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PROBLEMS IN THE REGULATION OF CARCINOGENIC CHEMICALS IN AN INTERNATIONAL PERSPECTIVE III. CRITICAL ASSESSMENT OF REGULATORY APPROACHES

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ABSTRACT

The real or perceived risk for cancer caused by man-made chemicals has had a major impact on over-all risk assessment as well as on risk management. Unfortunately, there is a lack of consensus on the international level with respect to the choice of appropriate methodology for quantitative risk assessment of carcinogens for regulatory purposes. In this article the approaches used in different countries are critically reviewed, both with respect to hazard labeling of chemical products as well as regarding risk assessment of emissions to the environment from point sources. The main difference between on one hand U.S. and the Nordic countries, and on the other the countries of the European Union (EU) and Canada, is that the responsible government agencies in the last mentioned group of nations take mechanistic considerations as well as type of tumor into account when extrapolating the findings from experimental animals to man. U.S. and the Nordic countries have used a more generalized, or generic approach, which is complemented by a quantitative estimation of risk.

In risk management there is a need for simplified approaches for the purpose of screening large numbers of chemicals, as well as methodologies which aim at an indepth analysis of single compounds. The complexities involved in applying quantitative cancer risk assessment to complex mixtures is illustrated by its practical use for assessing abandoned sites for deposition of hazardous chemical waste.

In setting rational priorities for risk reduction, the importance of making relevant risk-risk comparisons is underlined. This is illustrated by citing some examples of overreaction to negligible cancer risks from chemicals. The difficulties in bridging the information gap between countries, as well as the special problems associated with the export of carcinogenic chemicals to developing countries are briefly discussed.

RESUMEN

El riesgo real o percibido de cáncer causado por agentes químicos originados por el hombre ha tenido un gran impacto en la evaluación del riesgo total así como en el manejo de ese riesgo. Desafortunadamente hay una carencia de consenso a nivel internacional con respecto a la relacción de la metodología apropiada para hacer la evaluación cuantitativa del riesgo de carcinógenos con el propósito de su regulación. En este artículo se revisa críticamente la aproximación utilizada en diversos paises tanto con relación al peligro del marcaje de productos químicos así como con la evaluación del riesgo de emisiones al ambiente de fuentes puntuales. La principal diferencia entre, por un lado, EUA y los paises Nórdicos y por otro los paises de la Unión Europea (UE) y Canadá, es que las agencias gubernamentales responsables en el último grupo de naciones toman en cuenta consideraciones mecanicistas así como el tipo de tumor cuando extrapolan los hallazgos de los animales experimentales al hombre. Mientras que los EUA y

los países Nórdicos emplean una aproximación más generalizada o genérica que es complementada por la estimación cuantitativa del riesgo. En el manejo de riesgos hay necesidad de simplificar la aproximación con el propósito de probar cantidades elevadas de agentes químicos así como metodologías dirigidas a un análisis no muy profundo de compuestos sencillos. Las complejidades involucradas en la aplicación a mezclas complejas de la evaluación cuantitativa del riesgo al cáncer son ilustradas por el uso práctico para evaluar la deposición de desechos químicos peligrosos en sitios abandonados. Para fijar las prioridades racionales en la reducción del riesgo, se subraya la importancia de hacer relevantes las comparaciones de riesgo. Esto se ilustra citando algunos ejemplos de sobrerreacción a riesgos despreciables al cáncer de agentes químicos. Se discute brevemente sobre las dificultades en el llenado de los huecos de información entre países así como los problemas especiales asociados con la exportación de agentes químicos carcinogénicos a países en desarrollo.

BACKGROUND

In order that assessment of hazards from exposure to carcinogenic chemicals is to become more meaningful in the regulatory context, such evaluations should not only identify toxic chemicals, but also provide a *measure of risk* under realistic exposure situations, i.e. a *quantitative risk assessment* should be made. So far, quantitative cancer risk assessment based on mathematical modeling has been consistently used for regulatory purposes only in the U.S. Thus, it constitutes an integral part of the **U.S.EPA** system for assessing carcinogens, especially when evaluating the impact of emissions from industry and sites for disposal of hazardous waste, as well as for setting tolerances to residues of pesticides and other chemicals in food products and drinking water. In recent years quantitative risk assessment has also found increased use in some European countries, like **the Netherlands,** but to some extent also in **Germany** and **Sweden.** In Europe such evaluations have been limited to genotoxic carcinogens. When assessing chemical hazards for the purpose of labeling, the level of exposure may be difficult to predict, and quantitative aspects have, therefore, been of secondary importance.

In a recent international workshop analyzing the role of science in pesticide management it became clear, that in the assessment of data from animal studies there is little divergence between developed countries as to interpretation of most major toxicological end points *per se,* but major differences appear in the area of the hazard and risk assessment as well as risk management of carcinogens (Nilsson *et al.* 1993). With respect to this toxicological effect, consensus does often not exist between regulatory agencies even within the same country. There are many reasons for deviating policies in this area. One is certainly conflicting scientific opinions. However, the strong influence of non-scientific reasons on risk management decisions invoked by media and public opinion in this highly controversial field cannot be disregarded. Once a chemical has been branded a "carcinogen" by a regulatory agency, it has been very difficult to reverse such a classification, especially in a society where the decision process is open to public scrutiny, and where exaggerated and distorted notions of cancer risk with respect to manmade chemicals prevail among the public. In such countries the demands are very high with respect to validation of a regulatory approach that results in *lowering* previous risk estimates. The differences which exist between countries with respect to carcinogen risk management to some degree reflect disparate administrative traditions. Hazard evaluations in the EU have mostly been carried out on a case-by-case basis within closed expert committees. Unfortunately, this kind of decision process has been characterized by a considerable lack of transparency. The decision process in U.S., as well as in a Nordic country like Sweden, is much more open to public scrutiny, but is often highly influenced by a politicized bureaucracy prone to utilize scientific data in a selective fashion.

This article is the last in a series of three articles dealing with cancer risk assessment, where the previous contributions dealt with interpretation of tumors induced in experimental animals (Nilsson 1993) and the second, determination of carcinogenic potency (Nilsson 1994).

Terminology Used- The ***risk-assessment-and-management-process*** consists of three phases: Information gathering, risk assessment, and risk management.

In view of the ambiguity of various basic concepts which appear in the literature concerned with ***risk assessment,*** the terminology used here follows that defined by the National Research Council of the U.S. National Academy of Sciences (NRC 1983), and which has been adopted by the U.S.EPA (1986a) and recently also by the European Communities (EEC 1993b). The nomenclature also conforms to the definitions of "hazard" and "risk" as specified within the OECD Chemicals Programme (OECD 1982).

The broad integrated process of risk assessment of chemicals, involving identification, characterization, as well as quantification of the level of risk is described by the elements given in **Table I.**

Thus, *"hazard"* signifies the *potential* of a specific agent

TABLE I. ELEMENTS OF RISK ASSESSMENT

DATA INPUT FROM RESEARCH	RISK ASSESSMENT
Laboratory and field observations of adverse health effects caused by certain exposures	*Hazard identification* What adverse effects are caused by the agent?
Information on dose-effect (response) relationships. Methods for dose extrapolation	*Hazard assessment* What is the likelihood of an adverse effect at a given exposure (dose)?
Monitoring and/or mathematical modeling of exposure. Characterization of exposed populations. Use of "surrogate data"	*Exposure assessment* What exposure levels (doses) are currently expected, or projected under specified conditions?
Hazard assessment data + data from exposure assessment + uncertainty analysis	*Risk estimation* What are the estimated incidences of adverse effects in a given population? How accurate is my estimate?

for causing harm and represents an inherent property of the agent *per se,* e.g. that of toxicity. The characterization of dose-response (dose-effect) as well as the extrapolation of such relationships from experimental animals to man have a central role in *hazard assessment. "Risk"* represents the quantitative statement of the *probability* of occurrence of a defined adverse effect, i.e. it is compounded by the elements of *toxicity* ***and*** *exposure.* Thus, *risk characterization* constitutes the final process of defining the incidences of adverse health effects under actual conditions of exposure by integrating hazard and exposure assessments. *"Risk estimation"* is occasionally used as a synonym for "risk characterization", and some authors use risk assessment to describe the broad process of identifying, characterizing, quantifying, and evaluating the risk, as well as the cost and benefit factors that are associated with a certain activity or situation.

Exposure assessment is the determination of the magnitude, frequency, duration and routes of exposure of human populations and ecosystems. By actual measurement, or by modeling, the fate of a chemical is followed and quantitated from its source of emission until it reaches the surface of the target organism. In this context the fate and transport of contaminants in ground water usually presents the most complex problems. Exposure assessment mainly belongs to the realm of sciences like analytical chemistry, hydrogeology, and meteorology. Some important aspects of exposure assessment will be discussed below when dealing with a case study involving a hazardous waste site.

Risk management comprises an range of actions taken to minimize, reduce, or otherwise control specific risks posed by a certain situation. Inevitably it contains elements of policy.

Making predictions of health risks has previously been an exclusive task for the medical profession, but from the presentation given above, it should be obvious, that modern risk assessment of chemicals requires the participation of many different types of expertise, where no one discipline can claim monopoly in providing the most adequate answer to a very complex topic. Thus, a positive cancer test in a rodent species has little value unless we have a grasp of the uptake and metabolism of the compound in question in man. In addition, we need have to get adequate exposure data, preferably complemented by an estimate of the dose in the critical tissue where tumors are induced (target dose). The next step is to make a credible high-to-low dose extrapolation and derive some measure of potency of the carcinogen. Finally, using this potency estimate, real life exposure data must be introduced to obtain an appraisal of the absolute level of risk. As to the use of data from humans, contemporary epidemiology is to a high degree depending on methodology derived from advanced mathematical statistics. However, the problems associated with the use of epidemiological data will not be dealt with in this context.

REGULATORY SYSTEMS

Risk management with respect to hazardous chemical products can be divided into two action domains. One concerns direct contact with chemicals associated with the transport, trade, and use of such products, and the other is aimed at limiting emissions to the environment from the production, use and/or disposal of chemicals. In the first group of regulations, classification and labeling as well as standards for maximum contaminant

concentrations in various products (food, water, cosmetics, etc.) play a central role, whereas for the second category emission standards constitute the main regulatory point of reference. While the latter type of regulatory options are usually depending on some sort of quantitative risk assessment, this is mostly not the case for risk management by labeling.

