Current and Future Herbicide Risk Assessment in Europe and United States

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Abstract

The risk assessment process offers regulators, registrants, public interest groups and users a means of weighing apparent health and environmental effects of pesticides (herbicides) and other chemicals, and measuring their safety for use. This paper examines three key areas of risk assessment: (1) Maximum Tolerated Dose (MTD), (2) Cancer Classification and Risk Assessment, and (3) Ecological Risk Assessment. The American, European and International approaches in these important areas are compared and discussed in light of the current scientific knowledge.

Key words: risk assessment, herbicide, global harmonization

Introduction

Pesticide (herbicide) risk assessment practices in the United States and Europe have changed dramatically during the past 10 years since the adoption of quantitative procedures that link experimental hazards identified in animals and plant species with human or environmental exposure from a variety of sources, including air, water, soil, food and the workplace. Herbicide risk assessment and risk management comprise dynamic processes that can be used to weigh scientific evidence in order to formulate regulatory policy for the protection of human health and the environment.

All herbicides, because of their intended use, are toxic to some form of life. Risk assessments are, therefore, necessary to estimate a level of human or environmental exposure which will not result in adverse effects on human health or the environment. Risk assessment is an analytic process involving four integrated steps as recently identified by the European Union (EC, 1993) and the U. S. Government (U. S. National Research Council, 1983): (1) hazard identification, (2) dose-response assessment, (3) exposure assessment, and (4) risk characterization.

The basic process in human health risk assessment is to derive and compare the estimated human exposure (dose) with a no-observed-adverse-effect-level (NOAEL) for the most critical effect observed in human or animal toxicity studies conducted by a relevant route of exposure. Similarly, in ecological risk assessment, the process involves the derivation and comparison of the predicted environmental concentration (PEC) with the LC 50 or no-observed-effect-concentration (NOEC), determined in aquatic, avian and other terrestrial species. The risk assessment process can either result in an adequate margin of safety (MOS) or an inadequate margin of safety. In the latter case, higher tier risk assessment or mitigation procedures, usually involving exposure refinement or reduction, will be employed.

Unfortunately, many different testing and evaluation guidelines have been adopted and implemented by various countries, creating significant differences in risk assessments and regulatory decisions on herbicides. The need for international harmonization in the field of pesticide (herbicide) health and environmental risk assessment has been recognized for a number of years. This recognition prompted the development, by the Food and Agriculture Organization (FAO), by the World Health Organization (WHO) and by the Organization for Economic Cooperation and Development (OECD), of recommendations for the harmonization of data requirements and risk assessment methodologies.

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Recent efforts in national and international harmonization have provided a workable process by which the differences can be resolved in moving towards global harmonization of herbicide risk assessment and registration. This paper examines three key areas: (1) Maximum Tolerated Dose (MTD), (2) Cancer Classification and Risk Assessment,and (3) Ecological Risk Assessment. The American, European and International approaches in these important areas are compared in light of the current scientific knowledge.

Maximum Tolerated Dose (MTD)

Much of the controversy on MTD has been a result of inconsistencies in its definition and interpretation. These inconsistencies exist between the U. S. and most of the OECD countries. It is a source of disharmony between EC countries on one side and U. S. EPA on the other, in the registration and regulation of pesticides. It is therefore important to examine the MTD as it is defined and interpreted globally.

The OECD guideline for carcinogenicity studies gives this description of the MTD (OECD, 1987):

> The highest dose level should be sufficiently high to elicit signs of minimal toxicity without substantially altering the normal life span due to effects other than tumors. Signs of toxicity are those that may be indicated by alterations in certain serum enzyme levels or slight depression of body weight gain (less than 10 percent).

The EC Registration Directive (Directive 91/414/EEC, 1993 draft Annex II) describes the dose-selection process as follows (EC, 1993 a):

> The doses tested, including the highest dose tested, must be selected on the basis of results of short-term testing and the level of possible human exposure, and where available at the time of planning the studies concerned, on the basis of metabolism and toxicokinetics data, such that at the highest dose, definite but minimal signs of toxicity are elicited (viz, slight depression in body weight gain), without causing tissue necrosis or metabolic saturation, and without altering normal life span due to effects other than tumors. Higher doses causing excessive toxicity are not considered relevant to evaluations to be made.

The World Health Organization (WHO) in discussing the selection of dose levels and the validity of MTD concept, states (IPCS, 1990):

> Results of studies at dose levels many orders of magnitude above the level of human exposure . . . (are of) little relevance. Instead of using the MTD to select the top dose level, the use of properly designed biotransformation studies over a range of doses (including human exposure level) may provide a more rational basis for dose selection in long-term animal studies.

