengthen and develop mechanisms for the use of the methodology in the evaluation of environmental policies.
- Keep updated analysis tools used in assessing the impacts of air pollution on the health of people and ecosystems, such as emission inventories, air quality modeling and health impacts.
- Promote the use of the methodology in the analysis of mitigation of climate change, such as the control of black carbon emissions.
- Strengthen analysis capabilities pollution impacts on ecosystems and biodiversity.
- Assess environmental policy tools that are in the current environmental agenda.

Risk Assessment for Dioxins and Furans from Wood Burning for Cooking and Artisanal Brick Production in Mexico (*)

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Problem formulation

Chemicals of concern:

Dioxins, furans & dioxin-like PCBs

- Highly toxic, persistent, bioaccumulate and fat soluble
- They are formed either:
  - As by-products during production of some chlorinated chemicals
  - During combustion of organic materials in the presence of chlorine.

Receptors: All family members, emphasis on **children**

* B Cardenas, T Romero, M Richardson, L Cedillo and G Umlauf

Problem formulation

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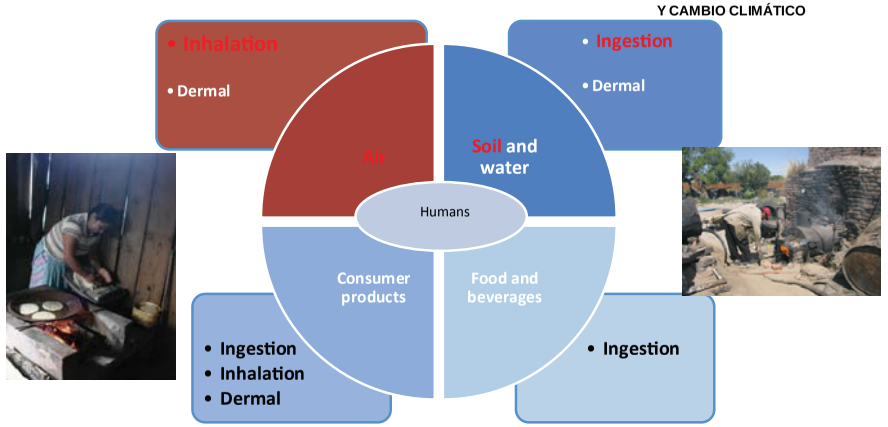
PATHWAYS:



Toxicity assessment
Current toxicological reference values for 2,3,7,8-TCDD

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- Tolerable daily intake (assumed threshold effect)
  - **WHO: 2.3 pg/kg-day**
  - **Canada: 2.3 pg/kg-day**
  - **Australia: 2.3 pg/kg-day**
  - UK: 2 pg/kg-day
  - Netherlands: 1 pg/kg-day
  - Japan: 4 pg/kg-day
- Cancer slope factor (assumed non-threshold effect)
  - US EPA: 0.001 (pg/kg-day)-1
  - CalEPA: 0.00013 (pg/kg-day)-1

Exposure Assessment

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$$Dose(pg/kg-day) = \frac{(C_i * IR_i) + (C_i * IR_i) + (C_i * IR_i)}{BW}$$

Where:
Ci = concentration in medium i (air and soil)
IRi = daily intake rate/interaction rate with medium i
BW = body weight of critical receptor

	Toddler		Child		Adult	
	Girl	Boy	Girl	Boy	Female	Male
Age[a] (years)	2-4		5-11		18 - 65	
Body weight[b] (kg)	11.8	12.3	18.2	19.6	48	55.3
Inhalation rate (m^3/day)[c]	9.3		14.5		15.8	
Ingestion rate (g/day)[c]	0.08		0.02		0.02	

- Weight data of the most vulnerable population is used
- Inhalation and ingestion rates reported by Health Canada (2008)

Exposure Assessment
Measures of PCDD/F emissions in Mexico

INSTITUTO NACIONAL DE ECOLOGÍA Y CAMBIO CLIMÁTICO

- Cardenas, et al. (2011) determined PCDD/F and PCB indoor concentrations and emissions factors for indoor wood open fires