Classification and Labeling- For many chemical products the exposure upon ultimate use may be difficult to predict, and one simple risk management option is to provide adequate information to the users about *potential* risks from handling the product. A common approach used in Europe to regulate chemicals has been classification in various categories, reflecting different levels of perceived intrinsic hazard. This classification may serve as a basis solely for labeling purposes. However, it can also be linked to other types of administrative actions, e.g. for eliminating carcinogens in consumer products as exemplified by regulations in the Nordic countries (Finland, Norway, Iceland, and Sweden), and recently also in some EU countries.

The Role of the International Agency for Research on Cancer (IARC)- In the **EU,** the **Nordic countries** as well as in the U.S. (U.S.EPA 1986a) a system more or less identical to the criteria issued by IARC (1982, 1987) has been employed in evaluating cancer data. The IARC principles for classification of carcinogens was first introduced by this author in the Swedish regulatory system for labeling in 1980 (Nilsson 1980) and was formally codified in 1982 (SNFS 1982, 1983). Other countries subsequently introduced similar concepts into their legislation.

The main limitation of the IARC classifications has been that they only cover the first *qualitative* evaluation phase in hazard and risk assessment; i.e. have the studies in question been adequately performed, and do they indicate an association between exposure and induction of tumors in the studied species? No consideration is paid either to carcinogenic potency which may vary by a factor of more than one million nor has, until recently, mechanisms of action, or pharmacokinetic data been considered. A further drawback of the IARC evaluation process is that this agency only reviews published data. This means that for certain compounds consideration is given only to a minor portion of all the information that has been generated. The quality of published studies from university laboratories are frequently inferior to many unpublished industry sponsored investigations generated in contract laboratories under strict compliance with international test guidelines and good laboratory practice (GLP). For achieving cost effectiveness, maximum use must be made of all available information, irrespective if the data have been published or not. The standpoint of IARC with respect to this issue is not accepted by other WHO associated bodies, like IPCS or JMPR, nor by most national authorities.

It is important to point out, however, that the imperfections of the IARC system when used for risk assessment does not mean that the information from IARC should be disregarded. On the contrary, the IARC evaluations represent an extremely valuable information source to be used in hazard identification. However, it has unfortunately not always been realized, that the IARC system is not suited for risk management purposes without complementary evaluation. The practical use of some carcinogens may implicate a negligible risk. For this reason national agencies, which use the IARC classification systems, have in some cases been forced to make radical deviations from their own established rules.

IARC (1987) has, e.g., classified the high-volume chemical *di(2-ethylhexyl)phthalate* (DEHP), as a 2B carcinogen on basis of liver tumors in rodents. DEHP is mainly used as plasticizer for PVC. With the exception for the U.S.EPA, and initially Denmark, other national regulatory agencies have not enforced a corresponding classification, although the basic criteria may be similar to those of IARC. Denmark, being a member of the EU, has subsequently been forced by the EC Commission to retract its classification on the national level. With respect to the U.S., it is important to note, that the use of this plasticizer has not been curtailed to any significant extent by regulatory action. This is explained by the fact that assessment in the U.S. is also based on an assessment of risk which demonstrates low exposures of the general public in combination with a relatively low carcinogenic potency. IARC (1987) has also classified one of the most commonly used artificial sweeteners, saccharin, as well as the widely used food antioxidant *butylated hydroxyanisole (BHA)* as 2B carcinogens, to be regarded as "possibly carcinogenic to humans". In terms of estimated risk to consumers, this view is obviously not shared by the responsible regulatory agencies for food control in any country.

Given the prestigious status of a WHO research center, the lack of in-depth scientific analysis of certain important aspects of carcinogenicity which characterizes the IARC series of "Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans" may seem surprising. However, the limitations of the IARC evaluation system can mainly be traced to the narrow mandate given by the Agency management to the responsible Working Group. Only with respect to genotoxicity have previously mechanistic aspects been considered, and only for the *purpose of strengthening* the evidence of carcinogenicity. Thus, based on the results from short-term tests, styrene as well as the styrene oxide were moved from *Group 2B* (The agent is possibly carcinogenic to humans) to *Group 2A* (The agent is probably carcinogenic to humans). However, recently there have been some notable changes of IARC scientific policy which will also allow for a *down-grading* of the evidence on basis of other mechanistic considerations.

In 1983 the IARC convened an ad-hoc working group of experts to assess to what extent mechanistic information could contribute to the evaluation of cancer risk. At that time it was concluded, that classification according to mechanism of action was premature. However, in June 1991 the issue was re-examined by another group of ex-

perts which arrived at a different conclusion. According to the consensus report "increased use of these [mechanistic] data in the overall evaluation may require modification of the criteria for the IARC categories" (IARC 1992a). Thus, it was suggested that *Group 3* (the agent is not classifiable as to its carcinogenicity to humans), which currently is used for those agents for which there are no or inadequate epidemiological data on human carcinogenicity, and less than sufficient evidence for carcinogenicity in animals: "may be extended to include agents for which there is sufficient evidence in animals and strong evidence that the mechanism of carcinogenicity in animals do not operate in humans". Further, the IARC advisory group "recommended that a discussion of possible mechanisms be included in the monographs when appropriate data are available." Factors to be taken into consideration when modifying the assessment of carcinogenicity data were:

(a) Evidence of genotoxicity
(b) Evidence of effects on the expression of relevant genes
(c) Evidence of relevant effects on cell behavior (e.g. mitogenic effects, cell proliferation)
(d) Evidence of time and dose relationships of carcinogenic effects and interaction between agents

Unfortunately, these guidelines give no advice on how these factors should influence classification, and the important question of carcinogenic potency was not addressed. Only some suggestions from the expert group were subsequently incorporated in into the 1992 IARC criteria (IARC 1992b) for classification, and *Group 3* may now include:

> "Exceptionally, agents (mixtures) for which there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans."

At the same time it is now possible to *upgrade* a 2A compound, for which evidence from humans is insufficient, to *Group 1* (The agent is carcinogenic to humans) based on mechanistic considerations. Thus, whereas IARC at present recognizes the importance of mechanistic considerations, this notion is still rejected by the regulatory agencies in the Nordic countries. However, U.S.EPA is currently considering mechanistically based criteria when assessing the significance of tumors in experimental animals (R. Hill, personal communication).

The induction of tumors at more than one site in an experimental animal is regarded by IARC and several national agencies as an indication of a strong carcinogenic potential. As a rule, this is justified. However, for certain non-genotoxic carcinogens, that act by a receptor mediated mechanism, this view may have to be modified. Thus, some antithyroid agents may induce tumors in the thyroid, the adrenal medulla, and possibly also in the pituitary by perturbing the pituitary-thyroid feedback control system as described in a previous article (Nilsson 1993). However, the finding of treatment induced tumors in more than one of these target organs does not necessarily make the chemical in question more hazardous than if tumors would only have been detected at one of these sites. Further, these tumors will probably have no significance at doses that will not influence the normal hormonal balance.

The European Union, EU*- The EU policy on chemicals control is handled by the Environment Directorate-General (DG-XI) in Brussels, Belgium. DG XI is empowered to pass legislation (regulations and directives) which is legally binding for all 12 countries of the European Union. One of the most important pieces of multinational legislation was the 1979 Council Directive amending the Directive 67/548/EEC related to the "Classification, Packaging, and Labelling of Dangerous Substances" (6th Amendment), and which has recently been followed by a 7th amendment on April 30, 1992 (EEC 1992). The EC labeling system essentially lacks provisions for classification according to carcinogenic potency, and the basic rules are the following (EEC 1993c):

Category 1 is reserved for established human carcinogens, and experimental carcinogens will go into either **Categories 2, or 3.** However, one of the basic premises when assigning a compound to the carcinogen **Category 2** has been that it should be based on "appropriate long-term animal studies" and "other relevant information". "Substances which cause concern for man owing to possible carcinogenic effects, but in respect of which the available information is not adequate for making a satisfactory assessment" are placed in **Category 3.** Another criterion for this last category is that "There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2". For several low-potency, non-genotoxic carcinogens the Commission has decided, that the animal model used has not been relevant for man, thereby barring carcinogen classification into group 2 (or in some cases, both group 2 and 3). In the most recent Directive, the conditions for distinguishing between categories 2 and 3 have been more explicitly stated. Thus, the following circumstances especially in combination could lead to classification in category 3:

1. "Carcinogenic effects only at very high dose levels exceeding the 'maximum tolerated dose'...
2. Appearance of tumours, especially at high dose levels, only in particular organs of certain species known to be susceptible to a high spontaneous tumour formation.
3. Appearance of tumours, only at the site of application, in very sensitive test systems (e.g. i.p., or s.c. application of certain locally active compounds), if the particular target is not relevant to man.

* After the Maastricht agreement the European Community, EC, as a political unit has been renamed the European Union (EU). The name EC is still retained e.g. for the legislative function of the EC Commission.

4. Lack of genotoxicity in short-term tests in vivo and in vitro.
5. Existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g. hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation).
6. Existence of a species-specific mechanism of tumour formation (e.g. by specific metabolic pathways) irrelevant for man."

For distinction between category 3 and no cancer classification, the following circumstances which "exclude a concern for man" are relevant:

7. "A substance should not be classified in any of the categories if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man.
8. If the only available tumour data are liver tumors in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories.
9. Particular attention should be paid to cases where the only available tumor data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence."

Thus, recent EEC amendments have to a large extent introduced various provisions for a more flexible approach to the qualitative interpretation of data from animal experiments based on mechanism of action, etc. For several groups of non-genotoxic chemicals some of which have been discussed in previous articles (Nilsson 1993, 1994) the application of the EC criteria for changing the classification from 2 to 3, or no classification, appear to be justified. Possible candidates for the implementation of these provisions are several non-genotoxic rodent liver carcinogens (including the peroxisome proliferators and some chlorinated compounds), non-genotoxic compounds which induce neoplasia in the rodent bladder and forestomach, compounds inducing protein droplet nephropathy in the rat, substances inducing thyroid follicular cell carcinomas by causing thyroid-pituitary imbalance, estrogenic substances inducing neoplasia of the mammary glands, pituitary and adrenal medulla, as well as certain metal carcinogens.