All three guidelines define minimal toxicity for selection of the highest dose. In contrast, the EPA takes the position of eliciting significant toxicity as its requirement for MTD (EPA, 1987):

> The highest dose to be tested in the oncogenicity study should be selected below a level which resulted in significant life-threatening toxicity in the subchronic study. The level should not be selected too far below a life-threatening level because the highest dose tested in the oncogenicity study should elicit significant toxicity without substantially altering the normal life span of the test species from effects other than tumor formation.

The consequences of selecting significant toxicity versus minimally toxic doses are enormous. As a result of differences in high dose selection, many rodent carcinogenicity studies were rejected by U. S. regulatory bodies, for not reaching MTD, even after they had been accepted by European and International Agencies. The repeated studies add little knowledge in terms of real hazard identification or risk assessment of pesticides and hence are a waste of resources. The high doses themselves may produce tumors in animals which are not relevant to situations where humans are exposed to much lower concentrations. Differences in MTD may cause unwarranted concerns about residues allowed in food. This difference could give rise to potential trade barriers between nations and serve to increase the growing skepticism with which governments and scientists are regarded.

Recent efforts in harmonizing high dose selection or MTD have met with some success. The October 1993 consensus text of the International Conference on Harmonization (ICH) of Technical Requirements

for the Registration of Pharmaceuticals for Human Use proposed five equally acceptable criteria for selecting the high dose (ICH, 1993): 1) dose-limiting pharmacodynamics, 2) a minimum of a 25-fold area-under-the-curve (AUC) ratio (rodent : human), 3) saturation of absorption, 4) maximum feasible dose, and 5) the MTD.

Another project underway is the international harmonization of risk assessment methodologies for carcinogens, mutagens, and reproductive toxins. Participants in this project include the WHO's International Program on Chemical Safety (IPCS), EC, OECD, and the U. S. EPA. Differences in approaches to high dose selection (MTD) hopefully will be harmonized in this process.

Cancer classification and risk assessment

A recent survey of risk assessment methodologies practiced by OECD and selected non-OECD countries was conducted by IPCS (Dragula, 1994). While the linearized multistage extrapolation model is used by U. S. in assessing cancer risks, most countries employed the No Observed Adversed Effect Levels (NOAELs) with safety factors for non-genotoxic carcinogenic risk assessment.

The U. S. EPA (EPA, 1986) assumption for all substances showing carcinogenic activity in animal experiments is that no threshold exists (or at least none can be demonstrated), so there is some risk with every exposure. Thus, the dose-response curve derived based on this assumption shows zero risk only at zero exposure. All other exposures entail some risk. All substances identified as Categories A or B, and some Category C carcinogens (see Table 1 for details on carcinogen classification) are subjected to the same linearized multistage extrapolation procedure in risk assessment. This is a conservative procedure used to estimate the hypothetical upper bounds on the cancer risk and cannot be related to expected disease incidence in an actual population. In fact, EPA generally attaches the following description to its risk estimates:

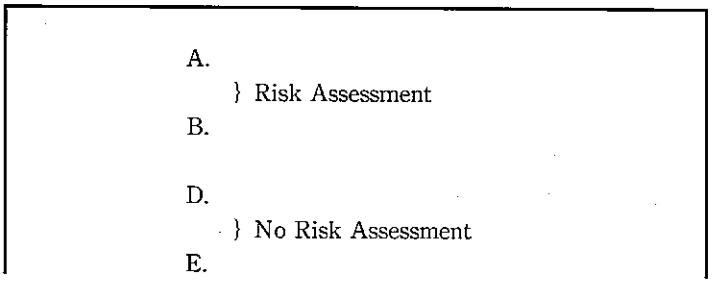
"The true value of the risk is unknown, and may be as low as zero."

In EC and most OECD and non-OECD countries, carcinogens are divided into genotoxic and non-genotoxic categories. For genotoxic carcinogens, it is assumed that no threshold exists for these agents. Non-genotoxic carcinogens are treated as threshold toxicants. A NOAEL and safety factor are used to set allowable daily intakes (ADIs). The mechanisms of tumor induction are often investigated.

No linearized extrapolation models are used in cancer risk assessment. The U. K. described its rationale for not providing linearized mathematical model as follows (U. K., 1991): "The Committee does not support the routine use of quantitative (linearized model) risk assessment for chemical carcinogens. This is because the present models are not validated, are often based on incomplete or inappropriate data, are derived more from mathematical assumptions than from knowledge of biological mechanisms and, at least at present, demonstrate a disturbingly wide variation in risk estimates on the model

Table 1 Human classification of carcinogens by EPA

A. Human Carcinogen
B. Probable Human Carcinogen
C. Possible
D. Inadequate Data
E. No Evidence (Negative)



adopted."