- Maiz, et al.,2010 and Umlauf et al., 2011 determined PCDD/F, PCB dioxin like, PM and HCB concentrations and emissions factors from artisanal brick production

RESULTS

Risk characterization
Open fires for cooking

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Receptors/ Pathways	Gender	Inhalation	Ingestion (indoor dust)	Total dose (air +dust)	Risk non cancer (Hazard ratio)	Risk Cancer (slope factor*Dose)
		(pg/Kg-day)				
Toddlers (2-4 y)	Girl	0.01	0.16	0.25	0.11	
	Boy	0.09	0.16	0.26	0.11	
Children (5-11 y)	Girl	0.10	0.03	0.13	0.05	
	Boy	0.09	0.02	0.12	0.05	
Adults (> o = 20 y)	Female	0.04	0.01	0.05	0.02	5.1 in 100,000
	Male	0.04	0.01	0.04	0.02	4.4 in 100,000

Risk characterization
Brick kilns

INSTITUTO NACIONAL DE ECOLOGÍA Y CAMBIO CLIMÁTICO

Receptors/ Pathways	Gender	Inhalation	Ingestion (soil)	Total dose (air +dust)	Risk non cancer (Hazard ratio)	Risk Cancer (slope factor*Dose)
		(pg/Kg-day)				
Toddlers (2-4 y)	Girl	3.15	0.12	3.27*	1.42	
	Boy	3.02	0.12	3.14*	1.37	
Children (5-11 y)	Girl	3.19	0.02	3.21*	1.39	
	Boy	2.96	0.02	2.98*	1.29	
Adults (> o = 20 y)	Female	1.32	0.008	1.32	0.5	132 in 100,000
	Male	1.14	0.007	1.15	0.6	115 in 100,000

*** Above WHO: 2.3 pg/kg-day Tolerable daily intake**

CONCLUSIONS AND RECOMENDATIONS

Open fires for cooking

INSTITUTO NACIONAL DE ECOLOGÍA Y CAMBIO CLIMÁTICO

- Use of indoor cooking fires may pose a significant health risk due to the levels of smoke and PM2.5
- The risk for the exposure to PCDD/F is considered essentially negligible even for worst case scenarios
- It would be valuable to repeat the estimation using the inhalation and ingestion rates for the Mexican population

Brick kilns

- According to this conservative scenario the risk is not acceptable for PCDD/F
- Therefore, further work needs to be done in order to assess risk including:
  - –Determine the risk with real scenarios and check if the risk is still high
  - – Conduct a personal exposure study with different age group
  - – Determine PCDD/F ambient concentration
  - – Carry out a food intake analyses (i.e. measure PCDD/F in chicken eggs)

General recommendations

INSTITUTO NACIONAL DE ECOLOGÍA
Y CAMBIO CLIMÁTICO

- Based on existing reports, the risk for the exposure to PAHs and PM2.5 need to be evaluated
- Background dose for PCDD/F at domestic level from diet needs to be evaluated.
- Factors associated to the risk and related to poverty for these communities needs to be considered

Risk Assessment and Risk Management: Applications and Practices in the Philippines

DENR – Environmental Management Bureau
Department of Health

University of the Philippines - Manila

Chulabhorn Research Institute (CRI)
Bangkok, Thailand
7-8 November 2012

Purpose

Overall, Risk Assessment and Risk Management as scientific and technical method or tool, respectively are used by the regulatory body as part of the decision-making process and managing the use of chemicals in a selective and discretionary manner to ensure public protection against unacceptable risks to health, safety, security and environment.