Cancer Classification i the U.S. and in the Nordic Countries- Although the classification criteria used by the **U.S.EPA** and by corresponding agencies in the **Nordic countries** like those of the IARC allow little flexibility in the interpretation of animal data, they do incorporate an additional *estimation of potency*. The concept for introducing potency and risk as important qualifiers in classification of carcinogens was proposed by this author and introduced in the Swedish legislation in 1982 (SNFS 1982). It was subsequently carried over to the new legislation (KEMI 1986). The method chosen for potency estimation by the National Swedish Chemicals Inspectorate, which was created in 1986, was based on the lowest dose that produces a statistically significant tumorigenic response (TD_x; Nordic Council of Ministers 1985). This standard was subsequently adopted by the other Nordic countries. Until now U.S.EPA has relied on the scientifically more adequate linearized multistage model (U.S.EPA 1986a). The limitations associated with these models has been discussed previously (Nilsson 1994).

There have been some obvious differences between the evaluation systems for experimental carcinogens of the U.S. and the Nordic countries versus those of EC and Canada. The U.S. as well as the Nordic countries have mainly followed a generic approach, where in contrast to EC little consideration is given either to interpreting the relevance of tumors induced in animals, or to mechanism of action. Since, on the other hand, the concept of potency has been introduced by the latter group of countries, the practical results from implementing the two systems need not differ dramatically. The reason for this outcome lies mainly in the fact, that non-genotoxic carcinogens or tumor promoters usually have a low carcinogenic potency.

As mentioned above, carcinogen classification in many countries has other regulatory implications than as a basis for labeling. In Sweden only products containing carcinogens of very low potency (TD_x around 500 mg/kg and above) may be sold to the public with the provision that the labeling contains the warning: *"A certain cancer risk cannot be excluded upon frequent exposures"*. The sale and use of other carcinogens is restricted to professional purposes and subject to a stringent legislation on occupational health. Mainly for political reasons, pesticides are judged by a stricter standard, and products that contain active ingredients for which there is some evidence that they induce cancer in experimental animals have, with a few exceptions, been totally banned in Sweden even for professional use. However, when any of these countries join the EU, they will have to accept the rules for classification and labeling prescribed by this multinational organization.

In Sweden and in several other countries a few potent experimental carcinogens (e.g. *2-acetylaminofluorene)* as well as some established human carcinogens like *benzidinè, bis(chloromethyl)ether, 2-aminonaphthalene,* and *crocidolite asbestos* listed in *Group 1* and in *Group 2A* by IARC (1987) have been totally banned also for occupational use. Compounds from a more extensive list of IARC 2A and 2B category compounds may only be used after obtaining special permission from the Swedish occupational health authorities, whereas a restricted list contains carcinogens to which threshold limit values (TLVs) have been assigned (e.g. a*crylamide, arsenic, benzene, ethylene oxide, vinylchloride).* When comparing TLVs from different countries, it is important to realize, that although they to a varying extent are based on scientific data, a number of other factors may influence the setting of these levels. Such non-scientific factors are technical feasibility of reducing exposure, industrial importance, pressure from labor unions, etc.

USE OF QUANTITATIVE RISK ASSESSMENT IN THE REGULATORY CONTEXT

It has already been mentioned that the **U.S.** has taken the lead in developing and implementing quantitative cancer risk assessment for regulatory purposes. For this purpose the U.S.EPA has consistently used the linearized multistage model for determination of 95% upper bound of risk. The limitations associated with the use of this model has been discussed in a previous article (Nilsson 1994). However, the U.S.EPA has been aware of the problems associated with overly conservative risk estimates derived in this manner, and it has been stressed (U.S.EPA 1986a), that the unit cancer risk (q^*_1) only provides a plausible *upper* limit for a risk that can very well be much lower. However, in reality, official U.S.EPA unit risk estimates are used by environmental engineers and decision makers more or less as absolute standards. The use of the misnomer "toxicity constant" for values derived from q^*_1 and RfD, and which can be found e.g. in the U.S.EPA manual for Superfund sites (U.S.EPA 1989a, 1989b), tends to promulgate this attitude. Thus, in spite of the well-meaning assurance that the formalized rules in this manual should not be used as "cook book" procedures, this is exactly what has been happening in the U.S. Further, the limitations and presumptions underlying risk estimates derived in such a context are mostly lost as U.S.EPA's evaluations are made use of by regulatory agencies in other countries.

The declared policy of U.S.EPA on assessment of carcinogens (U.S.EPA 1986a) states that "risk assessments will be conducted on a case-by-case basis, giving full consideration to all relevant scientific information". This also involves consideration of alternative models for doseresponse extrapolation. However, this excellent rule is not followed. Except for certain thyreostatic compounds (Paynter *et al.* 1988, U.S.EPA 1988), so far the U.S.EPA has been reluctant to relinquish the use of the linearized multistage model for cancer risk extrapolation. In actual real-life situations inflated cancer risk estimates may, therefore, result in distorted appropriation of resources needed to remedy more urgent risk situations.

While analyzing the situation in other countries, current research efforts, as well as hazard and risk assessment policies of U.S. Federal agencies, have been the focus of a critical analysis recently conducted by the Biological Applications Program of the powerful **Office of Technology Assessment of the U.S. Congress** (OTA 1993). In this context it is noted, that "EPA is the main player in developing and revising risk assessment guidelines", but that recent scientific developments in the area of risk assessment has had a very limited impact on the Agency's science policy assumptions:

> "OTA finds a particular lack of emphasis on collaborative research to evaluate and validate and validate new methods and models, especially in the important area of corroborating experimental results from animal studies with studies in humans."

The OTA further underlines that:

> "While industry and taxpayers pay billions of dollars in control and cleanup costs, everyone is left uncertain about how much safety has been purchased and how much risk has been left unaddressed".

In conclusion, OTA strongly urges the U.S. Congress to provide adequate funding for research in health risk assessment methodology and to promote central coordination by establishing a lead agency.

In response to widespread dissatisfaction with U.S.EPA policy, which to some extent has reflected in OTA's (1993) analysis as well as in a recent assessment carried out by the National Research Council (1994), the agency is currently considering some drastic changes (R. Hill, personal communication) of its 1986 Guidelines (U.S.EPA 1986a). A main proposed deviation involves departure from the generic approach by introducing the "mode of action" of tumor inducing agents, and where linear extrapolation is used only for genotoxic compounds. A linear extrapolation to an ED_{10} value for cancer incidence, instead of applying the default linear multistage model, represents another radical change of policy. The convergence of U.S. and EU practices when interpreting tumors in experimental animals providing a simple solution, the introduction of ED_{10} for linear low-dose extrapolation may be scientifically questionable in some cases (Nilsson 1994).

In Europe **the Netherlands** has been using a simple linear extrapolation for quantitative risk assessment for genotoxic carcinogens, similar to that which now is being considered by the U.S.EPA (Health Council of the Netherlands 1994, OTA 1993). To provide an ADI for non-genotoxic carcinogens, NOELs are divided by an appropriate safety factor of 10-1000, depending on the uncertainty in the data. For risk assessment of chemicals the Dutch regulatory bodies heavily rely on scientists from the National Institute of Public Health and Environmental Hygiene as well as on the "Advisory Committee 246" of the Dutch Health Council. **Canada** has implemented a policy very similar to the Netherlands with respect to carcinogens.

Quantitative risk assessment is relatively new to the regulatory field in **Germany,** but mathematical modeling of the same kind as is currently used by the U.S.EPA has been conducted only for a few compounds. However, one intends to allow for a greater flexibility in the choice of modeling (OTA 1993).

In **Sweden** quantitative cancer risk assessment, using U.S.EPA's linearized multistage model, has occasionally been carried out by the **Institute of Environmental Medicine, Karolinska Institute,** to support regulatory action enforced by the Swedish Environmental Protection Agency with respect to point emissions from industrial sources. The National Swedish Chemicals Inspectorate which has the central responsibility for control of all chemical products except food and food additives, pharmaceuticals and radioactive materials mainly relies on in-

house support for cancer risk assessment of individual chemical compounds and does not carry out quantitative risk assessment.

Although quantitative risk assessment of pesticides in the **U.K.** at the present is limited to a comparison of ADIs (AOELs) with predicted, or measured exposure levels, the Department of Health has recently published "Guidelines for the Evaluation of Chemicals for Carcinogenicity" (UKDH 1991). This document emphasizes the limitations in using mathematical models for estimation of risk, but it is, nevertheless clearly stated that:

> "For genotoxic carcinogens it is assumed that there is no discernible threshold and that any level of exposure carries a carcinogenic risk".

Further, that:

> "For carcinogens which do not appear to be genotoxic but for which no mechanism of action has been established, the prudent approach of assuming no threshold for the carcinogenic effect is adopted."

In other countries quantitative risk assessment for regulatory purposes seem to be virtually non-existing (OTA 1993).

The European Union (EU)- Although only a few member states of the EU implements quantitative risk assessment, the most recent Commission Directive (EEC 1993a) for new substances which must be notified, an evaluation is prescribed for dose-response (effect) assessment, exposure assessment, as well as for risk characterization. In an accompanying guidance document (EEC 1993b), an extensive presentation of these areas is given, including approaches for assessing environmental, work place, and consumer exposure to various types of products. Environmental exposure to chemicals from the textile finishing industry is covered in a separate section. However, with respect to carcinogens it has, obviously, not been possible to reach a consensus with respect to high-to-low dose extrapolation. The guidance document here simply states for mutagens and for genotoxic carcinogens that:

> "Unless a threshold mechanism has been clearly demonstrated, it is prudent to assume that an exposure threshold cannot be identified. This implies that, in such cases, there is some risk to health at any level of exposure. As stated in WHO (1994), 'there is no clear consensus on appropriate methodology for the risk assessment of chemicals for which the critical effect may not have a threshold, such as genotoxic carcinogens and germ cell mutagens....".

