Appendix A: International Risk Assessment

This appendix provides a snapshot of how other countries and international agencies practice health risk assessments. It highlights the risk assessment of chemical carcinogens because the methodologies for that type of assessment are better developed than those for other health endpoints. It also focuses on the various types of health risk assessment used by different countries and international bodies, specifically noting those cases in which quantitative risk assessments (QRAs) are employed. The definition of a QRA is subject to controversy and differs from country to country. For the purposes of this discussion, a risk assessment is characterized as quantitative when it generates numerical estimates relating the risk of developing cancer to particular levels of exposure to a chemical. Adding to the lack of uniformity internationally is the fact that countries and international bodies involved in monitoring human exposure to chemical carcinogens and other toxic substances have adopted their own processes of health risk assessment. The differences in their methods and definitions are due to a number of variables, including legislative and regulatory histories, government structure, public involvement, research and development, and cultural characteristics.

The information used to generate this appendix was obtained through written and oral correspondence with the relevant officials in each of the countries and international bodies that the Office of Technology Assessment (OTA) surveyed. OTA chose the countries and organizations that participated based on their activity in the field of risk assessment and availability of resources. A minimum of three sources for each country or body was examined; the same sources also had an opportunity to review and comment on a draft of this text.

How do these countries approach risk assessment? An important prerequisite for many of them in conducting QRAs is knowledge about the mechanism of carcinogenic action of a substance. Usually, only QRAs are performed for genotoxic carcinogens.[1] In addition, many industrialized nations that regulate chemical carcinogens tend to use a case-by-case approach: each chemical is subjected to an individual review that considers cancer mechanisms. Such countries as the United Kingdom and Germany rely primarily on expert judgment in risk assessments and regulatory decisionmaking, The risk assessment process in those nations involves the formation of expert advisory committees that make the actual decisions regarding exposure standards or regulations instead of the agencies. Those advisory bodies commonly use a ‘‘ weight-of-the-evidence’ approach, in which all of the available information and test data are evaluated in formulating a decision concerning a carcinogen.

Finally, the countries OTA surveyed support a variety of regulatory agencies, a characteristic common to the United States as well. As a result, just as the

[1] When a carcinogen acts by a genotoxic mechanism, it damages DNA and causes genetic changes (e.g., mutation of a gene), which may in turn lead to the abnormal development of human cells that may serve as a precursor for cancer (see ch. 2).

use (or nonuse) of QRA may differ among countries, QRA policies among a country's regulatory organizations may also vary. Because one agency uses QRA does not mean that other regulatory bodies in the same country also practice it. Moreover, regulatory organizations may use QRA for different purposes to develop standards of exposure or to establish regulatory or research priorities.

INTERNATIONAL BODIES AND RISK ASSESSMENT

Their increasing awareness of the risk of exposure to toxic chemicals has led several international bodies to develop programs addressing the need to identify, monitor, and assess toxic agents. The focus of each program differs, based on its structure and clientele. Nevertheless, these international bodies, along with regulatory agencies in the United States and other countries, have developed significant collaborations in fulfilling their overall missions to protect humans from exposure to hazardous substances.

The activities of these organizations encompass collecting data on hazardous chemicals, evaluating additives and pesticide residues in food, labeling and classifying both new and old chemicals, reviewing occupational exposure to hazardous chemicals, and promulgating guidelines for assessing chemicals. Much of the work of these international organizations is targeted at improving trade between countries by promoting the use of standardized testing, classification, and labeling procedures. OTA, in the following discussion, focuses on the more prominent chemical risk reduction programs and highlights any use of human health risk assessment, either qualitative or quantitative. The United States makes a substantial contribution to many of these organziations (table A-l). We emphasize the regulation of exposures to carcinogens, but not to the exclusion of noncarcinogenic chemicals.

International Agency for Research on Cancer

As part of the World Health Organization (WHO), the International Agency for Research on Cancer (IARC) was established in 1965 to promote international collaboration in cancer research. The main activities of IARC currently encompass collecting and disseminating data on cancer occurrence, searching for the causes of cancer, and conducting research aimed at preventing cancer. IARC is also exploring other aspects of cancer, including mechanistic aspects of carcinogenesis, genetic disposition toward cancer, and quantitative estimation and prediction (QEP) of cancer risks. QEP is IARC's approach to quantitative risk assessment.

Currently, 16 participating nations contribute resources for research and provide expert advice to IARC (IARC, 1991). Participating states also make financial contributions. Yet, despite that assistance, the agency reports that it is experiencing financial difficulties, which makes it difficult to recruit additional personnel to pursue all of its objectives. Notwithstanding these problems, the agency has initiated some new projects and is continuing those already under way (IARC, 1992b).

In addition to its affiliation with participating countries, IARC is also involved in numerous collaborations with other international agencies and national institutes. Numerous countries, especially those lacking resources, use publications containing the agency's evaluations and classifications of chemical carcinogens in formulating their policies on carcinogens.

Although IARC does not perform risk assessments in their entirety, it serves an important role in the initial stage of risk assessment—that is, in hazard identification of carcinogens using rodent bioassays. Participating countries, including the United States, conduct them and submit the results to IARC for review, evaluation, and publication in its series ***Monographs on the Evaluation of Carcinogenic Risks to Humans. During*** its review and evaluation process, IARC subjects chemicals to a classification scheme it developed to characterize their degree of carcinogenicity. One of the agency's major accomplishments has been establishing a process for evaluating and analyzing data based on the consensus of multidisciplinary experts and not on the basis of administrative or political concerns (Richter and Goldsmith, 1991).

IARC's *Monographs series is* one of its most important contributions to cancer research, To date, IARC has published 57 volumes of the series, which qualitatively evaluates and classifies more than 750 agents and complex exposures for carcinogenicity (IARC, 1993). The process begins by choosing candidates for hazard identification and classification from

Table A-l—Assessed and Voluntary Contributions by the United States to International Organizations

	1991 assessed (millions of U.S. dollars)	Percentage of total budget	Voluntary[b]	1992 assessed (millions of U.S. dollars)	Percentage of total budget	Voluntary
World Health Organization	$78.3	25%	N/A	$94.2	25 %	N/A
Organisation for Economic Cooperation and Development. . . .	45.6	25	$0.015	44.6	25	$0.005
International Labor Organisation	61.8	25	N/A	N/A	N/A	N/A
Food and Agriculture Organization . . .	70.0	25	N/A	N/A	N/A	N/A
Pan American Health Organization . .	42.0	61	N/A	45.4	61	N/A
International Agency for Research on Cancer	1.4	10	N/A	1.5	11	N/A

NOTE: N/A- not available.
[a] In many cases, there is a cap of 25 percent on the total budget percentage that the United States may contribute to an organization.
[b] Totals are incomplete. Voluntary contributions originate from a variety of sources, not necessarily the Federal Government.

SOURCE: U.S. State Department, World Health Organization/International Programme on Chemical Safety, 1993.

the results of surveys sent to governments of participating countries and to cancer experts (Richter and Goldsmith, 1991). IARC then uses international working groups of experts to evaluate a selected number of agents or exposures. The categorization of an agent or exposure is a matter of scientific judgment, reflecting the strength of the evidence derived from studies in humans, studies in experimental animals, and other relevant data. In cases in which there is sufficient evidence of human carcinogenicity, an agent or exposure is classified as carcinogenic to humans. Subsequent categories characterize agents as probably or possibly carcinogenic to humans, impossible to classify, and probably noncarcinogenic to humans (IARC, 1992a).

In the area of quantitative risk assessment, IARC is planning a workshop entitled 'Scientific Principles of Quantitative Risk Estimation and Prediction of Carcinogenic Risk' in October 1993. The workshop's main product will be a comprehensive publication on the scientific bases and state-of-the-art of QEP. Its main focus will be to review existing methods, but it will also describe the relevance of QEP for policy setting and attempt to provide some scientifically based guidelines for the use of QEP. The publication will be designed for a wide audience, including the scientific community, regulators, and national governments (IARC, 1992c). In addition, the workshop will serve as a forum to discuss and recommend the extent to which IARC should be involved in developing and conducting QEP (specifically, whether the state-of-the-art allows the definition of a scientific procedure) (IARC, 1992c).

The European Community

The European Community's (EC) pursuit of a unified internal market has forced it to address environmental issues directly. As a consequence, the EC has been working toward the "harmonization' of health, safety, and environmental regulations, to reduce competitive imbalances among EC countries and keep regulations from acting as trade barriers (U.S. Congress, OTA, 1992) (box A-l). The EC has also sought to protect the public and the working population from exposure to hazardous chemicals. With all of this in mind, the EC has turned to risk assessment for determining g standards of exposure and levels of risk and for harmonizing testing standards for chemicals.