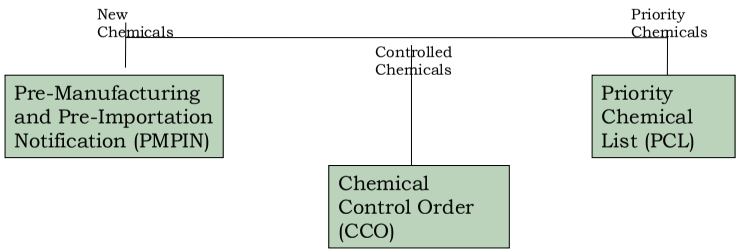
Applications and Practices

A. Regulation of new and existing (priority and controlled) substances

B. Chemical Emergencies

C. Research and Policy Development

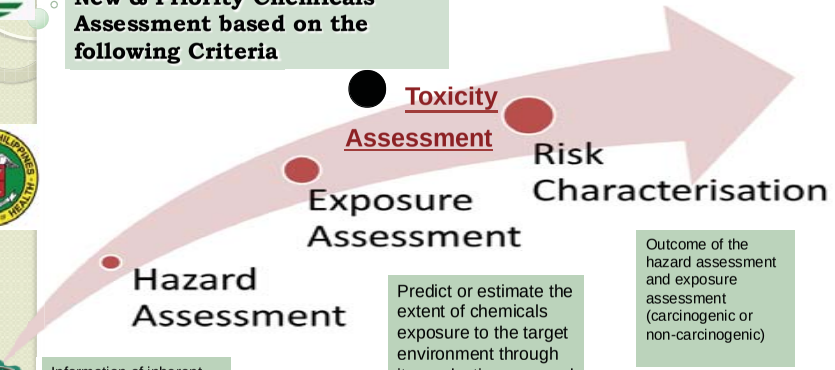
A. REPUBLIC ACT 6969
Toxic Substances and Hazardous and Nuclear Wastes Control Act of 1990
Title II Toxic Chemicals under DAO No. 92-29



Risk-Based Regulatory System for Industrial Chemical Substances

A. Regulatory Risk Assessment

New & Priority Chemicals Assessment based on the following Criteria



Information of inherent properties (Physical & Chemical Characteristics) - Nature of the physical (flammable), health (carcinogen) or environmental (aquatic) hazards + dose-response relationship

HAZARD ASSESSMENT BASED ON REVIEW OF LITERATURE - Item 2 (HAZARD IDENTIFICATION) of SAFETY DATA SHEET/ MATERIAL SAFETY DATA SHEET

Predict or estimate the extent of chemicals exposure to the target environment through its production, use and disposal + Toxicity Assessment

Outcome of the hazard assessment and exposure assessment (carcinogenic or non-carcinogenic)

Industrial Applications and Practices – Risk Management and Risk Communication

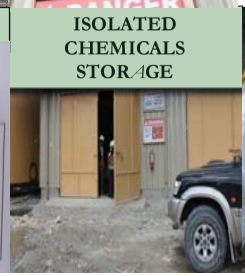
CONTAINERS AND FACILITY LABELING

Preventive and Control Measures

- Labeling
- Storage
- Pollution Control
- Treatment and Disposal
- Personal Protective Equipment
- Good Housekeeping Practices
- Self-Monitoring, Reporting and Recordkeeping

PPEs

ISOLATED CHEMICALS STORAGE



B. Chemical Emergencies

Cases of oil spills

Exposure Medium/Exposure Route	Residential Population
Ground water	
Ingestion	L
Inhalation	L
Sediment/Soil	
Skin absorption	L
Incidental Ingestion	L,C
Food	
Ingestion	L, C

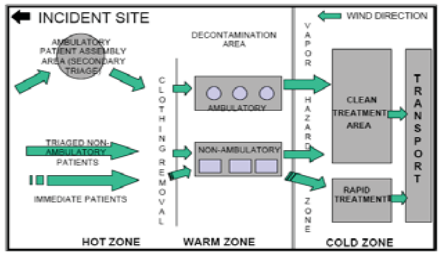
EXPOSURE ROUTES

Where: L = lifetime exposure
C = exposure in children may be significantly higher than in adults

C. Research and Policy Formulation

Risk Assessment and Risk Management are used as basis for research and policy-advisory development for:

- Post-spill/clean-up environmental site assessment
- Clean up goal or guidelines was applied to evaluate acceptable environmental criteria on "how clean is clean"
- Restoration, remediation and rehabilitation plan for the short and long-term period was proposed for the affected areas
- Existing guidelines for seafood safety had been established on an oil-spill incident and post-incident situations.