The linearized extrapolation model and the MTD used by U. S. EPA have also been severely criticized by others. Dr. Jay I. Goodman, in a paper in Molecular Carcinogenesis (1994), made the following statement (Ray, 1994):

"In freshman chemistry laboratory we are taught not to extrapolate beyond a standard curve because one quickly ends up in 'never-never land.' All too often the low-dose extrapolations from carcinogen bioassay results are based upon one data point, i.e., the estimated line is drawn from a single point, a practice that would not be deemed acceptable in a geometry class . . . The implicit assumptions underlying extrapolation from the MTD . . . do not appear to be valid. Therefore, both the criteria for selection of the high dose used and the default criteria that are employed for extrapolation from high-dose must be reevaluated in a critical manner."

Since 1986, our knowledge of carcinogenesis and risk assessment processes have continued to advance, leading U. S. EPA to initiate in 1994 (EPA, 1994) a revision of the 1986 Cancer Risk Assessment Guidelines (EPA, 1986). The major difference in the 1994 proposed revised guidelines compared with the 1986 guidelines concerns how evidence is weighed and used in support of decisions. Under the proposed revised guidelines, all scientific evidences will be used i.e. data on animal and/or human tumor effects, cancer mechanistic data and other key evidences. Risk characterization will include a robust qualitative and appropriate quantitative description of the conclusions instead of the current cancer classification scheme used by U. S. EPA (Table 1).

Other differences in the revised risk assessment process will include the following. The hazard identification step will include a description of the likelihood of hazard to humans and conditions of expression, i.e. a consideration of the route, level, frequency and duration of human exposure. The use of a hazard narrative instead of the current alphanumeric classification. In the dose-response assessment step, biologically based model will be used as the first choice for fitting and extrapolation. Depending on the mechanism of carcinogenesis, linear default or threshold model will be used in assessing safety of carcinogens.

Ecological risk assessment

Ecological risk assessment will become nearly as important as human health risk is today. This is evident from the recent activities noted within the EC (EC, 1993 a), U. S. EPA (EPA, 1993) and OECD (OECD, 1994) to develop various types of risk assessment schemes. A key ingredient of the ecological risk assessment process should be the ability to distinguish perceived risk from real risk. As outlined in Fig. 1, the primary aspects of the process are to compare exposure values with toxicity endpoints in order to determine potential hazard. Then by a suitable means ecological significance is assessed. One fundamental aspect of risk (Fig. 1) is the correlation between level of risk and the probability that a hazard might actually occur. The greater the probability, the greater the risk, and if too high, a risk management process takes over in order to mitigate risk back to an acceptable level. Therefore, key ingredients in ecological risk assessment are comparison of exposure to toxicity endpoints and evaluation of the probability that exposures will reach significant toxic levels.

To deal with the need for extensive data, computer-assisted model simulation of pesticide (herbicide) movement is being used to develop the multiple sets of data and to serve as the basis for exposure refinement. Computer simulation is selected because it is a very cost effective way to generate the large data sets needed for risk refinement. With modern computers and computing tools it is now possible to generate thousands of PEC estimates at a fraction of the cost of a single field study. Field studies can still be utilized if desired but they take on much more meaning and value if designed to support and improve the modelling process.

From the above discussion, the following risk assessment or risk refinement scheme is presented (Fig. 2):

Tier I - Simple first estimation of PEC from simple inputs, consisting of application rate, is compared to toxicity endpoints. Very conservative assessment which serves to identify the species of concern.