EC legislation pertaining to human health risk assessments has been mainly directed at: chemical safety, pesticide residues, food additives, and occupational exposure to chemicals. A common characteristic of most of the directives passed or proposed in those fields is that the member states or individual employers are responsible for performing any risk assessments, not the EC, Bodies of experts are used throughout this process, both by those performing the risk assessments and by the EC to design its directives and evaluate the end results.

EC directives mandate both qualitative and quantitative risk assessments, depending on the type of chemical and its usage. In the area of chemical control

Box A-l-Organization of the European Community

The European Community, which was established by a series of treaties in the 1950s, currently has 12 members, all Western European countries. Representatives of these member states serve on the various committees and institutions that comprise the EC. In addition to its select membership, the EC is unique among international bodies in that it has the power to mandate the adoption of its legislation by member states.

The EC legislates through regulations, directives, decisions, and recommendations. Regulations, the most stringent of the EC's legislation, mandate compliance by EC member states in direct accordance with the language of the regulation. Directives, which are the most common form of environmental legislation, are also binding on member states. However, member states have varying degrees of technological capability for complying with EC directives and in addition are free to choose a method of national implementation. Those factors and the EC's limited enforcement mechanisms can lead to significant time delays in a member state's compliance with a directive, despite assistance provided through temporary exceptions or financial support.

The original Treaty of Rome, which created the EC, did not include an explicit legal basis for addressing environmental issues. That deficit was remedied by the adoption of the 1987 Single European Act (SEA). The SEA, which amended the Treaty of Rome, addressed further areas of fragmentation and noncooperation within the EC and included an environmental amendment to the original treaty. The act codified a basis for the EC to require that members harmonize their national environmental regulations. It also allowed the EC to create environmental laws when the preservation of the environment was better ensured by its actions than by those of individual countries.

Before and after the existence of the SEA, the EC has approached the growing need for environmental legislation by developing environmental action programs. The first program was ratified in 1973, and the fifth was adopted in 1992. These programs have addressed a wide range of environmental regulation, including air, water, chemicals, waste, wildlife, environmental assessments, and site safety. To date, nearly 300 environment-related directives have been passed, but fewer have actually been implemented by the member states.

EC policy is executed by the European Commission, which has about 20 divisions or directorates-generals. The Environment Directorate-General is knownasDG-XI(11) and is somewhat similar to the U.S. Environmental Protection Agency. But, in response to a growing need for a centralized body to deal with environmental matters, an European Environment Agency (EEA) has been planned since 1990, with the role of collecting information and providing objective and comparative data on the state of the environment in member states. Unlike the U.S. EPA EEA is not designed to have enforcement power and will operate on a first-year budget of only $1.4 million, compared with to the U.S. EPA's current $6.5 billion. The EEA also lacks the authority to fund research, but supporters hope that it will eventuality be able to direct projects aimed at filling gaps in its database. Ironically, EEA has yet to begin collecting and disseminating data because of an ongoing debate about its geographic location.

SOURCES: Commission of the European Communities, 1990. Completing the single market: The removal of technical barriers to trade within the European Economic Community (Brussels); Hurwitz, L. 1992. The European Community and the Single European Act of 19S7: What Does It Mean? *Phi Kappa Phi Journal*, spring; Keyes, C. 1991. The European Community and Environment Policy: An Introduction for Americans (Baltimore, MD: World Wildlife Publication, 1991).

and safety, very basic qualitative risk assessments are used in evaluating "new' chemicals. The EC's initial effort at environmental policy came in this area with the 1967 directive on classification, packaging, and labeling of dangerous substances. After the passage of this directive, chemical control and safety became a prominent issue in EC environmental policy. An important addition to the 1967 directive came in 1979: known as the "sixth amendment, " this document established a harmonized testing and notification scheme for new chemicals. A seventh amendment, which further updates EC guidelines for chemical testing and assessment, was approved in April 1992 (Official Journal of the EC, 1992).

The EC's procedure for chemical testing was an important advance in harmonizing the chemical assessment guidelines of the various member nations, and, subsequently, the 1967 directive and its compo-

nents have served as a model for environmental regulation in other countries and through international organizations (e.g., the Organisation for Economic Co-operation and Development (OECD)) (CEC, 1987). The EC's tests mainly identify hazardous chemicals (box A-2). Qualitative risk assessments can be performed if more data are available, but risk assessments evaluating new chemicals are usually quite minimal. The results of these assessments, along with additional data on the chemical, are circulated among the EC member states to allow them to challenge the chemical's approval if they find fault with the information. These data may also be used to set priorities for testing.

In regulating workplace exposure to hazardous chemicals, EC directives mandate that employers perform risk assessments to determine occupational exposure limits (OELs) for toxic substances.[2] At this point, QRA has been performed by industry for genotoxic carcinogens for which there are sufficient data. In these cases, ad hoc expert advisory bodies are used on a case-by-case basis. Experts also determine no-observed-adverse-effect levels (NOAELs)[3] for nongenotoxic carcinogens and other toxic noncarcinogenic chemicals on a case-by-case basis. These figures are subsequently translated into OEL using the appropriate variables (Haigh, 1992).

One EC Council directive governs food additives. This framework directive requires that the EC consult a scientific expert body, the Scientific Committee on Food, on any matter that might affect public health. In practice, this legislation means that no food additive can be approved for use in the EC without a positive evaluation of its safety.

Risk assessments for food additives are generally qualitative and follow the determination of a NOAEL on the basis of extensive toxicity data. Industry (as a supplier or user) must provide the data, and the EC expert body evaluates them. The scope of the data required is similar to that required by WHO and other international groups that evaluate food additives (Official Journal of the EC, 1980). EC guidelines toward pesticide residues are based on WHO principles. The EC addresses the approach used in the case of the majority of pesticides in which the acceptable daily intake (ADI) is based on a chronic effect and this value is combined with other data to develop a maximum residue limit (MRL) for a pesticide.

The major thrusts of EC environmental policy are to ease trade barriers, protect public health, and prevent chemical accidents. As part of this agenda, the EC has played a direct role in the international harmonization of chemical testing and standardization. In addition to updating and developing new directives, there are plans under way to develop a set of harmonized procedures for member states to perform risk assessments (Murphy, 1992). Simultaneously, the EC is also involved in collaborations with other international bodies to establish harmonized risk assessment guidelines.

International Programme on Chemical Safety

The International Programme on Chemical Safety (IPCS) was officially organized in 1980 as a cooperative effort of WHO, the International Labor Organisation (ILO), and the United Nations Environment Program (UNEP) (box A-3). The program has two specific roles: to provide an international scientific consensus for assessments of chemical risks to human health and the environment and to promote the development of chemical safety measures by member states (IPCS, 1992a; Becking, 1992). In addition to coordinating IPCS's activities, the program's small staff also organizes the meetings of expert committees. Through these consensus committees, IPCS evaluates data for its publications. The resources for these activities come mostly from contributions by individual countries but also from contributions by WHO and UNEP (figure A-l).

IPCS develops environmental health criteria (EHC) that define, whenever possible, guidance values that member states may use to establish their own exposure limits for chemicals (Mercier, 1992). An EHC document primarily provides evaluated scientific information on a particular chemical that a member state may use to implement its own chemical safety program and determine national exposure standards or regulations.

2 OELs are limits set by government agencies to protect workers from occupational exposure to hazardous substances found in the workplace.

3 The NOAEL for a chemical is the highest dose tested in which no adverse effect is observed. The no-observed-effect level (NOEL) is the highest dose tested in which no health effect is observed.

Box A-2–Research in the European Community

The organizational structure of the European Community for research and technological development covers many disciplines and promotes joint research between research teams across member states. Since 1984, the EC has organized those activities through muitiyear framework programs that comprise multipl;e areas of research. Currently, the EC is in its Third Framework Program (1990-94) and is involved in research in 15 major areas.

The EC's first framework program was initiated in 1984, but it was the 1987 Single European Act that amended the founding EC treaty to include specific mention of an EC research and technological development strategy. With the development of this policy came some important trademarks of EC research. First, the development of the EC's framework programs is based on the expert advice of industry, the scientific community, and public authorities. The EC encourages research participants from these three groups; in addition, EC-sponsored research requires the collaboration of scientists from at least two different member states.

EC research funding comes in three forms: shared-cost projects in which the EC pays up to 50 20 percent of the total costs, concerted research actions in which the EC only covers meeting or travel expenses, and in-house research atone of the four establishments of the EC's Joint Research Center (JRC). At this point, approximately 80 20 percent of the EC's research is extramural, and 20 20 percent is intramural. The total amount that the EC spends on research is less than 5 percent of the total financial resources allocated to research and development by the EC member states.

Most of the intramural environmental research takes place at the newly organized Environment institute within JRC. To date, the risk assessment-related research 20 that has taken place has been primarily in the field of nuclear safety and waste. But, the emphasis on nuclear research has since decreased, thus allowing more research in other areas reated to the environment and human health.