SCENARIOS

1 - Detection on the presence of Endosulfan

2- Breakage during the retrieval operation and possible and potential chemical spills in the sea

3- Chemical spills reaching the land

ACTION PLAN

Continuous monitoring of water quality/ sampling and sediments established at strategic points to determine level and extent of pollution – DENR-EMB.

Perform toxicity evaluation of other chemicals in the cargo - DOH

Conduct regular assessment on the level of risk on public health on endosulfan.

Strengthen public health surveillance in nearby communities.

A health advisories to the community on preventive and protective measures in handling possible chemical exposures.

- Water quality and sediments sampling and analysis - DENR

DAO 2009-02 – Advisory on temporary banning the importation and use of endosulfan.

EXPOSURE ASSESSMENT

Small-Scale Gold Mining

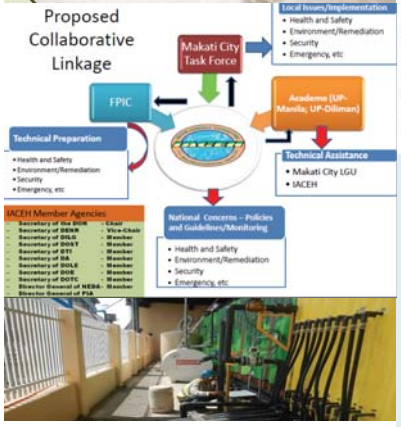
Fish Advisory Calculations:

			Consumption limit (g of fish/d	
Kg BW	caraballas	bangsi	bilong-bilong	budburon
	(0.0116 ug/g)	(0.0131 ug/g)	(0.0233 ug/g)	(0.065 ug/g)
<20 kg	107.76	95.42	53.65	19.23
21-<40	262.93	232.82	130.90	46.92
41- <60	435.34	385.50	216.74	77.69
61-<80	607.76	538.17	302.58	108.46
81- <90	737.07	652.67	366.95	131.54
> 90	784.48	694.66	390.56	140.00

- A fish advisory was provided to the local government unit
- Fish advisory not intended to replace fish in the diet but reduce consumption of fish with higher Me-Hg concentrations or dietary restrictions as advised to pregnant and lactating mothers, children and women of reproductive ages (NRC, 2000)

EXPOSURE ASSESSMENT

Pipeline Leak of Petroleum Substances in Makati City



Multi-Phase Extraction Technology for the Clean-Up

HUMAN HEALTH RISK ASSESSMENT

Activities Undertaken:

1. **Environmental Site Assessment Study**
2. **Vapor Intrusion**
3. **Human Health Risk Assessment (USEPA)**
   a. **Chemicals of Potential Concern**
   b. **Exposure Assessment**
   c. **Toxicity Assessment**
   d. **Risk Characterization**
      - **Carcinogenic**
      - **Non-Carcinogenic**
   e. **Remediation Action Goals**

Risk Characterization and Remedial Goals,Petroleum Leak

Chemical of Concern (HI)	Target Organ Basis
Benzene (8), TPH (C10-14) (225)	Blood
Benzene (8)	Immune system
Toluene (1), TPH (C10-14) (225)	Kidney
1,3,5 trimethylbenzene (0.5), TPH (C6-9) (0.2) TPH (C10-14) (225), TPH (C15-28) (6), TPH (C29-36) (95)	Liver

Groundwater COC	Remedial Goals (ug/L)
1,3,5-trimethylbenzene	476
Benzene	528
Toluene	6,895
Total Petroleum Hydrocarbons (TPH)	Remove to the extent practicable, until no measurable product thickness in monitoring

Creation of an Inter-Agency Task Force

Review of the Environmental Technology Verification (ETV) for the MPE

Provisional Reference Guidelines for Inhalation
ATSDR MRLs for inhalation:
Acute 0.009 ppm (0.029 mg/m³)
Intermediate 0.006 ppm (0.0195 mg/m³)
Chronic 0.003 ppm (0.00975 mg/m³)