Internationally, the **Joint FAO/WHO Meeting on Pesticide Residues (JMPR)** of the **International Programme on Chemical safety (IPCS)*** exerts considerable influence in the field of pesticide evaluation. IPCS (1990) has published a policy document called *"Principles for the Safety Assessment of Pesticide Residues in Food"*. In the case of dose-response relationships for carcinogenicity, it is stated:

> "The 1983 JMPR recognized that most of the mechanisms of chemical carcinogenesis were not fully understood. In view of the uncertainty surrounding the use of various mathematical models for carcinogenicity assessment, the Meeting decided that the use of safety factors remained a reasonable approach. It also recognized the importance of taking into account all biological activities of such agents in arriving at a safety assessment. This pragmatic approach is used by JMPR in the absence of satisfactory alternatives." (IPCS 1990).

From the scientific point of view, a combination of the EC classification criteria with relevant quantitative risk assessment procedures would seem to constitute the most adequate basis for evaluating carcinogens within the regulatory context, provided that independent scientific expertise is allowed to play a major role.

CANCER RISK ASSESSMENT FOR COMPLEX MIXTURES: THE HAZARDOUS WASTE SITE

The problems involved in applying quantitative cancer risk assessment is suitably illustrated by practical risk assessment of the complex mixtures mostly found at abandoned sites for deposition of hazardous chemical waste. Programs for clean-up of such sites have been initiated in several countries, but the multibillion dollar U.S. "Superfund" effort under the *Comprehensive Environmental Response, Compensation and Liability Act* (CERCLA) of 1980 as well as under the *National Oil and Hazardous Substances Pollution Contingency Plan* (NCP) undoubtedly constitutes the biggest coordinated effort of its kind that has ever been undertaken. During more than 10 years' experience, a logical and structured strategy for risk assessment and risk management has been developed in the U.S. for this purpose. This is the main, but not exclusive reason why "the American way" has been selected here as the basis for the following method for risk assessment of hazardous waste (U.S.EPA 1989a, 1989b, Zamuda 1989). However, when applying Superfund methodology outside the U.S., certain modifications, as indicated below, may be appropriate. Since almost all hazardous waste sites contain a mixture of carcinogens and non-carcinogens, for the sake of completeness the presented methodology includes both types of compounds.

Overview of the U.S. "Superfund" Approach- The main reasons why management of abandoned dump sites for chemical waste presents one of the most difficult tasks in chemicals risk management are the following:

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* IPCS is jointly sponsored by WHO, ILO, and UNEP.

- A mixture of many chemicals are often present
- Exposure may occur by multiple routes
- Ground water contamination is often involved

As a result, any comprehensive system used for over-all risk evaluation for most hazardous waste sites must be simplified to a high degree in order to be practical. The first step in implementation of the Superfund efforts was to rank approximately 30,000 hazardous waste sites known to the U.S.EPA using a *Hazard Ranking System* and place the worst offenders on a *National Priorities List.* Whether or not clean-up is technologically possible or worthwhile, as well as any judgments passed on the amount of clean-up needed, are issues addressed in the *Remedial Investigation and Feasibility Studies* (RI/FS) conducted for the listed sites (U.S.EPA 1985a, 1989a, 1989b).

Data Requirements– Below, risk assessment as the basis for the RI/FS is going to be discussed. The first step involves quality assurance of existing data. If these are of poor quality, no amount of sophisticated modeling will compensate for this deficiency. The most important categories of such baseline data are:

- Analytical data (chemicals in surface water, ground water, air, and biological samples).
- Background contamination (natural occurrence of e.g. arsenic, agricultural pesticide use, etc.)
- Hydrogeology of the area
- Soil characterization
- Meteorological information (prevailing wind direction, etc.)
- Topography
- Demography (affected populations)

More often than not, it is found that existing data are inadequate both with respect to quality and coverage. As to quality assurance, the analytical methods as well as the sampling procedures must be critically evaluated. The identity and quantities of the contaminants present are critical for the whole risk assessment process. Records of previous disposal history are notoriously unreliable and the only way to obtain satisfactory information is usually to drill wells in the area for the purpose of taking soil and water samples. When performing this type of sampling, the unequal distribution of chemicals, which often occurs, must be taken into consideration. If chemical waste is enclosed in buried drums, which are still intact, the contents may escape detection unless a direct hit occurs while drilling. A thin layer of non-aqueous phase liquids, which have a low solubility in water, may float on top of an aqueous phase, or be perched on top of an aquifer. Insoluble solids may be localized to a few sectors in the site, whereas highly water soluble compounds are widely distributed through leaching; the last mentioned type of leachable contaminants may not appear in very high concentrations, but may be distributed throughout a large volume, adding up to a substantial quantity.

Overview of the "Superfund" Public Health Evaluation Process (RI/FS)- The Superfund risk assessment is conducted in two phases. A *baseline public health evaluation* is first made, based on site conditions and projected exposure levels. Here attention is primarily focused on the expected risks in case no action is taken. This evaluation is conducted as soon as a sufficient understanding has been obtained of the chemicals involved, their toxicity, as well as the exposure pathways of main concern. In addition, certain preliminary clean-up goals for selected chemicals based on acceptable risk levels will be made.

In the second phase, a *more refined assessment* is made of the consequences of various remedial options, and environmental concerns may also be important in determining an adequate level of clean-up. As to the latter aspect, in comparison to human health issues, not so much attention has been given to environmental risks in the U.S. One reason being that ecotoxicology is still a very young science, and part of the problem are the difficulties associated with predicting the degree of environmental damage based on laboratory tests on selected target organisms.

The baseline public health evaluation consists of the following steps:

1. Selection of indicator chemicals
2. Determination of human exposures (human intakes)
3. Estimation of risk
4. Assessing the remedial options

Selection of Indicator Chemicals- Sampling carried out at hazardous waste sites often demonstrates the presence of a very large number of chemicals, and it may be both impractical and unnecessarily time consuming to assess the risk of each one. To avoid these difficulties, the Superfund evaluation is based on selected chemicals, referred to as indicator chemicals, that pose the greatest potential health hazard at a site. Parameters that will influence the selection of indicator chemicals are

- Toxicity
- Volume
- Persistence (stability, biodegradability, bioacccumulation)
- Environmental mobility (in air, water, and soil)

It should be emphasized, that the selection of indicators does not represent an adequate risk assessment, and should only be seen as a procedure for *ranking* the individual chemicals found at a specific site according to potential hazard. Thus, the "indicator scores" obtained have little meaning outside the framework of this evaluation process.

Toxicity- In the U.S. Superfund program the hazard scoring is based on "toxicity constants" for non-carcinogens derived from the LOELs (Lowest Observed Effect Levels) for chronic effects times a severity factor. "Toxicity constants" for potential carcinogens are based on the

dose at which 10% incremental carcinogenic response is estimated to occur (ED_{10}). This approach may have certain advantages, but there seems to be little justification in using LOELs instead of ADIs (RfDs), and to replace carcinogen potency factors (CPFs) with an ED_{10}. Also, the use of a severity factor the application of which will always involve a considerable degree of subjectivity may unnecessarily complicate the initial scoring process.

Because of the probable differences in dose-response mechanisms (non-threshold versus threshold), noncarcinogens (n), and potential carcinogens (c) and are scored and selected independently. The following modified algorithm provides *indicator scores (IS)* based on *toxicity indices (T)* that are easier to derive and apply outside the Superfund context:

$$(2)\ IS_n = \Sigma\ (C_{nj} T_{nj})$$
$$IS_c = \Sigma\ (C_{cj} T_{cj})$$

where IS_n or IS_c = Indicator score for chemical $n(c)$ (unitless).
C_{nj} or C_{cj} = the calculated daily intake per kg body weight of chemical n(c) in medium j based on standard assumptions.
T_{nj} or T_{cj} = a *toxicity index* for a non-carcinogenic chemical, *n*, or for a carcinogenic chemical, *c*, with respect to the appropriate route of intake, *j* (units, inverse of dose).

Daily intakes are derived for water, air and soil, respectively, from representative and validated site monitoring data using the following standard assumptions:

Body weight of an adult = 70 kg
Body weight of a child = 10 kg
Daily water consumption = 2 liters
Volume of inhaled air for 24 hr = 20 m^3
Amount of ingested soil = 100 mg/day (10 kg child)
100% absorption in the gut and in the lung

Here, the *toxicity index for a non-carcinogen, T_{nj},* is simply the inverse of the ADI (U.S. equivalent, RfD), and the *toxicity index for a carcinogen, T_{cj},* is set equal to its carcinogen potency factor (CPF, slope factor, q_1*; dimensions = $(mg\ per\ kg\ and\ day)^{-1}$) as derived e.g. by the linearized multistage model. Although the multistage model has been criticized from certain aspects in a previous article (Nilsson 1994), its widespread use has, nevertheless, resulted in the generation of potency data for a fairly large set of carcinogens. It should also be remembered, that risk assessment of the numerous chemicals found at a hazardous waste site represents a very inexact process, and at a preliminary stage the accuracy of the U.S.EPA model will in most cases be adequate.

If, at a later stage it is concluded that the presence of a certain carcinogen will be critical for the overall risk assessment, the use of alternative models for calculating cancer potency for this compound may be considered, and a re-evaluation performed. Some experts would, no doubt, prefer to score non-genotoxic carcinogens together with non-carcinogens using an ADI based on a safety factor which usually is larger than the usual factor 100. When performing a final evaluation, it may also be suitable to introduce more accurate estimates of absorption in man for the critical substance; by ingestion, skin contact and inhalation.

Useful sources for ADIs (RfDs) and CPFs include the *U.S.EPA IRIS (1993) database, the U.S.EPA Health Effects Assessment Summary Tables* (U.S.EPA 1994), *the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles,* as well as the *Joint FAO/WHO Meeting on Pesticide Residues (JMPR) publications* (ADIs only). The U.S.EPA Summary Tables also contain carcinogenic CPFs for a number of radionuclides.