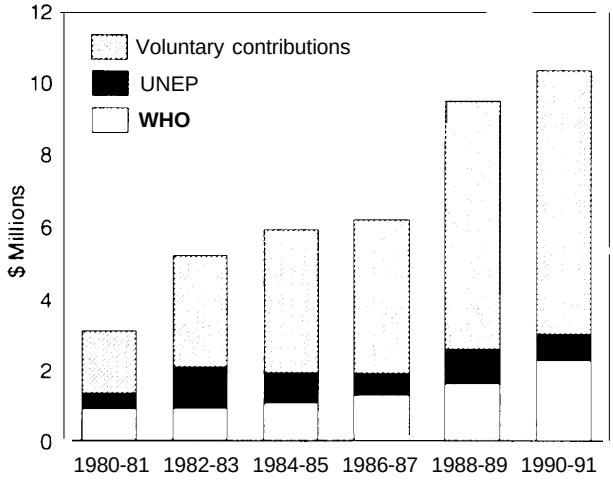
Much of the research done at JRC is in support of corresponding EC legislation, with the collaboration of the relevant directorates. The Environment Institute has worked with DG Xl, the Environment Directorate-General, in classifying various carcinogens, and there is ongoing collaboration to establish harmonized guidelines for chemical risk assessments. The Environment institute has aso extended its resources to DG V, the Health and Safety Directorate-General, to generate monographs on chemical carcinogens.

Since 1989, the Environment institute has helped collect data for determining the carcinogenicity of chemical agents. in conjunction with this work, the institute also maintains a chemical databank the Environmental Chemicals Data and information Network (ECDIN). This database contains exposure information and data on the effects of chemicas that are harmful or suspected to be hazardous to the environment or humans, or both. The database also has a specific data file on carcinogenicity.

The Maastricht Treaty, designed to enhance cooperation among member states, confirms the objective of EC research and development policy: to strengthen the scientific and technological bases of EC industry and encourage it to become more competitive internationally. Regarding issues related to the environment and health in the Fourth Framework Program (1994-98), the EC intends to improve the scientific basis of its environmental health policies and regulations, in addition to performing quantitative risk assessments for major pollutants.

SOURCES: Commission of the European Communities. 1990. completing the single market: The removal of technical barriers to trade within the European Economic Community (Brussels); Commission of the European Communities. 1991. Directorate general XII for science, research, and development. Environment 1991-1994, information package (Brussels); Commission of the European Communities. 1992. Research after Maastricht An assessment, a strategy (Luxembourg, Brussels; CEC); Commission of the European Communities. 1992. Treaty on European Union; Commission of the European Communities. 1992. EC research funding: A guide for applicants (Bon, Germany: Economica Verlag); Commission of the European Communities. 1992. Working documents of the commission concerning the fourth framework program of community activities in the field of research and technological development, 1994-199S (Brussels).

Figure A-l--Contributions to the International **Programme on Chemical Safety, 1980-91**



SOURCE: World Health Organization, *International Programme on Chemical Safety: Progress* Report (April 10, 1992), p.5.

Chemical information provided by IPCS is also available to other specialized organizations and the United Nations (Stober, 1992).

Through international consultation, IPCS sets priorities for chemicals to be assessed, based on criteria that include the threat of adverse health and environmental effects, levels of exposure, and national and international concerns. The evaluation process involves several steps, including a draft document based on available scientific literature and a consensus meeting of independent experts. The groups of experts develop consensus evaluations that are incorporated into various published documents (the more substantive being EHCs), more than 140 of which have been produced to date (IPCS, 1992b). In their deliberations, the groups consider only the scientific questions. Socioeconomic and political factors do not have a part in this process because those risk management decisions are the responsibility of member states (Becking, 1992).

The final product of this evaluation process (generally an EHC document) can be used as a reference for making regulatory health policies, especially by those countries that lack the resources to perform their own assessments. EHC documents may also be monographs addressing methodological issues. The monographs critically analyze current methods of testing and approaches to predicting health and environmental risks and discuss improved testing strategies for producing reliable and comparable results (IPCS, 1992b).

When IPCS addresses carcinogenicity, it treats both the issue of mechanism and the need to evaluate carcinogens on a case-by-case basis. In the WHO Drinking-water Quality Guidelines and the WHO Air Quality Guidelines for Europe, QRA methodology is used for estimating human exposure risks for genotoxic carcinogens (WHO, 1984; 1987a; 1989). In making those recommendations, WHO adopted some aspects of the U.S. Environmental Protection Agency (EPA) quantitative risk assessment methodology. Member states and other regulatory bodies have the prerogative to perform their own QRA.

IPCS is also responsible for the toxicological assessments of food additives and contaminants, and pesticide and veterinary drug residues that are carried out jointly by WHO (through IPCS) and the Food and Agriculture Organization (FAO). The results of these collaborations are recommendations on the levels of ingestion that are considered to be safe. They are used for setting standards, primarily through the Codex Alimentarius Commission (box A-4). Member States may also use these recommendations in setting their standards of exposure.

IPCS has a growing interest in exploring QRA methodology and in using this process to enhance its work in promoting chemical safety. A comprehensive EHC document, *Principles for the Assessment of Health Risks from Exposure to Chemicals, is* planned for publication in late 1993; the document examines QRA and the estimation of risks from epidemiology and animal data (Secretariat of IPCS, 1992; Becking, 1992). In addition, IPCS is conducting an extensive survey of human health risk assessment approaches and procedures in various countries, the results of which should be available in late 1993. The primary goal of this project is to harmonize risk assessment guidelines among different countries. That goal also applies to several of IPCS's ongoing and upcoming collaborations.

The future holds an expanded role for IPCS as a result of the Agenda 21 document adopted at the United Nations Conference on Environment and Development (UNCED) held in June 1992. Planning and discussions were held prior to the conference, specifically at a December 1991 meeting of government-

Box A-3--Organization of the International Programme on Chemical Safety

Out of the three cooperating agencies of the International Programme on Chemical Safety, the World Health Organization serves as the executing body for the program and has an important role in human health risk assessments. The International Labor Organisation coordinates with the IPCS by providing scientific support and using IPCS data in an effort to harmonize their methodology for classifying, labeling, and identifying hazardous chemicals found in the workplace. The United Nations Environment Program participates in IPCS mainly through its International Register for Potentially Toxic Chemicals, a program that prepares chemical data profiles for risk evaluation candidates and maintains a list of chemicals undergoing toxicity testing and review. The International Agency for Research on Cancer also participates in evacuating information on chemicals, but with a focus on carcinogens.

In addition to its cooperating agencies, IPCS also works closely with other international governmental and nongovernmental organizations, associations, and professional bodies that are active in the field of chemical safety. One of the more significant collaborations is with the Food and Agriculture Organization to jointly evaluate chemicals found in food. The IPCS also works closely with the Organisation for Economic Co-operation and Development, the European Community, and numerous other bodies involved in chemical risk assessment and management

IPCS's central organizing body is located within the WHO headquarters in Geneva, Switzerland, except for one section located at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. One of the roles of the central unit is to plan and coordinate work being done by the member states, often through participating institutions, or individual scientists working with IPCS. Although all member states benefit from the work of IPCS, only a small number of countries (currently 30) have actually formally agreed to support the program; fewer still provide financial aid or intellectual resources, or establish participating institutions to work with the program. Regulatory and research agencies in the United States-namely, the U.S. Environmental Protection Agency (EPA), the Food and Drug Administration, the National Institute for occupational Safety and Health, the Agency for Toxic Substances and Disease Registry, and the National Institute for Envvironmental Health Sciences--make a significant contribution to the work of IPCS, with EPA being prominent in the area of risk assessment methodology.

SOURCES: International Program on Chemical Safety (I PCS). 1992a. Information brochure; International Programme on Chemical Safety. 1992b. Progress report by the Director-General, 45th World Health Assembly. Geneva: WHO; Becking, G. 1992. International Programme on Chemical Safety: Development of Environmental Health Criteria for Lead. Research Triangle Park, NC.

designated experts, convened at the request" of the Preparatory Committee for UNCED. As a result, Chapter 19 of Agenda 21 calls for developing an intergovernmental mechanism for promoting risk assessment and management of chemicals internationally (UNEP, 1991).

In its new capacity under the Agenda 21 mandate, IPCS will coordinate an intergovernmental forum, sometime in late 1993, on the environmentally sound management of chemicals. IPCS's enhanced role will also entail undertaking technical work in this area, providing mechanisms for ensuring coordination of relevant international activities, as defined by UNCED (IPCS, 1992b). IPCS will use a series of advisory conferences to further define its new role.

Organisation for Economic Co-operation and Development

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organization of 23 industrialized countries and the EC (box A-5). Several Central and Eastern European countries participate in the activities on an observer basis. OECD was established in 1%1 to provide a forum for member counties to discuss issues of common interest and coordinate and harmonize their national policies. In 1970, this forum was officially expanded to include environmental issues with the establishment of the Environment Committee (OECD, 1989). To address the control of chemical risks to health, the OECD Environment Committee established the Chemicals

Box A--Codex Alimentarius Commission

The Codex Alimentarius Commission (CAC) is an expert body jointly supported by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), both of which are specialized agencies of the United Nations. The codex was established in 1962 to protect consumer health and ensure fair practices in the food trade. Standards promulgated by CAC most often serve as references and recommendations for less developed countries that lack resources to determine their own food standards.