Proposed Effluent Limitation for Benzene: Maximum Value (except hydrostatic testing dischargers) 5.0 ug/L
Proposed Effluent Limitation for BTEX (sum of Benzene, Toluene, Ethylbenzene, and m,p,o-Xylenes): Maximum Value 100 ug/L

Government Coordination Mechanisms

IATAC	• **Inter-Agency Technical Advisory Council of RA6969** • DENR, DOH, DTI, DOST, DND, DFA, DOLE, DOF, DA, Director of PNRI, Representative from the non-governmental organization on health and safety
IAC	• **Inter-Agency Committee on Occupational Safety and Health** • DOH-NCDCS, UP NPCIS, ECOP, LACC, FFW, TUCP, TUPAS, PCOM, IIRR, QCISCI, IOHSAD
PPTAC	• **Pesticide Policy and Technical Advisory Committee** • DENR, DOH, DOLE

Gaps and Problems

- **Limited or unknown sources of information drawn from epidemiological, environmental and toxicological data in the country.**
- **Limited capacity building and expertise in the use of Risk Assessment and Risk Management**
- **Limited public awareness raising and consciousness/attitudes on matters pertaining to hazards and risks of chemicals**
- **Limited resources in addressing, implementing and sustaining the risk assessment's results and recommendations.**

General Recommendations

- Strengthening capacity-building of APEC Regulators participants from basic (2012) to intermediate and advance modules of Risk Assessment (RA) and Risk Management (RM) depending on the outcome of this introductory level training-workshop and the common needs and requirements of countries.
- Adoption of a standard Risk Assessment Guidelines and Procedures for industrial applications to be used by countries.
- Consideration of Risk Assessment Procedures in the regular review and evaluation of high importation and production of toxic chemicals without any regulatory or interim approval from importing countries on or before the year 2020.

General Recommendations

- Establishment of reference laboratory and coordinating center for risk assessment and risk management in the Region.
- Strengthen capacity for environmental (aquatic) toxicity testing and epidemiology studies.
- Funding support for related research activities.
- Access and availability of information, research studies and database for the Region.

Specific Recommendations

Based on the highlighted case of oil spills :

- Conduct of Environmental Monitoring for Oil Spill Incidents for a minimum of two years at least

- Preparation of Seafood Management Action Plan
  - Seafood banning advisories
  - Level of concerns
  - Lifting of restrictions

- Risk Management in Oil Spill Incidents
  - Risk Assessment
  - Remediation and clean-up action goals

U.S. TSCA New Chemicals Program

Scope of the Program and Authorities

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Overview of TSCA New Chemicals Program

- Initiated in 1979 with publication of the TSCA Inventory.
- New chemical notifications must be submitted to EPA for substances not on the TSCA Inventory.
- "Chemical substances" includes new intergeneric microorganisms.
- Not a registration program – it is a notification program that provides for EPA review.

PMN and MCAN New Chemical Notifications

- TSCA requires a manufacturer or importer of a new chemical substance to submit a "premanufacture notice" (PMN) or Microbial Commercial Activity Notice (MCAN) to EPA 90 days before the date of intended start of production or import of the subject substance.
- During that 90-day review period, EPA assesses whether the manufacture, processing, distribution in commerce, use or disposal of the substance presents or may present an unreasonable risk to human health or the environment.

PMN Exemptions

- **PMN or MCAN Not Required for:**
  - R&D Chemicals
  - Exempted Polymers of Low Concern (only annual reporting)
- **Submission of Exemption Application Required:**
  - Low Volume (≤ 10,000 Kg/Yr) - 30 Day Review
  - Low Release/Exposure (LOREX) - 30 Day Review
  - Test Market Exemption (TME) - 45 Day Review
  - Tier I and Tier 2 Biotechnology Exemptions
- For exemption applications, EPA also assesses whether the manufacture, processing, distribution in commerce, use or disposal of the substance presents or may present an unreasonable risk to human health or the environment.