A Hypothetical Example- The following simple example may illustrate the use of the indicator score concept: At a certain hazardous waste site the following chemicals were identified in water and soil samples:

- free cyanide (CN^-)
- 1,2,4-trichlorobenzene
- dicamba (herbicide)
- trichloroethylene
- chromium(6)
- bis(cloromethyl)ether

Of these chemicals, *bis(chloromethyl)ether* has been classified by IARC in Group 1, and *trichloroethylene* has been classified as carcinogen by the U.S.EPA (1985b) as well as by the Swedish National Chemicals Inspectorate. *Chromium(6)* is considered as a carcinogen by the respiratory route, but there is no adequate supporting evidence for carcinogenicity by ingestion. In this case chromium(6) will be scored as a carcinogen (inhalation) as well as a non-carcinogen (ingestion). Representative concentrations at the site (geometric mean) for the six chemicals, ADIs (RfDs), cancer potency factors (CPFs), and standard intakes based on presence in ground water, inhaled air, and ingested soil are shown in **Table II.** The modified indicator score (IS) is the sum of concentration (C) times the toxicity index (T) for each medium. In this small group of compounds, *cyanide, 1,2,4-trichlorobenzene,* and *chromium(6)* give the highest scores among the non-carcinogens, while *bis(chloromethyl)ether* clearly ranks as number one among the carcinogens. The ADIs and CPFs are known for all the identified chemicals. However, for many compounds found at hazardous waste sites this is often not the case. For substances that have been less well investigated from the toxicological point of view, an approximate estimate based on whatever information is available must then be obtained from a qualified expert.

The Importance of Physico-Chemical Data- It was mentioned above, that in addition to toxicity, factors like *persistence (biodegradability, bioacccumulation)* as well as *environmental mobility (in air, water, and soil)* are important when selecting indicator chemicals. Without actually investigating

TABLE II. INDICATOR SCORES FOR CONTAMINANTS

CHEMICAL	MEDIUM *water* Conc. mg/L	*water* Intake CT mg/kg		*air* Conc. mg/m³	*air* Intake CT mg/kg		*soil*[1] Conc. mg/kg	*soil*[1] Intake CT mg/kg	
Non-carcinogens									
cyanide (RfD-0.02) **IS_n = 55**	10	0.29	14.5	ND	—	—	80	0.8	40
dicamba (RfD=0.03) **IS_n = 1.0**	0.4	0.01	0.3	ND	—	—	2.0	0.02	0.7
1,2,4 -trichlorobenzene (RfD-0.01) **IS_n = 74**	8	0.23	23	0.1	0.03	3.0[2]	48	0.48	48
chromium (6) (RfD=0.005) **IS_n = 77**	0.9	0.026	5.2	0.5	0.01	2.0[2]	35	0.35	70
Carcinogens									
trichloroethylene (oral CPF=0.01[3] inh. CPF=0.01) **IS_c = 0.03**	80	2.3	0.023	0.6	0.17	0.002	12	0.12	0.001
chromium (6) (inh. CPF= 41; oral CPF=NA) **IS_c = 0.4**	0.9	0.026	NA[4]	0.05	0.01	0.4	35	0.35	NA[4]
bis (chloromethyl) ether (oral and inh. CPF=220) **IS_c = 3.1**	ND	—	—	ND	—	—	1.4	0.014	3.1

[1] for a 10 kg child (See text); [2] In absence of establisched inhalation RfDs, oral RfDs have been used. [3] U.S. EPA 1985b; [4] NA = Not aplicable; chromium(6) is considered to be carcinogenic only by inhalation; ND = Not detected

these parameters in full detail, certain physical properties may be used as ***surrogate data*** at this initial screening stage. These are *water solubility, vapor pressure (Henry's law constant), organic carbon partition coefficient (K_{OC}), octanol/water partition coefficient (K_{OW}), chemical/photochemical stability as well as the quotient biological oxygen demand/chemical oxygen demand (BOD/COD)* (The last mentioned two parameters are not utilized by the Superfund process for selection of indicator chemicals). Commonly used sources for this type of information are the *U.S.EPA Superfund manuals* (1989a, 1989b) and the monograph by *Verscheuren* (1983). It should be mentioned, however, that the accuracy of some of the individual data may need verification.

Water solubility- Highly soluble chemicals can be rapidly leached from wastes and contaminated soil and are generally mobile in ground water. Solubility is one of the controlling factors affecting leachate strength and migration of chemicals from waste sites. From this point of view a high solubility indicates a high potential for exposure. Soluble organic chemicals tend, on the other hand, to be more readily biodegradable than those with a low solubility.

Vapor pressure (Henry's law constant) is a measure of volatility, and should be considered at sites where air exposure pathways are important.

The organic carbon partition coefficient (K_{OC}) is a measure of the relative adsorption potential for organic compounds and is a great importance, especially with respect to aqueous pathways. K_{OC} is expressed as the ratio of amount of chemical adsorbed per unit weight of organic carbon to the concentration of the chemical in solution at equilibrium. Therefore:

$$(2) \qquad K_{OC} = \frac{\text{mg adsorbed/kg organic carbon}}{\text{mg dissolved/L solution}}$$

The normal range of K_{OC} values is from 1 to 10^7 with higher values indicating greater adsorption potential. K_{OC} is chemical-specific and essentially independent of soil conditions. Further, it shows a good correlation with the octanol/water partition coefficient (K_{OW}) an indicator of solubility in fat and which is related to bioaccumulation. The significance and interpretation of K_{OC} varies with different exposure pathways. For ground water low values

indicate faster leaching from the waste source into an aquifer and relatively rapid transport through the aquifer. Thus, for a chemical with a low K_{OC}, which is present at a site where groundwater exposure is important, and where there is a high soil concentration of the chemical, consideration should be given to select this chemical in spite of a low IS score. This may still hold when available ground-water monitoring data indicate only low concentrations of the same chemical. A combination of low K_{OC} and high soil concentration indicates that significant releases of the chemical to ground water may occur in the future.

For surface water pathways, K_{OC} also has several significant implications. A high K_{OC} indicates tight bonding of a chemical to soil, which means that less of the chemical will be dissolved in site runoff, but also implies that runoff of contaminated soil particles will occur over a longer time period. Once a chemical gets into surface water, a high K_{OC} may be of great concern because it indicates a bioaccumulation potential.

Chemical stability and BOD/COD are important for assessing persistence. Important removal processes are phase transfers (e.g., water to air, soil to water), chemical transformations (hydrolysis, photolysis), and biological transformation. Information on the stability of a chemical in presence of water and oxygen should always be retrieved. The biochemical oxygen demand (BOD) represents the oxygen consumption by an aerobic mixed microbial culture when degrading a certain quantity of the tested organic substance during a specified time period. The chemical oxygen demand (COD) is the theoretical number of oxygen equivalents consumed in oxidation of the same compound by permanganate or acid dichromate. A high BOD/COD ratio indicates that the compound is readily degradable, whereas a low ration indicates slow degradation.

Final Selection of Indicator Chemicals- When making a final selection of the indicator chemicals, all pertinent information should be integrated in the same work sheet, as illustrated in **Table III** for our hypothetical waste site. Among the non-carcinogens *cyanide* and *chromium(6)* are particularly worrisome from the point of view of soil and groundwater contamination; less so with respect to cyanide when present at low concentrations in surface water, since it is fairly rapidly oxidized and does not bioaccumulate. Chromium(6) will relatively rapidly be reduced to less toxic chromium(3) in surface water containing organic material. *1,2,4-Trichlorobenzene* is a potential problem with respect to both ground and surface water; monitoring data indicates a substantial groundwater contamination; it has a high K_{OC} and high K_{OW} indicating a bioaccumulating potential when released to surface waters. Dicamba should not be given a high priority.

Of the carcinogens, *bis(chloromethyl)ether* has a high IS_C, and is an established human carcinogen (IARC 1987). At a first glance this compound seems to constitute the largest threat to human health at his site. In absence of remedial action, chromium(6) and trichloroethylene, may also constitute a potential cancer hazard; the first mentioned chemical due to contamination of surface soil,

TABLE III. FINAL SELECTION INDICATOR CHEMICALS

CHEMICAL	IS	Water sol. (mg/L)	Volatility (mm Hg)	K_{OC}	Persistence
Non-carcinogens					
cyanide	55	very high	very low	low	low
dicamba	1.0	6500	0.04	high	moderate
1,2,4-tri-chlorobenzene	74	30	0.3	9200	log k_{OW}=4.3
chromium (6)	77	very high	very low	very low	high (groundwater)
Carcinogens					
trichloro-ethylene	0.03	1100	58	126	log k_{OW} = 2.4
chromium (6)	0.4	very high	very low	very low	high (groundwater)
bis (chloromethyl) ether	3.1	very high	30	1.2	$t_{1/2}$«12 hr

generating dust close to the site, but both compounds are also present in high concentrations in the water of the monitoring wells. Bis(chloromethyl)ether is, on the other hand, a highly unstable compound that is rapidly hydrolyzed in water. This is certainly the reason why it was not detected in the water samples. For this reason, there will be negligible exposure via surface or ground water, but its presence in a few of the soil samples (leaking drums?) may indicate potential exposure via ingestion by children playing at or near the site, or via airborne soil particles. The carcinogens present must, evidently, be subjected to further detailed analysis.

All six chemicals above, with the possible exception for dicamba, would be included for further assessment if they were the only ones found at a Superfund site. However, the number of chemicals detected are typically much larger. Out of this larger set 10-20 are usually selected as indicator chemicals. One factor which is very important in real life situations, is the total volume of the chemical which is present at the site. Monitoring may not indicate very high concentrations in any particular medium, but if contamination is spread over a large area, this may indicate that the total amount of the chemical is high.

Determination of Human Exposure

Identification and Characterization of Exposure Points- An exposure pathway consists of four necessary elements:

- A source and mechanism for release of the chemical
- A transport medium (air, water)
- A point of potential human contact
- A human exposure route

The total risk posed by a hazardous waste site is the sum of the risks from each exposure pathway. These risks may not always be additive because they may represent risks to different populations. In many cases release, transport, and exposure occur by the same medium, but often intermedia transfers occur, e.g. evaporation from surface water into the atmosphere, or exposure from ingestion of fish from a contaminated lake. For each combination of release source and transport medium the location of highest likely individual exposure (exposure point) is then identified. However, Superfund risk assessment is concerned with individual risk as well as risk to exposed populations. Thus, besides locations with highest individual exposures, exposure points with lower predicted risks, e.g. a public water supply, are included if a larger population is a potential target.