CAC is an intergovernmental body composed of 137 countries. It carries out its duties related to food standards through a variety of committees. Three committees are involved in qualitative risk assessments: the Codex Committee on Pesticide Residues (CCPR), the Codex Committee on Food Additives and Contaminants (CCFAC), and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF).

The bodies that complete scientific evaluations of chemicals (but are not a part of CAC) are the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). JMPR, which is composed of scientists invited by both WHO and FAO, determines acceptable daily intake (ADIs) for additives and contaminants in food and maximum residue limits (MRLs) for pesticides in food. The scientists invited by WHO use toxicological information to develop ADIs for pesticide residues whereas FAO committee members use Good Agricultural Practices data to develop MRLs for pesticide residues in food commodities. The information developed by JMPR, which is purely scientific, is passed on to CCPR for consideration in establishing standards.

Participants in sessions of CCPR are delegates from member States. CCPR considers the recommendations of JMPR and generally adopts MRLs that JMPR has developed. These recommendations go through a long stepwise procedure that, in most cases, ultimately results in the adoption of MRLs by CAC. CAC and its committees are much more politically oriented and make recommendations about exposure after considering nonscientific variables (Kaferstein, personal communication). The entire procedure surrounding the development and adoption of MRLs takes several years to complete.

JECFA operates in much the same way as JMPR, except that FAO representatives develop specifications for the identity and purity of food additives. The JECFA's Scientific evaluations are passed along to CCFAC, which operates in a manner similar to that of CCPR. Principles for assessing food additives and contaminants and for pesticide residues have been prepared by the International Programme on Chemical Safety and published by WHO.

SOURCES: World Health Organization. Description of the Joint FAO/WHO Expert Committee on Food Additives and the Codex Alimentarius Commission, 1992; World Health Organization. Guidelines for Drinking Water Quality, Vol. 1 (Geneva: WHO, 1984); World Health Organization. Principles for the Safety Assessment of Food Additives and Contaminants in Food. IPCS Environmental Health Criteria No. 70; Geneva, World Health Organization, 1987; World Health Organization. Description of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and the Codex Alimentarius Commission, 1992b.

Programme in 1971. In its evaluations, the Chemicals Programme does not perform risk assessments; rather, it focuses more on identifying chemicals that pose hazards to both man and the environment and the needs of management. One of the Chemical Programme's early accomplishments was the creation of the Chemicals Testing Program in 1978 to prepare "state-of-the-art" reports on the best testing methods for generating data useful for the hazard assessment of a chemical. The program test developed guidelines and these are being continuously updated as new methods and technologies come into practice (OECD, 1989; Visser, 1992).

In addition to guidelines for assessing new chemicals, the Chemicals Programme has also promulgated principles for good laboratory practice (GLP) (Visser, 1992). The testing guidelines, in combination with GLP, provided support for the decision by the OECD council on mutual acceptance of data among member countries. That decision states that data generated during the testing of chemicals in an OECD member country in accordance with OECD test guidelines and

Box A-5--Organization of the OECD

The central authority of the Organisation for Economic Co-operation (OECD) and Development is the Council, a body composed of representatives of each of the member countries and the CEC. The Council and OECD itself operate by consensus in part because OECD is not a supranational organization but a center for discussion in which governments express their views, share information, and seek to harmonize policies. in some instances, the Council may wish to formally state its consensus, and in those eases, it publishes a decision or a recommendation. Because the Council works by consensus, its actions often take a long time to prepare. As a basis for its decisions, the Council adopts the standards employed by its most advanced members. consequently, decisions are more substantive for countries with less developed environmental legislation and regulations. in contrast to decisions, recommendations are not legally binding, but countries must consider them very seriously. Environmental issues are addressed through both mechanisms.

Much of the Council's supporting work is done by working parties, expert advisory groups, and committees. Committees that cover expansive topics are further divided into specific groups, such as the Chemicals Group. The main focus of the Chemicals Programme is generating information about specific chemicals, preventing and reducing the risk of exposure to chemicals, and harmonizing chemical testing procedures to reduce trade barriers and minimize duplicative testing among member countries.

SOURCES: Organisation for Economic Co-operation and Development, Environment Directorate, OECD Co-operative Risk Reduction Activities. Paris, 1992; Organisation for Economic b-operation and Development. OECD Environment Directorate. Chemicals Division, The OECD Chemicals Programme. Paris: OECD, 19S9.

GLP shall be accepted in other member countries for purposes of assessment and other uses relating to the protection of man and the environment (OECD, 1989).

OECD member countries that comply with the council's decision and the recommendations for testing guidelines and GLP apply these approaches to several types of chemicals, including pesticides, drugs, and food additives. The OECD recommendations present guidelines for testing chemicals, but not candidates for testing. The latter are determined by member countries, each of which uses the data and performs a risk assessment on that chemical to determine a level of risk.

Another important OECD endeavor relating to chemical management is collecting and disseminating information about existing chemicals. Through the 1987 Screening Information Data Set (SIDS) project, the OECD Chemicals Programme is coordinating a multicountry effort to develop data on a number of high production volume (HIV) chemicals, generally chemicals that existed before recently introduced regulations required large amounts of data prior to production and marketing. Basic information is unavailable on many of these chemicals, and to promote cooperation and reduce costs, the burden of testing is divided among member countries on a voluntary basis, using gross national products as a guide for dividing the tasks. The United States plays a prominent role in this international joint effort, assuming responsibility for testing 25 percent of the SIDS chemicals (Van boy, 1992).

Once SIDS data have been collected and evaluated, they are placed in the United Nations International Register for Potentially Toxic Chemicals, which is available worldwide. OECD will collaborate with IPCS for a more comprehensive review when enough data are collected or generated, and OECD member countries will jointly assess the data gathered for the HPV chemicals. The data are also evaluated to determine if risk reduction measures should be taken (Visser, 1992).

Developing risk reduction strategies for existing chemicals is fast becoming an important part of the Chemicals Pro-e's function. In this effort, OECD uses risk assessments performed by member countries; in addition, IPCS publications review the life cycle of specific chemicals and examine current national risk reduction and chemical control measures. Subsequently, OECD prepares a strategy for regulating and reducing exposure to toxic chemicals. This risk reduction activity was initiated in May 1990 with a five-chemical pilot project. A meeting in November

1992 determined that the OECD approach to risk reduction would rely on sharing and exchanging information on the management of specific chemicals. Information concerning national risk reduction strategies will make comparative analyses possible and may assist member countries in developing their national strategies (OECD, 1992).

Currently, OCED is collaborating with IPCS to develop harmonized risk assessment guidelines and explore quantitative risk assessment methodologies. This collaboration is significant in promoting the use of risk assessment, but to date OECD's more important role has been in harmonizing chemical assessment guidelines. These efforts will facilitate trade among member countries and, by cooperating with other countries and international organizations, will increase the body of knowledge on hazardous chemicals.

International Labor Organisation

The International Labor Organisation has been a specialized agency of the United Nations since 1946, but it has been in existence since 1919 (box A-6). ILO is a tripartite body that serves as an international meeting ground for delegates from governments, workers, and employers, and as a central source of information on labor and social policy (ILO, 1991).

ILO has examined many issues in the workplace, including occupational safety and health. In addressing occupational exposure to hazardous chemicals, ILO does not perform risk assessments or set occupational exposure limits (OELs). Rather, it promulgates statements based on information that has already been compiled by such bodies as PCS, which it helps to support (Clevenstine, 1992). ILO's work is primarily targeted toward disseminating information to developing countries that lack the necessary resources and expertise to monitor occupational exposure to hazardous chemicals (Obadia, 1992).

Pan American Health Organization

The Pan American Health Organization (PAHO) is a regional office of the World Health Organization and thus part of the United Nations. Incorporated into WHO in 1949, PAHO acts as a public health agency serving Latin American and Caribbean countries. Together with WHO, PAHO and other regional offices plan and coordinate health activities on a global basis, including implementing and establishing programs, strengthening health services, and training health workers (PAHO, 1992).

PAHO's policies are determined by its governing bodies: the Pan American Sanitary Conference, the Directing Council, and the Executive Committee. Each authority includes representatives from member states and is responsible for approving recommendations to the members of PAHO for improving the standards of health for their particular countries and for the region as a whole (PAHO, 1992).

PAHO is involved in a number of activities in the area of environmental health, including the preparation of technical and training materials on toxicology, environmental epidemiology, and risk assessment. The organization gives special emphasis to reducing environmental and occupational exposures to pesticides and heavy metals (PAHO, 1992). With regard to standards generated from risk assessments of exposure to various chemicals, PAHO generally refers to values developed by WHO/IPCS and the Codex Alimentarius Commission.