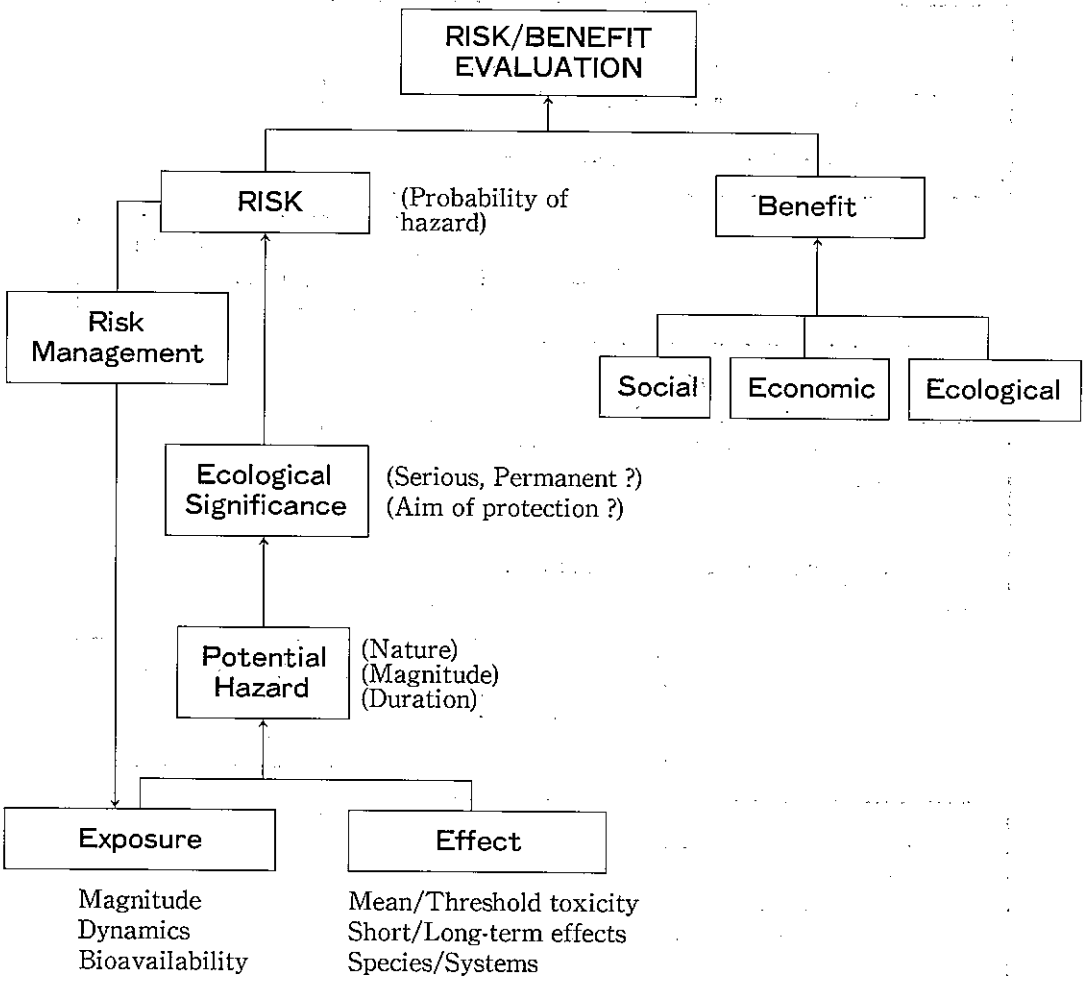


Fig. 1 Environmental risk assessment scheme

Tier II - Model simulation with standard worst-case scenarios of soil and weather as inputs. Scenarios are defined probabilistically and are set to identify the 90 th percentile PEC. The main purpose of this activity is to identify the use areas of ecological concern. There may also be some activity to identify the benefits of mitigation.

Tier III - Model simulation with many scenarios of soil and weather as inputs. The purpose is two fold: (1) to identify probabilistically the sensitive locations within a use area of concern, and (2) to evaluate mitigation/management techniques that can minimize level of risk.

Tier IV - Landscape modelling to take into account the relationship between treated locations and sensitive habitats. All of the previous tiers assume habitat is at the edge of the treated area. This tier steps beyond and examines landscape factors that influence the ultimate PECs for the sensitive habitat.

This tiered process of exposure refinement and thus risk refinement in ecological risk assessment is similar to that proposed recently in the U. S. by the Aquatic Risk Assessment and Management Dialogue Group (ARAMDG) (ARAMDG, 1994), and by FOCUS, the European modelling working group that has been working on ecological risk assessment for ground water.