Estimation of Exposure Point Concentrations- After the main potential exposure pathways have been determined, environmental concentrations for each indicator chemical is estimated more accurately at each of the exposure point locations which have been identified. This is achieved in two steps. First the amount of chemicals is estimated that can be released to the environment by the various sources identified terms of *present* release rates. Given these release quantities, an assessment of the current environmental transport and fate of each indicator substance is made. By combining site monitoring data with environmental modeling, the extent and duration of the projected *future* human exposure in the absence of any remedial action is then determined.

It is beyond the scope of this review to present environmental exposure assessment in any detail, and for further guidance the author is recommended to consult the literature available in the field (IAEA 1982, Travis 1985, U.S.EPA 1989b). Basically, two types of data are used: Monitoring information and data from environmental modeling. For an adequate exposure assessment both types of input are usually required.

Monitoring data have the advantage of being actual measurements of concentrations on and in the vicinity of the site. However, it should be remembered that they represent current and/or past conditions, but do not give a clear indication of future conditions. Over-reliance on monitoring data may result in the underestimation of risk from chemicals which are only slowly released. Further, monitoring data in the vicinity of the site may not be representative of the true extent of the contamination in the area.

Environmental modeling has the advantage that an idea of long-term developments can be obtained, but suffer from the disadvantage that their use are associated with a considerable degree of uncertainty. Techniques to estimate environmental concentrations vary in sophistication from simple, desk-top methods that provide rapid, order-of-magnitude projections, to more rigorous approaches involving computer modeling. Ground water transport modeling, in particular, has been found to present great difficulties, and most current models have not been sufficiently validated.

Models that have been extensively used in the Superfund context include the *Atmospheric Transport Model (ATM)* or the *U.S.EPA Industrial Source Complex Long Term Model (ISCLT)* (U.S.EPA 1987), a Gaussian dispersion model appropriate for simulating the atmospheric transport of chemicals from a variety of source types. Dispersion models simulate physical processes of transport and dilution of airborne pollutants, and have a more general applicability directed towards describing time-averaged conditions. Principal data requirements are source characterization (stack emission, area sources like storage piles, erosion, etc.), source emission rates and a meteorological input consisting of wind speed, wind direction, and atmospheric stability. Simple air dispersion models may be used to determine maximum air concentrations for screening purposes, whereas more elaborate models are needed for more complicated situations, e.g. for interaction of multiple sources and geographically complex terrains. A commonly used surface water model is the *Exposure Analysis Modeling System (EXAMS)* which

simulates the ultimate distribution and concentration of organic chemicals in aquatic systems (Burns *et al.* 1982). *The Analytical Transient One-, Two-, and Tree-Dimensional Simulation Model (AT123D)* is a groundwater transport model that is designed to simulate the rate of transport and transformation in the saturated zone (Yeh 1981). In addition to modeling to estimate exposure from air, surface and groundwater, the *U.S.EPA Terrestrial Food Chain Model* (U.S.EPA 1986b), or an improved version thereof (Travis *et al.* 1986) can be used to calculate exposure through ingestion of contaminated plants, from consumption of products from animals which have fed on contaminated plants, as well as from ingestion of fish caught from local contaminated surface waters.

Risk Assessment- At this phase acceptable estimates of the exposure at each critical location should be available. If there exists some kind of official standard for the indicator in question, like a drinking water standard, the estimated levels can now be compared to such values directly. The problem is that only for relatively few substances do adequate standards exist which have been based on a proper hazard evaluation. However, ADI (RfD) values and carcinogen potency factors can be found for a larger number of chemicals, and a simplified process utilizing such data is described below.

Using standard assumptions for air, water and food intakes, the total intake of indicator chemical is calculated for each exposure location. Using our previous example, it is assumed, that after in-depth analysis significant exposure to residents close to the hypothetical site could only be demonstrated for *cyanide, 1,2,4-trichlorobenzene, chromium, bis(chloromethyl)ether,* and *trichloroethylene.* For the noncarcinogens the chronic risk is then assessed **(Table IV)** by determining a Hazard index, defined as the sum of the ratios between the estimated total chronic daily intakes (CDI) and the ADIs (RfDs). Since the hazard index in our example is much larger than 1, this indicates, that there is a risk for long-term toxicological effects in residents close to the site, and that some kind of remedial action is warranted.

Individual life time cancer risks are calculated by multiplying the total chronic daily intake (CDI) with the carcinogen potency factor (CPF). For the most exposed individuals close to the site the results of the cancer risk assessment in our hypothetical example are shown in **Table V.** The added total cancer risk is around 6%, mainly due to a possible exposure to contaminated soil at the site. Even if this represents an exaggerated worst case situation (children playing close to, and at the site itself), the projected level of risk is clearly unacceptable. A much smaller cancer risk also seems to exist due to the presence of trichloroethylene in drinking water.

Risk Management Assessing the Remedial Options- Risk estimation may be based on a set of three different options: Realistic assumptions, conservative assumptions, and worst cases assumptions. On which assumption emphasis should be laid may differ according to circumstances and is also a matter of policy, but it is often advantageous to have estimates based on all three options. Which of the above mentioned assumptions that is used for risk characterization should under all circumstances be stated. At hazardous waste sites in the U.S., the U.S.EPA calls for a reasonable maximum exposure estimate under current and future land-use conditions. In practice, this does not amount to a worst case situation, but represents a conservative alternative. In view of the differences between U.S. and other countries in assessing non-genotoxic carcinogens, some adjustments of current Superfund practice may be appropriate for use outside U.S. A particular carcinogen selected according to Superfund criteria is often found to "drive" the whole risk assessment procedure. In case a large capital investment is at stake, it may be found desirable to re-interpret the basic cancer data for this chemical and to re-evaluate the adequacy of the scientific basis for calculation of its cancer potency. If the required expertise is available to accomplish such a task, interpretation of the experimental data could e.g. be based on the principles laid down by the Commission of the European Communities (EEC 1993c).

Remedial action may include provision of alternative water supplies, containment of wastes (capping, etc.),

TABLE IV. CALCULATION OF CHRONIC HAZARD INDEX

	Intake by (mg/kg)					
CHEMICAL	Air	Water	Soil	Fish	CDI	CDI/ADI
cyanide	—	0.04	—	—	0.04	2.0
1,2,4-trichloro-benzene	—	0.02	—	0.001	0.021	2.1
chromium(6)	0.001	0.06	0.001	—	0.062	12
Hazard index						16.1

TABLE V. CALCULATION OF CANCER RISK

CHEMICAL	Intake by (mg/kg) Air	Water	Soil	Fish	CDI	Individual lifetime risk
chromium(6)	0.001	—	—	—	0.001	0.04
bis(chloromethyl) ether	—	—	0.0001	—	0.0001	0.02
trichloroethylene	—	0.006	—	—	0.096	0.001

bulk excavation of wastes for incineration, landfill or treatment, on site vitrification whereby organic contaminants are destroyed and metals trapped in a glass-like matrix, etc. When deciding to clean-up an abandoned waste site, it is of paramount importance to check that the clean-up measures will not result in a higher total risk than what is the case if no remedial action is taken. In the baseline public health evaluation process, the risk from exposure by main potential pathways have already been identified, but they should be re-assessed for each specific remedial alternative under consideration.

At which risk level remedial action should be triggered is very much depending on the size of the population affected, and for a proper assessment worst cases situation should be complemented with a more representative exposures for people living around the site. Remedial action under Superfund is usually initiated at cancer risks ranging from one in 100,000 to one in 1,000,000, and this is why clean-up under Superfund is largely driven by the presence of carcinogens. In our hypothetical case, preventing exposure of children to contaminated soil which is technically feasible within a limited budget, e.g. by capping of the site will drastically reduce this potential risk.

Some exposure routes identified for the baseline analysis may not exist for certain remedial alternatives, while some new exposure routes may result. As mentioned above, capping of the hypothetical site above will prevent exposure of children against ingestion of chromium, trichloroethylene, and traces of bis(chloromethyl)ether by soil ingestion, and minimize exposure to contaminated dust close to the site. Taking down this kind of exposure to a negligible level would bring out trichloroethylene via drinking water as the major cancer risk. However, to reduce exposure to this solvent via water would conceivably involve much higher capital expenditures. Further, long-term pumping and airstripping treatment of groundwater may appreciably increase the potential for inhalation exposure. Thus, for any kind of remedial action a renewed assessment of trichloroethylene would seem desirable. Excavation of the site may be associated with a significant occupational hazard associated with potential exposure to the potent human carcinogen, bis(chloromethyl)ether.

As pointed out in the previous articles (Nilsson 1993, 1994), U.S.EPA's risk hazard assessment of trichloroethylene (U.S.EPA 1985b) is based on induction of liver tumors in rodents, the relevance of which to man has been seriously questioned. Data from epidemiological studies also seem to indicate, that the carcinogen potency factor has been considerably overestimated. In addition, the projected intake of trichloroethylene by water from wells in the vicinity of the site would be lower than that to chloroform formed by chlorination of most public drinking water supplies (Ames *et al.* 1987). Chloroform has also been classified as a carcinogen by U.S.EPA (IRIS 1993). Under these circumstances the potential hazard posed by trichloroethylene can hardly viewed as a primary concern. Nevertheless, the high concentration of chromium(6) in drinking water at our hypothetical site would require immediate action on basis of other types of toxicity. If only a few residents are involved, the installation of adequate filters in the homes may suffice, but if a larger population is exposed, other technical solutions must be found.

One of the greatest problem in risk management associated with hazardous waste sites is the contamination of groundwater. Once chemicals have contaminated an aquifer, they remain for a very long time. The best current techniques may lower the concentration of contaminants and prevent further contamination of the groundwater supply, but it is usually almost impossible to restore the ground water quality to previous conditions. One horrifying example from the highly industrialized East Coast of the U.S. is related below.