PAHO not only relies on risk assessments conducted by WHO and its supporting agencies, but it also participates in the process itself through its Pan American Center of Human Ecology and Health in Mexico. One aspect of the center's role is to provide relevant authorities with training in different aspects of risk assessment. For example, the center offers courses on using risk assessment for regulatory purposes and to identify a population at risk of exposure to toxic chemicals. Quantitative risk assessment is approached, but other options are usually pursued because there is not enough information available to conduct QRA. Much of the training done at the Pan American Center is supported by financial and expert assistance from EPA (Finkelman, 1993).

Another facet of PAHO's activities is coordinating research on various aspects of environmental health, including quantitative risk assessment for carcinogens. Under PAHO oversight, QRA has been conducted for some heavy metals (e.g., lead and arsenic) and a few pesticides. At this point, no QRA has been completed for food additives. Funding for this research generally comes from sources outside PAHO, but PAHO and the Pan American Center act as facilitators.

Box A-6-Organization of the International Labor Organisation

The International Labor Organisation (ILO) has a number of operating mechanisms, including a yearly general assembly (International Labor Conference), an executive council (Governing Body), and permanent staff (International Labor Office). ILO also employs subsidiary bodies such as regional conferences, industrial committees, and meetings of experts. These subsidiary bodies, coupled with formal contacts between ILO and its constituents, provide the impetus for drafting international standards, Suoh standards are prepared by ILO and adopted by the International Labor Conference after open discussion. ILO reports on compliance among members, which is monitored by panels of experts.

At the yearly assembly, **members pass the standards in the form of conventions or recommendations. Conventions require ratification by member states; the ratification serves as a pledge by a state that it will adapt its national legislation accordingly. Recommendations do not require ratification; they serve mainly as guidelines** for members in developing their policies for the workplace. In both instances, ILO does not have the power to enforce its labor standards, but it does monitor compliance.

In addition to its conventions and recommendations, ILO produces numerous publications, including the Encyclopedia of Occupational ***Health and Safety,*** which contains information about many aspects of workers' health, accident prevention, and improvement of occupational health. ILO also supports the International Occupational Safety and Health information Center. The center evaluates relevant data on occupational safety and health, making its databases, bibliographies, and analyses available worldwide through on-line computer access, CD-ROM, and printed publications.

SOURCE: The International Labor Organization. F-for Americans. 1SS1.

QUANTITATIVE RISK ASSESSMENT IN OTHER COUNTRIES

The Netherlands

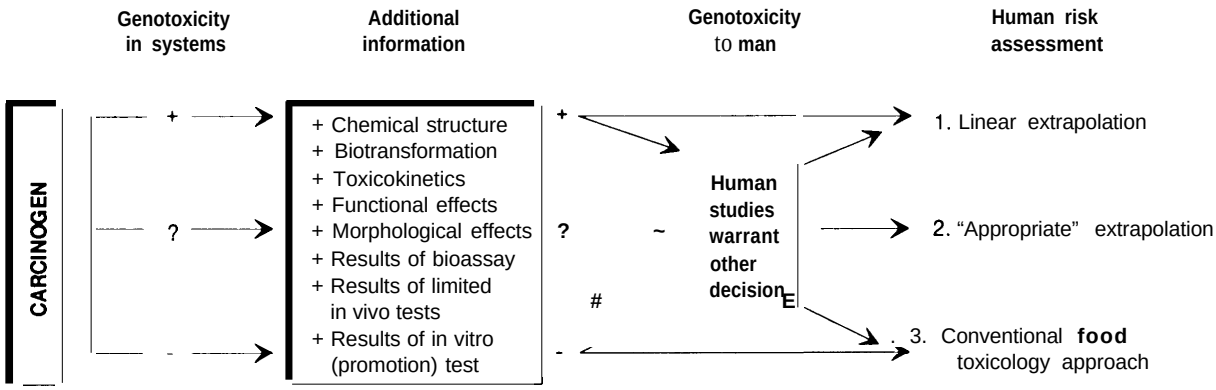
In the Netherlands, regulators use quantitative risk assessments to determine the probability of risks to human health from carcinogens that have been definitively categorized as genotoxic. Figure A-2 outlines the Dutch process for risk assessment. The method is currently used by all Dutch agencies involved in health risk assessments and is based on knowledge about the mechanism of action of a chemical carcinogen.

In the Dutch QRA process, researchers initially evaluated a chemical to determine its genotoxicity in animals they use. They use subsequent information about functional effects and chemical structure, the results of bioassays, and other relevant data to lessen uncertainties relating to the carcinogen's genotoxicity in humans. When it is impossible to eliminate completely the risk of exposure to a genotoxic carcinogen, the Dutch opt to use a very simple linear extrapolation model to determine a dose-response value for human exposure (Kroes, 1979, 1987; Health Council of the Netherlands, 1980, 1988).

The Dutch advocate a conservative approach in their regulatory actions. In performing QRA, they generally prefer a basic, conservative linear extrapolation model, based on the lowest dose that produces an effect, unless experimental data suggest otherwise (Kroes, 1987). If there are sufficient data, they may use more appropriate extrapolation models, which the Dutch feel creates more flexibility in their risk assessment process. At this time, the Dutch have considered highly sophisticated extrapolation models. But, because the data that are available are often insufficient and variable, Dutch regulators believe that such highly developed models would create a false sense of certainty (Swaen, 1992, 1993). The Dutch defend their use of a simple linear extrapolation of animal data to humans with several arguments: linear extrapolation is a very conservative approach; the metabolic rate of humans is lower than that of animals and is also inversely proportional to age and weight; DNA repair processes appear proportional to body weight; and the sensitivity of man to known human carcinogens is about equal to that of experimental animals (Kroes, 1987).

In comparison to genotoxic chemicals, carcinogens that act by a nongenotoxic mechanism are evaluated by the same process but using a different pathway (figure

Figure A-2—Risk Assessment Procedure for Carcinogens in the Netherlands



SOURCE: R. Kroes, Contributions to toxicology towards risk assessment of carcinogens. *Archives of Toxicology* 60:224-228, *1987.*

A-2). The final risk estimate for a nongenotoxic chemical carcinogen constitutes a NOAEL divided by an appropriate safety factor of 10 to 1,000, depending on the amount of uncertainty in the data. The final value represents an acceptable daily intake[4] for the substance.

Several agencies in the Netherlands employ QRA as a means of regulating human exposure to carcinogens, but those health risk assessments are not performed by the agencies themselves. Instead, expert advisory committees recommend limits on exposure using a '' weight-of-the-evidence' approach on a case-by-case basis. In the Netherlands, Advisory Committee 246 of the Dutch Health Council, assisted by ad hoc experts in the field, addresses questions about the risk of carcinogenic compounds to the general population. In its deliberations, the committee usually considers the National Institute of Public Health and Environmental Hygiene's review of the literature on suspected carcinogens and the institute's proposals for classifying and assessing the risk of these agents. The Ministry of Welfare, Health, and Cultural Affairs and the Ministry of Housing, Physical Planning, are the regulatory bodies that most often request advice from Committee 246 concerning human health risks from exposure to carcinogen's (Swaen, 1992, 1993).

The responsibility for establishing occupational health standards lies with the Ministry of Social Affairs and Employment and another expert advisory panel, the Dutch Expert Committee on Occupational Standards (DECOS). Together, these bodies formulate priorities regarding chemical evaluation. DECOS fulfills its role by determiningg a health-based occupational exposure limit (OEL); in turn, a separate tripartite committee evaluates the economic and social impact of the OEL (Swaen, 1993). After considering recommendations from DECOS and the tripartite committee, the ministry then establishes a maximum accepted concentration (MAC), the greatest exposure level permitted for a chemical carcinogen in the workplace. The MAC is similar to the ADI, but it applies to the workplace rather than to exposures from food or the environment.

Most risk assessment-related research is conducted through government institutes, universities, or private organizations. The Dutch Government supports no internal research facilities; instead, it provides extramural grants. At this point, a wide range of topics is being explored (van der Heijden, 1992).

Canada

In 1988, the enactment of the Canada Environmental Protection Act (CEPA) created a mandate for carrying out risk assessments. (Up to that point, QRA had been conducted only for a few select chemicals.) As a result of CEPA, Canada has developed an agenda

[4]This value reflects a threshold or level at which there is no longer evidence of harmful effects caused by exposure to a carcinogen or other toxic substance.

to assess 44 potentially toxic chemicals by March 1994 and to perform QRA if they are found to be toxic (Granville, 1992, 1993).