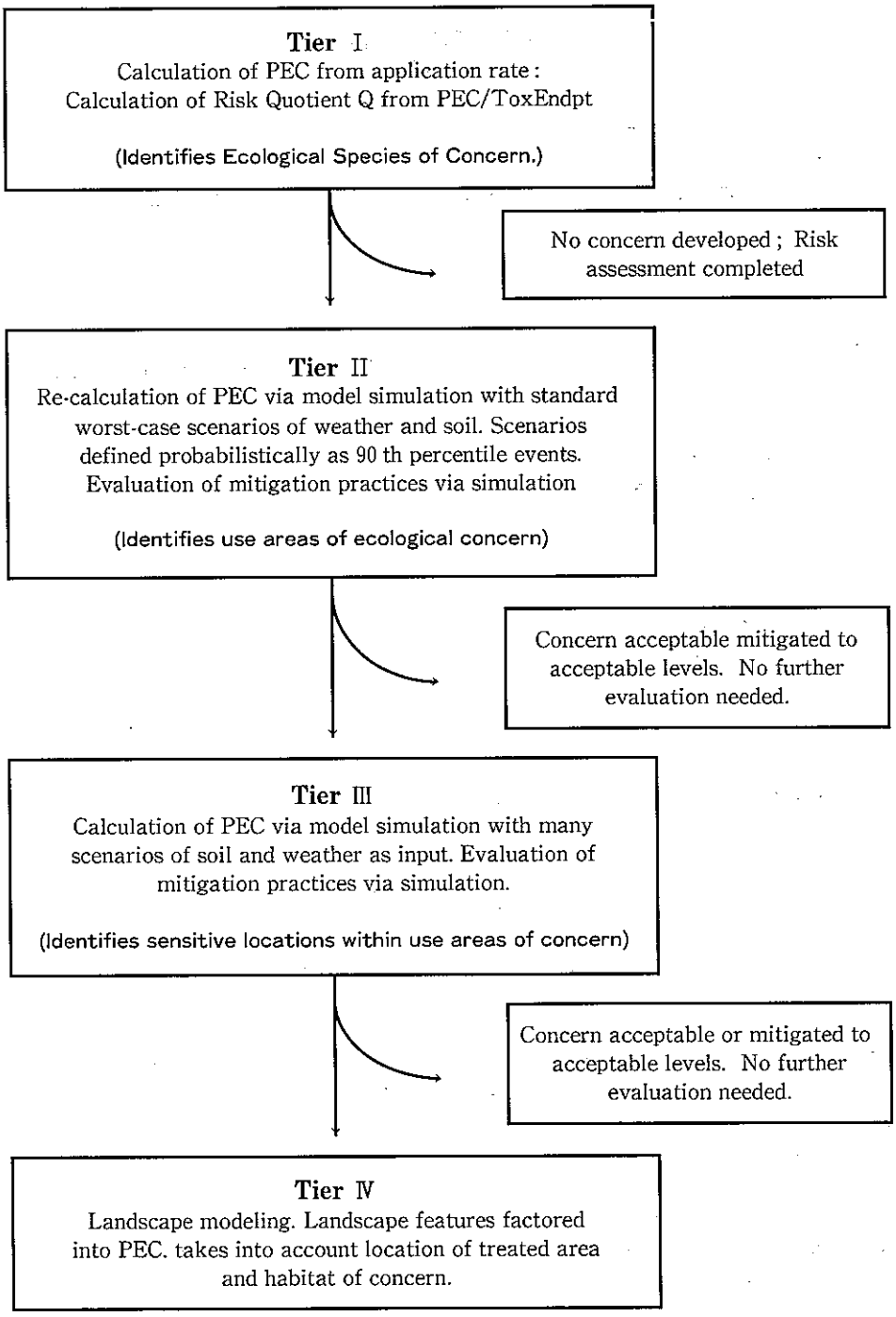


Fig. 2 Ecological risk refinement

Conclusion

The risk assessment process offers regulators, registrants, public interest groups and users a means of weighing apparent health and environmental effects of pesticides (herbicides) and other chemicals, and measuring their safety for use. All herbicides, because of their intended use, are toxic to some form of life. Risk assessments are, therefore, necessary to estimate a level of human or environmental exposure which will not result in adverse effects on human health or the environment. Risk assessment is an analytic process involving four integrated steps as recently identified by the European Union (EC, 1993) and

the U. S. Government (U. S. National Research Council, 1983) : (1) hazard identification, (2) dose-response assessment, (3) exposure assessment, and (4) risk characterization.

Unfortunately, many different testing and evaluation guidelines have been adopted and implemented by various countries, creating significant differences in risk assessments and regulatory decisions on herbicides. Recent efforts in national and international harmonization have provided a workable process by which the differences can be resolved in moving towards global harmonization of herbicide risk assessment and registration. This paper examined three key areas : (1) Maximum Tolerated Dose (MTD), (2) Cancer Classification and Risk Assessment, and (3) Ecological Risk Assessment. The American, European and International approaches in these important areas are compared in light of the current scientific knowledge.

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Discussion

Kanazawa, J. (Japan): Regarding the assessment of herbicide risk, there are two important problems, namely the contamination of drinking water by herbicides in relation to human health and side-effects of herbicides on the phytoplancton such as algae as the major organism in the aquatic food chain.

Answer: 1. The program worked out by WHO is the most acceptable approach to the problem of contamination of drinking water by herbicides. 2. As for the effect on algae, studies on other aquatic plants should be carried out over a period of 5 years and also the construction of simulation models for the decay of molecules of chemicals in water should be promoted to develop protective measures.