Information Required to Be Submitted by a Manufacturer

- Chemical Identity
- By-products and impurities
- Estimated production/import volume
- Proposed uses and amounts for each use
- Human exposure information
- Disposal methods and estimates of releases to the environment
- Existing test data in notifier's possession or control concerning human and environmental effects
- Pollution Prevention/Safer Substitutes information

5

Objectives of EPA's Assessments

- Questions asked:
  - Does sufficient information exist to evaluate the human health and environmental effects of the substance?
  - Does the substance present an unreasonable risk of injury to health or the environment (hazard + exposure = risk)?
  - Will the substance be produced in substantial quantities, and (a)enter the environment in substantial quantities or (b) may there be significant or substantial human exposure?
- If EPA does make an unreasonable risk finding or a substantial exposure/release finding, EPA efforts focus on developing risk management options that allow the substance to go into commerce in a manner that protects health and the environment.
- If EPA does not find a basis for an unreasonable risk or a substantial exposure/release finding, the new substance may enter U.S. commerce unrestricted.

6

Overview of EPA Assessments

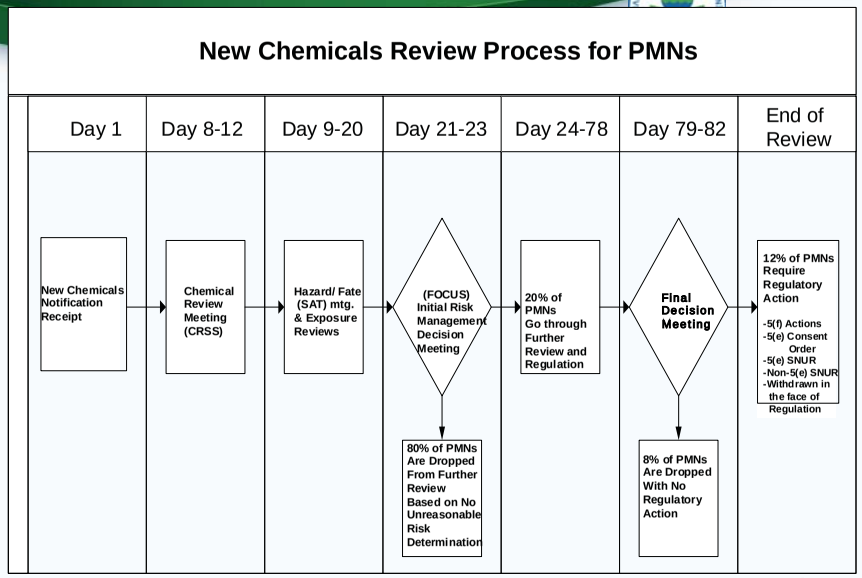
- TSCA requires new chemical manufacturers to submit only studies/data in their possession or control (i.e., no minimum set of toxicity or fate studies are required).
- Because no test data are required to be submitted with a notification, predictive models/technical tools and professional judgment must be utilized by EPA to assess potential risks.
- Evaluation of risks from new chemicals are considered throughout their product life cycle.
- EPA focuses on exposure to workers, site-specific assessment of environmental and general population exposure, and consumer exposure (using models).

7

Factors that EPA Considers in Taking Regulatory Action

- Magnitude/Type of risk
- Number/Types of individuals exposed
- Availability of substitutes (relative risks)
- Benefits (environmental/human health)
- Other potential uses (might they increase risks?)
- Regulatory History (Consistency in risk management decisions)