CEPA and other recent developments in risk assessment have led to numbers of increasing examples of nationally or provincially developed exposure standards in Canada Historically, Canadian regulatory bodies have relied on exposure standards and occupational exposure limits generated by other countries (e.g., Sweden, Denmark, and the United States) and organizations (e.g., WHO and the American Conference of Governmental and Industrial Hygienists). In some instances, the Canadian Government has not considered using risk estimates developed by the U.S. EPA because Canadian authorities see these figures as overly conservative. They also contend that the adversarial nature of the political system in the United States can distort the evaluation of scientific data (Granville, 1992 and 1993).

In regulating chemical substances, the responsible Canadian authorities do consider carcinogenic mechanisms. For nongenotoxic chemicals, researchers determine a NOAEL and tolerable daily intake (similar to an acceptable daily intake). Conversely, for genotoxic carcinogens, authorities previously used unspecified methods under a policy that aimed to reduce health risks as much as possible. The mandate to perform assessments of toxicity for chemicals under CEPA has since given rise to a need for an established QRA process in Canada. In response, Canadian Federal regulatory agencies have adopted QR.A methodologies, although their QRA process is constantly evolving as new information is incorporated.

At this time, the QRA approach being taken under CEPA for genotoxic carcinogens involves estimating an ''exposure/potency index' (EPI). This index compares the expected exposure of a population with an estimate of the potency of the carcinogenicity of a chemical. The potency estimate is derived from experimental epidemiologic or animal data by determining the dose that would cause a carcinogenic response in 5 percent of the test subjects in the study. The resulting EPI provides the agencies with a tool to prioritize possible future control options (Granville, 1992, 1993; Health and Welfare Canada, 1992). In general, QRA in Canada is performed on a case-by-case basis, and the most appropriate model is chosen in each instance. The Canadians believe that allowing for flexibility in the use of models will lead to a more accurate assessment.

Within Canada, the separate provinces have jurisdiction over occupational health matters (including the setting of OELS), and most public health and environmental issues within a province's borders are subject to various Federal/Provincial agreements and legislative mandates. The Canadian Government regulates issues of national relevance, under such legislation as the Food and Drugs Act and CEPA.

Canada has two primary national regulatory agencies involved in environmental protection. The Department of the Environment (called Environment Canada) regulates the quality of the environment (e.g., ambient air and water), and Health and Welfare Canada (HWC) oversees the human health component with activities such as generating air and drinking water quality guidelines. HWC is also responsible for regulating hazardous substances in food and drugs, as well as providing advice to other agencies about human exposure to pesticides and hazardous consumer products. Risk assessment, both qualitative and quantitative, is widely conducted within HWC (Granville, 1992, 1993; St-Aubin, 1992, 1993).

As noted above, regulating hazardous substance in the workplace falls predominantly under the direction of the individual provinces. The Canadian Government, however, is responsible for Federal workplaces and federally regulated industries (e.g., interprovincial transportation and communications) (St-Aubin, 1992, 1993). It uses primarily expert judgment and, in the case of Ontario, advisory committees such as the Ontario Joint Steering Committee on Hazardous Substances in the workplace. That committee, which makes recommendations to the Ontario Minister of Labor, also comprises a task force that evaluates the process and criteria for establishing exposure values and limits for hazardous substances in the workplace (St-Aubin, 1992, 1993). Because each province adopts its own OELs, they vary across Canada. The ministers responsible for such regulation in the provinces meet regularly, but they do not always coordinate their choices of OELs.

Risk assessment research in Canada is evolving, and a wide range of sponsors and topics, such as modeling and mutagenicity, are being actively explored within the research agenda. Health and Welfare Canada performs the majority of health assessment research

and provides several extramural grants to universities and private organizations. Overall, in comparison to the amount of risk assessment-related research conducted in the United States, the level of such research in Canada is significantly less and on a much smaller scale (Granville, 1992, 1993).

United Kingdom

In the United Kingdom, the government does not use QRA to generate a probability for the risk of cancer from exposure to certain chemicals. British regulators place little reliance on the quantitative assessment of carcinogens because they believe that the statistical models used to extrapolate dose-response effects from animals to humans are not valid and are fraught with uncertainty (Department of Health, 1991).

Regulatory approaches to controlling exposure to chemical carcinogens in the United Kingdom are based on mechanistic considerations. If a chemical acts by a genotoxic mechanism, the British Government assumes, as a matter of prudence, that the compound does not have a threshold; that is, any exposure will be associated with an increase in the risk of cancer in the exposed population. If a nongenotoxic mechanism is involved, regulators consider it possible to identify a safe level of exposure, provided that they can understand the mechanism involved (Department of Health, 1991).

Chemicals displaying genotoxicity are evaluated using expert judgment and a weight-of-the-evidence approach. In evaluating such compounds, expert advisory committees consider all of the available evidence (including human data, animal data, mutagenicity data, and structure/activity relationships).[5] If they conclude that the compound should be considered a potential human carcinogen that acts by a genotoxic mechanism, they then recommend action to reduce levels of exposure to as low as is reasonably practical or to eliminate exposure entirely (Fielder, 1992, 1993).

As noted earlier, the United Kingdom does not endorse the use of mathematical models to generate risk estimates for genotoxic carcinogens. Such models have been developed to relate responses from exposures in high doses in animal tests to low-dose human exposure. Although U.K. researchers say they are interested in mathematical models, U.K. regulatory authorities and their expert advisers remain unconvinced about their utility. They note several reservations: no model has been validated; the data used with the models are incomplete or inappropriate; the models are based more on mathematical assumptions than on established biochemical mechanisms; risk estimates vary widely depending on the model us@ and the models give the impression of precision, which cannot be justified from the approximations and assumptions on which they are based (Department of Health, 1991).

For suspected carcinogenic compounds operating through well-understood nongenotoxic mechanisms, researchers evaluate animal studies to determine the NOEL, which is then divided by a safety factor to derive an ADI. The safety factor reflects the uncertainties of extrapolating findings in animals to humans and of interindividual variation (Department of Health, 1991). ADIs are also used to calculate maximum residue levels for pesticides on food (Fisher, 1992).

In the United Kingdom, the Health and Safety Executive is responsible for all aspects of occupational safety. The work of the Executive is overseen by the Health and Safety Commission. The expert Working Group for the Assessment of Toxic Chemicals (WATCH), which reports to the Commission's Advisory Committee of Toxic Chemicals (ACTS), reviews the scientific evidence required to establish occupational exposure limits. In its evaluations, WATCH considers only scientific information, but ACTS may also assess the socioeconomic aspects or technical feasibility of controlling exposure. As a consequence, two types of occupational exposure limits are established in legislation: occupational exposure standards and maximum exposure limits. Occupational exposure standards are set at a level at which there is no indication of risk to the health of employees; a maximum exposure limit is set when such a level cannot be identified and any exposure may involve some residual risk, *or* when such a level cannot be achieved in practice and socioeconomic factors need to be taken into account (Health and Safety Executive, 1992).

The Ministry of Agriculture, Fisheries, and Food specializes in setting tolerances for chemicals in food. For pesticides and nongenotoxic carcinogens, the

[5] **Structure-activity** relationships compare the chemical structures of substances to make inferences about toxicity and identify candidates for further testing (see ch. 3).

ministry formulates maximum residue levels using ADIs. Instead of performing a QRA for genotoxic carcinogens, exposure to those pesticides is either eliminated or reduced to the lowest practicable levels (Fisher, 1992).

Finally, the Environment Food (Medical) Division of the Department of Health advises the British Government on the health aspects of chemical toxicity in food, consumer products, and the environment in general. In this regard, the division provides the Secretariat with a number of independent expert advisory committees, such as the Committee on Carcinogenicity of chemicals in Food, Consumer Products, and the Environment, which advises the British Government on all aspects of chemical carcinogenicity. In 1991, this committee revised its guidelines for evaluating chemicals for carcinogenicity (Department of Health, 1991).

Germany

In Germany, QRA is relatively new to the regulatory field (Turck, 1992, 1993). Previously, German regulatory authorities did not quantify the risk from exposure to carcinogens or other toxic substances because the inherent acceptance of a qualitative risk estimate does not comply with principles established by German environmental laws (Turck 1992, 1993). But, as the need for a quantitative form of risk assessment became increasingly necessary, the Germans surveyed QRA methodologies used by other countries.

The QRA methodology of the U.S. EPA has had a strong impact on the German regulatory committees exploring the process, but the committees have not mandated use of the U.S. methodology. Believing that a case-by-case determination of candidates for QRA leads toward more accurate estimations of risk the committees have advocated greater flexibility in the choice of modeling. Despite these precautions, however, there are still many critics of QRA in Germany. The notion of allowing any degree of risk to humans diverges from the German emphasis on eliminating dangers to the public's health, a basic objective of German environmental laws. To date, little QRA has been completed, and intense debate and discussion regarding the ideas and methodology surrounding QRA are currently under way (Turck 1992, 1993; Pott, 1992).