At the Whitmoyer Laboratories Site, Meyerstown, Pennsylvania, which is heavily contaminated with arsenic and some organics like aniline, groundwater at the site was found to contain up about 10,000 ppm of inorganic arsenic, with over 30 wells affected in the surrounding area. These wells had arsenic levels ranging from 0.01 ppm to 300 ppm. In 1965 ground water was started to be extracted and the arsenic precipitated. By 1971 a total of 200,000 kg had been recovered in this manner, and the concentration of arsenic in the monitoring wells at the site was actually reduced to between 10 to 30 ppm. However, since about 2 million kg of arsenic had been deposited in a leaking vault, and the soil was still heavily

contaminated over a large area, leaching into ground and surface water continued. In 1990 the concentration in some of the monitoring wells was back up to around 200 ppm (ERM 1990). After a renewed focused risk assessment under Superfund, an attempt to restore the site using technology will eventually be made. Depending on type of remedial action, the projected costs for clean-up of this site has been estimated at between 6 and 13 million USD (U.S.EPA 1990). However, even when using best available technology, the arsenic contamination in soil and groundwater of this area will remain a serious problem far into the future.

PLACING CANCER RISK FROM CHEMICALS IN PERSPECTIVE

Population Size- If the object of our case study above had been an abandoned chromium mine located in a dry and sparsely populated area, it would hardly be considered a national priority for clean-up. When, on the other hand, 75,000 tons of chromate containing wastes have been deposited within the borders of Mexico City, as is the case at Municipio de Tultitlan (Gutierrez-Ruiz *et al.* 1990), a completely different perspective on overall risk emerges.

The importance of defining the size of the exposed target population cannot be over-emphasized. Assuming a yearly excess cancer mortality risk of 10^{-4}, i.e. one in 10,000, induced by exposure to a specific agent, this corresponds to one fatality per 100 years in an exposed local population of 100 people. The same risk applied to the entire population in New York of 8 million amounts to 800 persons per year. Given a balanced choice between the two alternatives for risk reduction, common sense dictates that resources should be allocated towards saving the 800 lives per year rather than the one single life over a period of hundred years. For political reasons, and depending on media attention, often little distinction is made between the two situations. Further, the inhabitants in the small community of 100 persons may demand the same level of safety as e.g. the inhabitants of New York.

The *Chernobyl accident* may be cited as another example. Measurements of radiation dose to the 24,000 people living between 3 and 15 km from the Chernobyl plant indicate, that the total integrated dose which will be received by this population during their lifetime from the Chernobyl nuclear accident will be 10,500 manSv (1.05 million man-rems), and for the total population in Byelorussia and the Ukraine (75 million) the collective dose will be about 290,000 manSv (IAEA 1986). Contrary to the reporting in news media, the dosimetry (in contrast to the health monitoring) carried out by the previous Soviet authorities has, in general, been found to be valid by an independent group of experts under the *International Chernobyl Project* (IAEA 1991). Actually, in the official records for some significant radiation sources like radioactive strontium and plutonium in soil as well as strontium and caesium in milk the doses were found to be overestimated. Using the most recent conservative risk estimate from the BEIR V committee (1990) of 0.08 deaths in cancer per manSv, the estimated collective doses mentioned above will result in 840 extra deaths in cancer in the area close to the reactor, and a startling 23,200 extra deaths for the larger population. However, these projected risk estimates seem somewhat less alarming when compared with the expected normal incidence of cancer during a life-time for the two populations; 5,000 and 15 million, respectively. Smoking will certainly claim more lives than exposure to radiation in this larger population.

Risk-risk comparisons- Government agencies' concern in various countries for risks induced by man-made chemicals varies from a virtual total disregard, as is the case in many developing countries, to gross overreaction in chemophobic societies, like U.S. and some of the Nordic countries. According to several estimates the cancer risk in e.g. Sweden due to benzene exposure from all sources (including occupational) may be placed at about 2 cases per year in a population of 8.7 million (Swedish Cancer Committee 1984, Victorin *et al.* 1993). The risk to the public is roughly of the same magnitude as the risk of being killed by lightening. In spite of this negligible risk, all self-service gasoline stations in Sweden must be labeled with a cancer warning with skull and crossbones. In comparison with the peril of dying from benzene exposure, other hazards associated with filling petrol at gas stations (cars, criminals, etc.) probably pose much greater risks. However, the most damaging result of such overambitious information efforts may be an erosion of the respect for the message contained in a cancer warning, leading to underreaction in a situation where a substantial risk, e.g. at the work place may be present.

The common goal in the U.S. is to regulate any life-time cancer risk that lies above 1 in 100,000 to 1 in a 1,000,000. This means, that the elimination of a factor which causes one case of cancer in a population of one million, results in lowering the cancer incidence from 200,001 to 200,000 during the same time period. It should be remembered, that the normal life-time risk for cancer in the industrialized Western world is about one in five. In developing countries with a shorter expected life span it is somewhat lower. If the regulatory goal in the U.S. is considered justifiable or not, is up to the policy makers to decide.

By introducing the concept of risk-risk comparison, a more realistic attitude towards cancer risks can be promoted. In our hypothetical hazardous waste site discussed above the hypothetical cancer risk from the presence of trichloroethylene at about 20 µg/L was compared to exposure to trihalomethanes, like chloroform, which have been found to be present in normal chlorinated drinking water at about 80 µg/L in the U.S. (Ames *et al.* 1987). Unfortunately, except for pharmaceuticals, risk-risk comparisons are rarely considered by national regulatory agencies concerned with chemicals. Further, such agencies do not seem very well equipped to face the problem of replacing toxic substances, having important uses, with

alternatives which may be problematic from other aspects, or that have been less thoroughly investigated.

For certain pesticide uses the risk-benefit situation is analogous to that encountered when prescribing drug treatment for a disease. The hazards associated with pesticide use must be balanced, not only against increased food output, but also with respect to prevention of crop contamination by highly toxic (and carcinogenic) mycotoxins (see below). The inadequate attention paid by regulatory authorities in Sweden to the role of mycotoxins in the etiology of human cancer was underlined by the Swedish Cancer Committee (1984).

Industrial chemicals, pesticides, mycotoxins and food additives sort under different regulatory agencies or even ministries between which co-operation is usually less than optimal. It is, therefore, not surprising, that for regulatory purposes comparisons are not made between risks from pesticide residues in food on one hand, and risks associated with dietary factors, food additives, or toxins on the other. If solanine and chaconine were pesticide residues, potatoes would not be permitted on the market in most developed countries because of their high content of these toxic alkaloids (20-100 mg/kg), and also because these substances have not been adequately tested for long-term effects. Although exposures to man-made and natural chemicals occur by identical routes of administration and contribute to the same toxicological end points, they are, regrettably, being judged by completely different standards.

Society's implementation of a double standard is particularly obvious in the regulation of presumed carcinogenic pesticides. An example is provided in the analysis by Nilsson *et al.* (1993). In **Fig. 1** the hypothetical relative life time cancer risks for the general population due to exposure to the pesticides propoxur (home owner use) and daminozide (dietary exposure) are compared to those derived from sodium saccharin present in 2 cans of soft drinks per day and to eating 50 g of the common cultivated mushrooms of commerce *(Agaricus bisporus)* twice a week.

Although it is highly questionable if the tumors induced by propoxur in rodents are at all relevant to the human exposure situation, this pesticide has been classified as a carcinogen in the U.S. as well as in Sweden. Sodium saccharin has been used as reference for propoxur because both compounds seem to induce tumors in the rodent bladder by a similar mechanism.

Daminozide (Alar) is converted in the organism to an asymmetric hydrazine derivative (UDMH). The common mushroom contains potent genotoxic carcinogenic hydrazine derivatives that induce a high incidence of malignant tumors at multiple sites in the mouse, in particular in forestomach, bone, and lungs (Toth and Erickson 1986). Although more potent than either daminozide or UDMH, chemically and mechanistically these hydrazines provide a relevant basis for comparison with the computed dietary risk from daminozide. This risk is here represented by the computed dietary risk before U.S.EPA canceled all food uses (about 3 in 100.000). The life time cancer risk from eating 50 g ordinary mushrooms twice a week has been included in the same diagram.

As can be seen from Fig. 1, the hypothetical risk from

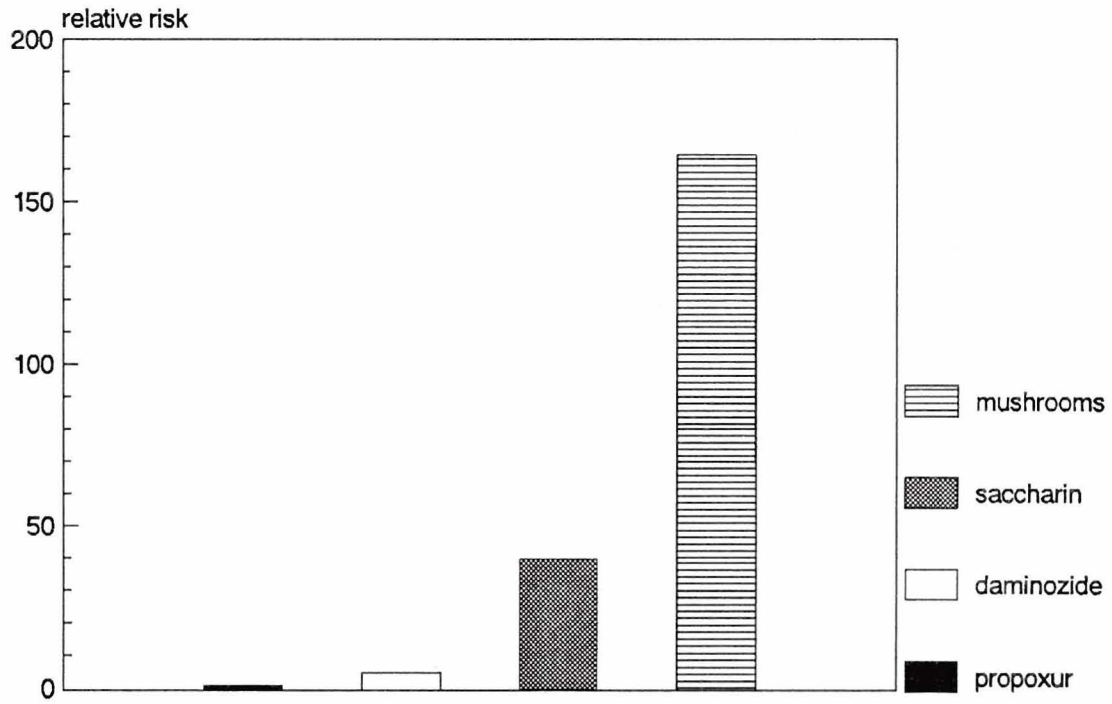

Fig. 1. Relative life-time cancer risks for exposure to propoxur (applicators), saccharin (soft drinks), and from eating common cultivated mushrooms *(Agaricus bisporus)* (From Nilsson *et al.* 1993).

exposure to propoxur, as well that associated with food use of daminozide, is much lower than that associated with saccharine in soft drinks, and is negligible compared to that resulting from the consumption of cultivated mushrooms twice a week. The computed lifetime risks correspond to about three cases of cancer in 10,000 for consuming two cans of soft drinks (0.6L) per day containing approximately 200 mg of sodium saccharin, and a risk of about two cases in 1,000 for eating 15 g commercial mushrooms per day. This is to be compared with the risks in the range one in one million to one in a trillion for current U.S. exposures to propoxur.