8

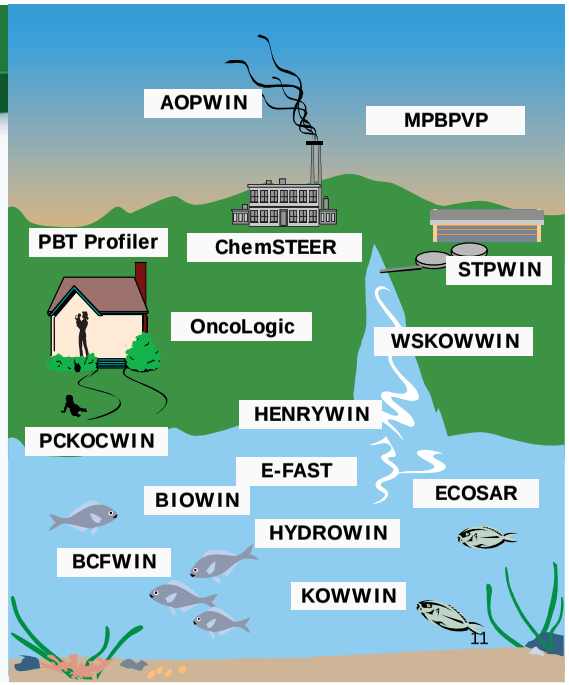


EPA's Assessment Models

- Regulatory decisions are often made in the absence of data
  - ~80% of notifications submitted with no test data; over the past 8 years, ~16% of notifications included human health tox data and ~10% included ecotoxicity data
- Therefore, EPA uses a suite of tools and computer models coupled with in-house expertise and databases on analogous chemicals to predict hazards and exposures.
  - Exposure assessment models are used to estimate worker, general population, and consumer exposures using both standard (default) scenarios and case-specific assessments.
  - Structure Activity Relationship (SAR) analysis is used in lieu of test data to assess hazard and environmental fate.
- Models and databases have been developed over a 30-year period by EPA and others in the scientific and technical community to screen new chemicals in the presence of limited data.

New Chemicals Models/Tools

- Once released, will the chemical go to air, water, soil, sediment?
- How long will the chemical stay in media?
- Will the chemical present a hazard?
- Could this be a PBT?
- Who will be exposed and for how long?



NCP Regulatory Outcomes

- **Regulatory Options for PMNs and MCANs**
  - Drop from further review
  - Drop with a concern letter
  - Regulate pending development of information:
    - Unilateral § 5(e) order (prohibit or limit manufacture pending testing)
    - Negotiated § 5(e) consent order based on unreasonable risk coupled with a § 5(a)(2) Significant New Use Rule (SNUR)
    - Negotiated § 5(e) consent order based on substantial exposure and/or release
    - Stand-alone § 5(a)(2) Significant New Use Rule (SNUR)
  - § 5(f) action to ban or limit manufacture
- **Regulatory Options for Exemption Applications**
  - Grant
  - Grant with Conditions
  - Deny

Potential Control Measures in Risk-based §5(e) Consent Orders

- Testing, triggered at a certain production volume
- Protective equipment requirements for worker protection
- New Chemical Exposure Limit (NCEL) for worker protection
- Worker training programs
- Distribution/use restrictions
- Restrictions on releases to water, air, and land
- Recordkeeping requirements

Since 1979…

- **TSCA Inventory**
  - Original TSCA Inventory: ~62,000 substances
  - New Chemicals added since 1979: >22,000
  - Total Chemicals now on TSCA Inventory: >84,000
  - New Chemicals as a % of the TSCA Inventory: 27%
- **New Chemical Notifications Reviewed (as of Sept. 2012)**
  - Total valid PMN Notifications: ~37,700
  - Total valid Significant New Use Notices (SNUNs): 61
  - Total valid Exemption Notifications: ~14,600 (Includes ~2,500 polymer exemption notifications received prior to March 30, 1995)
  - Total valid Notifications reviewed: ~52,300
  - EPA now reviews about 1,000 PMNs/Exemptions per year
- **Regulatory Outcomes (as of Sept. 2012)**
  - Number of 5(e) Consent Orders signed: >1,500
  - Number of SNURs issued: >1,700
  - PMNs withdrawn, often in face of regulatory action: ~1,900

Electronic Premanufacture Notice (e-PMN) Software

- e-PMN Final Rule – effective 4/6/2010
  - Must use the new e-TSCA/e-PMN software to prepare new submissions after 4/6/2010
  - Electronic submissions are made via EPA's Central Data Exchange (CDX)
  - Electronic submissions were phased in over 2 year period:
    - EPA accepted CDX submissions at any time
    - CDX became mandatory after 4/6/2012
    - EPA accepted paper submissions until 4/6/2011
    - EPA accepted CD submissions until 4/6/2012
- A new version of the e-PMN software will be made available in early 2013

Thank you