Although German authorities do not widely practice QRA, strict regulation of known human carcinogens does occur. To date, all proven human carcinogens have been subjected to stringent regulations focusing partially on the best available technology (BAT) or, in the case of drinking water regulations, on international EC directives. It is also commonplace for decisions concerning the regulation of chemical carcinogens and other hazardous chemicals in Germany to be made by multipartite expert committees on a case-by-case basis. Those committees use a NOAEL/ADI approach to QRA for other hazardous noncarcinogenic chemical (Turck, 1992, 1993).

In Germany, expert advisory committees and other Federal agencies provide regulatory agencies with information and recommendations on exposure levels for hazardous chemicals and carcinogens. The recommendations of the advisory committees are not binding; as regulatory bodies, only the ministries are capable of requiring compliance with exposure standards through ordinances or by law (Turck, 1992, 1993).

One of the better known advisory bodies is the Deutsche Forschungsgemeinschaft (DFG), or German Research Agency. This body receives financing from the German Government to engage groups of experts to study issues pertaining to occupational exposure to toxic substances. Within DFG is a commission that uses qualitative risk assessments of carcinogens and makes recommendations to the Ministry of Labor on maximum allowable concentrations (MACs) of noncarcinogenic hazardous chemicals in the workplace. Those MAC values are similar to ADIs for pesticides or food additives, except that no safety factors are applied. The list of values in Germany is similar to (though not necessarily in number) the OELs set by the U.S. Occupational Safety and Health Organization (OSHA) in the United States (Brickman et al., 1985; Greim, 1992; Turck, 1992 and 1993).

In addition to the Ministry of Labor, other German regulatory agencies include the Ministries of the Environment and of Health. The Ministry of the Environment legislates emissions, air pollutants, food contaminants, and the overall state of the environment; the Ministry of Health determines standards for exposure to hazardous chemicals in drinking water, food, and drugs and establishes pesticide residue levels in food. As is the case in many countries, Germany often considers other exposure levels that have been

established by other bodies or nations for the purpose of setting standards for hazardous chemicals. Although German authorities give primary attention to values generated by WHO, they also consider, although to a lesser extent, values generated in the United States. When determining ADIs for food contaminants or MRLs for pesticides found in food, the expert committees that advise the Ministry of Health often consider values promulgated by the Codex Alimentarius Commission (box A-2).

Denmark

Regulatory agencies in Denmark employ QRA to a limited extent when determining exposure standards for carcinogens (Dragsted, 1992). In cases in which a toxic substance is a potential candidate for QRA, substitutes for that chemical are first examined in an effort to eliminate exposure to the original carcinogen, Subsequently, QRA is used when a nonthreshold, genotoxic carcinogen cannot be replaced by another chemical, if the necessary data exists (Larsen, 1993),

In the control of toxic substances, Danish regulatory authorities recognize carcinogenic mechanisms (and thus apply QRA methods to genotoxic carcinogens), and determine ADIs for nongenotoxic carcinogens and other noncarcinogens. The basic toxicological data used to generate exposure standards are generally the same across the various regulatory agencies in Denmark, but the reamer in which the data are used differs according to the problem being addressed. The Danes also use a case-by-case approach when evaluating data for a toxic substance, although reliance on expert advisory committees is not as extensive in Denmark as in other countries, such as the United Kingdom (Carlsen, 1992).

The central authorities or, to a much lesser extent, regional authorities are the most likely source of risk assessment of toxic substances (Carlsen, 1992). One of the central regulatory bodies in Denmark is the Danish Environmental Protection Agency, which has jurisdiction over the monitoring of human exposure to pollutants in air and drinking water. Like other regulatory agencies in Denmark, the Danish EPA attempts to harmonize and modify its exposure standards according to guidelines and data published by WHO, OECD, and the EC (ATV, 1992a). QRA is used specifically in establishing values for exposure limits (tolerable daily intakes) for genotoxic carcinogens that cannot readily be eliminated from drinking water (Carlsen, 1992).

Currently, Denmark's National Food Agency of the Ministry of Health administers regulations for food additives. ADIs are determined by using principles outlined by the Joint FAO/WHO Committee on Food Additives to form the basis of permitted use levels (Larsen, 1992a). Denmark bans all food additives that are characterized as genotoxic carcinogens; it sets ADI's for nongenotoxic carcinogens and other noncarcinogenic agents.

Food contaminants and pesticide residues are also regulated by the National Food Agency. The agency uses guidelines promulgated by the Joint WHO/FAO Committee on Pesticide Residues and risk assessment to determine such exposure limits as tolerable daily and weekly intakes for various contaminants and ADIs and minimum residue levels for pesticides (Larsen, 1992). QRA has been used for proven genotoxic carcinogens but only to a very limited extent. One major reason for its constrained use is the lack of proper toxicological data, especially from well-conducted studies. Such data are deemed unnecessary for performing a scientifically sound QRA. In 1993, assessment and regulation of pesticide residues will gradually be transferred to the EC (Larsen, 1993).

Occupational exposure standards (e.g., threshold limited values) are published by the Directorate of National Labour Inspection after discussions and agreements with the authorities and representatives of labor and employer organizations (ATV, 1992b). As part of those negotiations, the parties consider threshold limit values proposed in the United States and similar MAK (Maximale Arbeitsplatz Koncentrationen) values established by the German Research Council (Poulsen, 1992).

Sweden

Sweden uses QRA to determine exposure risks, but primarily it employs quantitative approaches for assessing the impact of industrial "point-source' emissions, QRA is almost nonexistent in the methods used to determine the carcinogenic risk of pesticides and occupational chemicals. Yet, despite this limited use of QRA, some parts of the Swedish regulatory community have expressed the desire to "modernize [Sweden's] treatment of chemical carcinogens and have risk

assessment become common practice (Nilsson, 1992 and 1993).

In the general process Sweden uses to evaluate chemicals, the initial step is identifying a carcinogen or toxic substance, which is termed "hazard identification" in the United States. At this point, Swedish authorities pursue a weight-of-the-evidence approach as they consider published data and publications by the International Agency for Research on Cancer in deciding whether to classify a chemical as a carcinogen. After this initial determination, a carcinogen may be handled in different ways, depending on its path of exposure to humans and the agency that regulates it.

The Swedish Government generally regulates genotoxic carcinogens to ensure the lowest possible levels of exposure. They evaluate compounds with a nongenotoxic profile through a QRA. Regulators calculate either NOAEL or a lowest-observed-adverse-effect level (LOAEL) using available data. ADIs in turn are used to calculate maximum residue levels of pesticides in food and OELs for occupational carcinogens.

One of the more prominent regulatory organizations is the Swedish Environmental Protection Agency. It is comparable to the U.S. Environmental Protection Agency, except that chemicals entering into commerce for national and international trade is handled by another body, the National Swedish Chemicals Inspectorate. The Swedish EPA sets exposure standards for a variety of carcinogenic and noncarcinogenic chemicals and uses QRA to assess the risks from human health for industrial emissions. Like other European countries that practice QRAs, Sweden considers carcinogens with a pronounced genotoxic mechanism as prime candidates for QRA (Ahlborg, 1992), As part of that process, the Swedish EPA performs mathematical modeling to extrapolate from the responses of animals exposed to high doses of potential carcinogens to humans exposed to lower doses. The agency also evaluates these carcinogens using a case-by-case approach in which each chemical is assessed individually, as opposed to the more generic approach common in U.S. regulatory agencies, which use guidelines for risk assessments (see ch. 5).

The National Swedish Chemicals Inspectorate (NSCI) regulates human exposure to all chemicals used in trade, including pesticides. In the case of new chemicals, NSCI places the burden of testing on industry. For existing chemicals, once NSCI has identified a carcinogen, it looks for a possible replacement so that the chemical carcinogen may be banned. In addition, it permits low-potency carcinogens (often nongenotoxic) to be used only by professionals, in conjunction with protective equipment. Use of these carcinogens in nonprofessional settings is illegal, a policy similar to the zero-tolerance approach promulgated by the Delaney clause in the United States. NSCI does not perform quantitative risk assessments (Nilsson, 1992, 1993).

The Swedish Food Authorities monitor, the level of pesticide residues and additives in food. In assessing carcinogens, this body turns to the Codex Alimentarius Commission, the Joint Meeting on Pesticide Residuies/ World Health Organization, and the Joint Expert Committee on Food Addictives/World Health Organization for information on ADIs and maximum residue levels. The Food Authorities evaluate carcinogens and other hazardous chemicals case-by-case. The also work to enforce good agricultural practices as dictated by the EC.

The Swedish National Board of Occupational Safety and Health regulates exposures in the workplace. It also categorizes carcinogens and uses these classifications to create the Swedish list of occupational exposure limits, which are similar to standards published by the U.S. Occupational Health and Safety Administration.

Italy

Compared with the United States, chemical regulation is less developed in Italy.[6] To date, the Italians have not attempted QRA for chemical carcinogens (Forni, 1992), although they have explored the statistical modeling used in QRA (Galli, 1992). Instead of QRA, they conduct qualitative risk assessments, with international organizations serving as the primary source of information on methodology.