With respect to the presence of potent toxins in common foods, it is of interest to note, that no pesticide product exhibiting the toxicological properties of the common mushroom would have the slightest chance to become approved for registration today in a developed country. This raises the question if regulation as currently implemented of pesticides that are suspected of having carcinogenic properties is at all cost-effective, when aiming at the desired risk levels usually considered to be negligible for the general population (in the U.S. usually 1 in a million), or could these resources be spent more effectively elsewhere for the general prevention of cancer?

There is no doubt that for highly exposed smaller populations, like workers, the cancer risks induced by certain industrial chemicals can be high. However, the exposure scenario for other groups is usually quite different. The causes of cancer in the general population have been comprehensively analyzed by the *Office of Technology Assessment of the U.S. Congress* (Doll and Peto 1981) as well as by the *Swedish Cancer Committee* (1984), appointed by the Swedish Government and placed under the chairmanship of the Nobel Prize laureate Sune Bergström. In the reports from these bodies it is concluded with respect to man-made chemicals, that industrially produced chemicals, in comparison to life-style related factors, evidently make a very modest contribution to the *over all* cancer incidence in the general population of industrialized nations.

SPECIAL PROBLEMS ASSOCIATED WITH THE EXPORT OF CARCINOGENIC CHEMICALS TO DEVELOPING COUNTRIES

The assessment of carcinogenic properties of chemicals may differ considerably between highly developed countries, a fact that has caused considerable confusion in developing nations and has occasionally resulted in the creation of non-tariff barriers of trade. Information about the carcinogenic properties of specific chemical products imported to a developing country originates from various sources: industry, international and national organizations, technical literature, newspapers, etc. The importance of the producer as a source of knowledge in this context is obvious, and was again underlined in a recent international survey on pesticides (Nilsson *et al.* 1993). Thus, the government agencies responsible for approval and registration of pesticides in countries like Egypt and Thailand almost exclusively relied on the importer/producer for toxicological data. One frequently encountered problem is that the local importer/registrant for pesticides in a developing country can submit a biased selection of reports to obtain registration. This information may not always be complete with respect to major adverse effects to health and/or to the environment. How could one conveniently detect such information gaps for a pesticide?

According to the experience of this author, the most complete pesticide registration database is available at the Office of Pesticide Programs of the U.S.EPA.* This Office will upon request provide a brief summary of all relevant material for individual pesticides in the form of so called "Tox Oneliners" which list all submitted reports. These summaries are also supplemented with short notes on the main findings as well as a classification of each study with respect to quality. Using the "oneliners", officials responsible for registration of pesticides in a developing country can easily check locally submitted files for obvious information gaps. However, when assessing the supercondensed toxicological information contained in these documents, their specific relation to the context of U.S. pesticide legislation should not be forgotten, especially with respect to carcinogenic effects. For this reason, the evaluator is well advised also to consult e.g. the reports from the **Joint FAO/WHO Meeting on Pesticide Residues (JMPR)** published by FAO in Rome, where all toxicological information has been evaluated by an international team of experts representing the various regions of the world.

Information on regulatory action taken by industrialized countries is often distributed to certain contact points in developing nations regularly so from international organizations and several U.S authorities. This information may, or may not reach the appropriate destination. The absence of such information to the user may have several explanations; Thus, when working as a WHO advisor in a developing country of major importance, this author found that the valuable documents on hazardous chemicals produced by the **International Programme on Chemical Safety** (IPCS), and which for years had been regularly sent free of charge to this, as well as to other governments, had never reached further than the library store room at the responsible ministry. The main problem with export of chemicals today is certainly not that information on the hazardous properties of specific chemicals is difficult to obtain from the exporting nations; the main obstacle is often a malfunctioning local distribution of adequate information presented in such a way that it can be readily understood by those who really need it. In most developing countries the responsible authorities lack either the competence, resources, or motivation or a combination of all of these requirements to perform this task. For this reason, industrial ventures from developed countries operating in these parts of the world share a heavy responsibility for implementing adequate precautionary measures on their own initiative.

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The London Guidelines for the Exchange of Information on Chemicals in International Trade (FAO/UNEP 1991) as amended on May 25 1989, define notification procedures for chemicals that have been banned or severely restricted in exporting countries. The purpose of this notification routine is to give the competent authorities in importing nations the opportunity to assess the risks associated with such chemicals, and to institute appropriate actions with regard to the notified chemical products. In addition to information exchange and export notification, the London guidelines lay down principles for a **Prior Informed Consent Procedure (PIC)** which presumes a formal decision by the importing country as to whether or not they wish to receive future shipments of chemicals which have been banned or severely restricted. When a chemical has been banned or severely restricted by 5 or more countries, IRPTC of UNEP notifies each country participating in the PIC information exchange network and provides the designed national authorities with a decision guidance document pertaining to the chemical in question. Although well intended, the achievements of this program have been limited. The most serious drawback is that the "candidate list" of chemicals to be included in the PIC procedure is pitifully small and almost completely restricted to pesticides. Also, the format for reporting the information to be supplied must be considered inadequate in some respects. Little is known about how the information obtained by the importing countries in this way is used and disseminated.

When information about regulatory decisions are obtained by whatever channel, it must be remembered that this information is rarely adopted to the needs of a reader in another country. For this reason national regulatory decisions are often cited out of context and misinterpreted. Often such news circulate for the first time in a less than adequate fashion in the news media. However, it is not always justified to put the whole blame on a faulty news communication. In dealing with national agencies, one main problem encountered is the lack of transparency in the decision making process *per se,* coupled with a certain reluctance to explicitly state the whys and wherefores.

Should man-made chemicals be given priority with respect to induction of cancer in Third World populations? Not necessarily. Fungi are the most common cause of postharvest deterioration of field crops. FAO in 1977 estimated that about 1 billion tons of world agricultural products might be threatened by molds (FAO 1977). Besides economic loss, this kind of infestation may result in the production of highly toxic (and carcinogenic) mycotoxins (Pestka and Casale, 1990). The problems are accentuated in tropical and sub-tropical climates, where mycotoxins is a major health concern. Although, potentially hazardous, it should not be forgotten that the rational use of fungicides as well as insecticides is essential for the prevention of such contamination (FAO, 1977).

Whereas it can safely be stated, that in many areas the risk posed by carcinogenic mycotoxins may, in general, be much greater than residues from carcinogenic pesticides in food (Ames *et al.*, 1990a, 1990b; Nilsson *et al.*, 1993), this does not mean that the use of hazardous man-made chemicals should be underestimated. On the contrary. In comparison with highly developed countries, the use of hazardous chemicals often presents a radically different scenario in developing nations. **DDT** was characterized by a very low human toxicity, but it had a high biaoccumulation potential in the food chains of ecosystems. Banning of this insecticide opened the door for pesticides that are much less persistent, but which are often much more hazardous to human health an important factor to be taken into consideration in countries where pesticide poisonings claim many lives. Many hazardous compounds, which can safely be handled in a technologically advanced society, may pose an unacceptable risk in countries lacking an infrastructure for implementing adequate risk-reduction measures. This includes a number of carcinogenic compounds, like arsenic, asbestos, benzene, beryllium, etc., to which large populations of workers in countries where occupational health legislation remains weak are still exposed at unacceptably high levels .

CONCLUSIONS

In the regulatory environment the impact of science is often secondary to other sources of influence. Nevertheless, scientific integrity as well as common sense demand that risk management decisions are based an attempt to estimate real risks rather than perceived risks.

Since only a limited fraction of the total national budget is available for risk prevention, knowledge of the approximate magnitude of risks from exposure to various sources of carcinogenic agents is necessary when setting rational priorities for risk management. Although the discrepancies found between various countries in choice of methodology for quantitative risk assessment calls for international harmonization, any system adopted for regulatory purposes must contain enough flexibility to permit an assessment on a case-by-case basis based on in-depth analysis. More accurate methods for hazard assessment can be developed by taking mechanistic aspects into consideration. However, depending on the area of application, simplified approaches for screening purposes are also required. The methods currently used in the regulatory process must undergo a continuous revision to accommodate scientific progress.

By introducing the concept of risk-risk comparison, a more realistic attitude towards cancer risks can be promoted. Such comparisons demonstrate e.g., that the risk from pesticide residues in food have, in general, been grossly exaggerated, especially when compared to the presence of potent natural carcinogens. Unfortunately, national governments seem to lack an over-all risk management policy and adequate mechanisms to implement a comprehensive program for total risk management.

The use of hazardous chemicals in developing countries is associated with special problems, mainly due to the lack of an infrastructure for implementing adequate risk-reduction measures and inadequate distribution of

information that can readily be understood by the local users of chemicals. For this reason, industrial ventures from developed countries operating in these parts of the world share a heavy responsibility for risk-management.

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