In setting standards for exposure, it is common practice in Italy to analyze all published and unpublished data and to consider risk assessment-related information and exposure standards promulgated at

6 As quantitative risk assessment and risk assessment per se is much less developed in Italy, a smaller number Of Sources was used in developing this discussion as compared to other countries.

the international level by organizations such as WHO, EC, IARC, the U.S. Food and Drug Administration, and the U.S. EPA (Galli, 1992). Such a process is especially common for nations that lack expertise and resources in risk assessment.

Much of Italy's exposure level-setting effort comes from the National Advisory Committee on Toxicology, which serves as an advisory body to the Italian Ministry of Health on several issues, including the regulation of carcinogens in the workplace. This committee has also established guidelines for identifying and classifying carcinogens and maintains a list of chemical carcinogens based on data from IARC publications, Yet despite its responsibilities, this committee does not have the authority to propose exposure limits. Legislation limiting exposure to hazardous chemicals generally comes in the form of decrees by the Italian Government or the ministries of health or labor (Foa and D'Angelo, 1985).

The task of proposing exposure limits is also addressed by ISPESL (Istituto Superiore per la Prevenzione e la Sicurezza del Lavoro), which relies on recommendations by the ILO or EC directives that address occupational exposure to carcinogens and other hazardous chemicals in the workplace (Foa and D'Angelo, 1985). As a member of the European Community, Italian policy regarding occupational exposure reflects relevant EC directives (Forni, 1992).

Japan

Japan practices some risk reduction and regulation of hazardous chemicals. However, very little information was available on this subject, and efforts to obtain it from the appropriate Japanese authorities were unsuccessful.

Developing Countries

Risk assessments in developing countries are usually conducted with assistance from international organizations, such as WHO, PAHO, Codex Alimentarius Commission, or the U.S. EPA. Most developing countries do not have adequate mechanisms or resources for developing chemical safety regulations, much less enforcing them.

Summary

Internationally, risk assessment is undergoing evolution and expansion. The United States is at the forefront of research and methodology in this field, especially for QRA. But several other countries and a number of international organizations have also adopted or increased their utilization of risk assessment to enhance the protection they offer against exposure to hazardous chemicals. Most of the countries OTA surveyed perform some form of qualitative risk assessment; in contrast, evidence of QRA was rare. OTA found however that QRA was an established part of regulatory practice in the Netherlands and Canada and is becoming more apparent in the regulatory policies of Germany and Sweden.

International bodies, such as IARC, IPCS and OECD, play an important role in controlling and monitoring human exposure to hazardous chemicals. They also have a strong influence on international trade and are invaluable in disseminating information about chemical safety to developing countries and nations that lack the necessary resources to perform their own assessments. Moreover, these organizations serve as central coordinating bodies for both interagency collaborations and cooperation between different countries.

In examining how various countries used risk assessment, OTA identified many characteristics of their risk assessment processes. Those countries that do perform QRA do so only for genotoxic carcinogens. Many also preferred case-by-case and weight-of-the-evidence approaches when considering data for use in a risk assessment.

Finally, many foreign regulatory authorities have indicated that they disagree with several aspects of the QRA process used in the United States, including the way U.S. regulators handle the uncertainty of extrapolation models and their overly conservative estimates of risk. As a result, many countries that look to the United States for guidance in QRA have at the same time attempted to remedy the problems they perceive in the process. They have also tried to make their systems more flexible and to allow for improved estimates in risk calculations.

The countries and international organizations discussed in this appendix use risk assessment to varying degrees, depending on the function and clientele of their programs. Qualitative risk assessment is much

more prevalent than QRA, although recent developments will probably lead to increased use of QRA methodologies.

THE FUTURE OF RISK ASSESSMENTS: COLLABORATION, HARMONIZATION, AND TRADE

The issues of guideline harmonization, trade, and interagency cooperation are inseparable when addressing risk assessment in a global context. For several reasons-developments at the 1992 United Nations Conference on Environment and Development in Rio de Janeiro, the desire to reduce nontariff barriers to trade, and ongoing efforts to promote chemical safety—risk assessment has become an important component of the agendas of environmental health bodies worldwide. These factors have motivated several international groups to pursue harmonization of risk assessment guidelines and form collaborative efforts to explore and promote the utilization of risk assessment methodologies.

The benefits of international collaboration on risk assessment and chemical safety appear quite logical. Cooperative efforts bring about a more efficient use of expertise and financial resources. They also provide an opportunity to share data and reduce the chance of duplicate testing. As noted earlier, collaborations in the areas of chemical testing and test guideline harmonization are influential in eliminating trade barriers as well as advancing the state of the science. Finally, global partnerships allow government and industry in the industrialized nations to assist developing countries with chemical safety and assessment (Mercier, 1992).

On the agency level, international organizations have taken the initiative to develop harmonized guidelines for risk assessment. PCS, through its Environmental Health Criteria documents, has published common principles for risk assessments pertaining to drinking water, air quality, pesticide residues, and food additives. IPCS is also coordinating a global survey of risk assessment practices related to human health, with the formal purpose of working toward more harmonization in procedures for risk assessment.

Another international organization, OECD, has taken important steps toward harmonizing guidelines for hazard assessment and avoiding the creation of nontariff barriers to trade. Through its Chemicals Program, OECD updates its guidelines for testing in accordance with advancements in technology and methodology. The OECD chemicals Program also provides its member states with standards for good laboratory practice in an effort to promote the mutual acceptance of data between member countries. Finally, OECD is involved in an international effort to harmonize the classification of hazardous chemicals.

The EC has also taken measures to reduce barriers to trade among its members and concentrate its efforts in the area of chemical safety. Although the EC has already implemented harmonized testing, classification, and labeling of toxic chemicals, a recent amendment (Directive 92/32/EEC) to the 1967 directive on classification and labeling further updates the EC's guidelines for chemical testing and assessment (Official Journal of the EC, 1992).

In addition to the international bodies and organizations that are developing individualized policies concerning risk assessment guidelines and the enhancement of trade, they are also collaborating on some of these same issues. One established example is IPCS, a cooperative program of WHO, FAO, and ILO. Under a formal agreement, OECD and IPCS have also been sharing information and resources to harmonize risk assessment methodologies, with IPCS focusing more on the human health aspects and OECD on the environment. That collaboration has been enhanced by Agenda 21 at the 1992 UNCED in Rio de Janeiro (see below) (Smith, 1992, 1993). Finally, several conferences have taken place--and several more are planned-that examine national and international approaches to QRA principles and methodologies.

Arguably, the most significant development in such collaborations is a result of the 1992 United Nations Conference on Environment and Development in Rio de Janeiro. Chapter 19 of the Agenda 21 document ratified at the conference deals with the environmentally sound management of toxic chemicals (UNCED, 1992). It proposes six areas of chemical safety and management that should be addressed by international collaborations (table A-2). As noted earlier, a UNCED preparatory meeting in London in 1991 proposed an intergovernmental mechanism (IGM) to address risk assessment and chemical management internationally. Chapter 19, which was recently approved by the United Nations General Assembly (Mercier, 1992), contains an invitation to the executive heads of WHO, ILO, and UNEP to convene intergovernmental meet-

Table A-2-Six Proposed Program Areas from Chapter 19, Agenda 21 of the June 1992 UNCED in Rio de Janeiro

- (a) Expanding and accelerating international assessment of Chemicl risks.
- (b) Harmonizing classification and labeling of chemicals.
- (c) Establishing an information exchange on toxic chemicals and chemical risks.
- (d) Establishing risk reduction programs.
- (e) Strengthening national capabilities and capacities for management of chemicals.
- (9 Preventing illegal international traffic in toxic and dangerous products.

SOURCE: United Nations Conference on Environment and Development, Agenda 21, Chapter 19: Environmentally Sound Management of Toxic Chemicals Including Prevention of Illegal International Traffic in Toxic and Dangerous Products. Plenary session in Rio de Janeiro, June 14, 1992.

ing within a year. Through an expansion of its activities, IPCS will become the central executer of this IGM proposal and will recruit the assistance and expertise of several other international organizations (e.g., OECD, FAO, and CEC), national authorities such as the U.S. EPA, and relevant nongovernmental organizations (IPCS, 1992b).

International cooperation in dealing with chemical safety and risk assessment is extensive and will be enhanced even more through the proposals of Chapter 19. Negotiations on world trade, especially the General Agreement on Tariffs and Trade (GAIT') and the North American Free Trade Agreement, will also benefit from the ongoing collaborations. A common problem that arises in those negotiations and in the world trade arena is the difference in standards between two or more countries and the unwillingness of the country with more stringent regulations to compromise. This complex situation may also arise in negotiating harmonized risk assessments and chemical safety guidelines. However, the potential benefits for human health, world trade, and the environment of harmonizing chemical safety and assessment guidelines may make such international collaborations worthwhile.

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