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TOXICOLOGY

NEWSLETTERS

"Nature has introduced great variety into the landscape, but man has displayed a passion for simplifying it. Thus he undoes the built-in checks and balances by which nature holds the species within bounds."

- Rachel Carson, Silent Spring

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Pesticide Risk Assessment

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1. Preamble

Pesticides are widely used in agricultural production to prevent or control pests, diseases, weeds, and other plant pathogens in an effort to reduce or eliminate yield losses and maintain high product quality. Although pesticides are developed through very strict regulation processes to function with reasonable certainty and minimal impact on human health and the environment, serious concerns have been raised about health risks resulting from occupational exposure and from residues in food and drinking water. Occupational exposure to pesticides often occurs in the case of agricultural workers in open fields and greenhouses, workers in the pesticide industry, and exterminators of house pests. Exposure of the general population to pesticides occurs primarily through eating food and drinking water contaminated with pesticide residues, whereas substantial exposure can also occur in or around the home. *Therefore, the risk assessment of the impact of pesticides on human health is not an easy and particularly accurate process because of differences in the periods and levels of exposure, the types of pesticides used (regarding toxicity and persistence).* The general public and government policymakers want clear, definitive answers; and answers to questions on the relationship between pesticides and public health are based largely on information generated through risk assessment.

The goal in risk assessment is to assign risk potential on an objective basis. This short write up provides background information on the risk evaluation process; *it is intended to foster an understanding of how risk assessments are concluded, what assumptions are used, and how conclusions are drawn.*

2. Pesticide Registration and Safety

Pesticide registration is a scientifically-based, legal, and also administrative process, where a wide variety of effects associated with the use of a pesticide product and its potential effect on human health and the environment is assessed.

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The registration is an important step in the management of pesticides as it enables authorities primarily to determine which pesticide products are permitted to be used and for what purposes, and also to exercise control over quality, usage rates, claims, labelling, packaging and advertising of pesticides, thus ensuring that the best interest of end-users, as well as the environment, are well protected.
In addition, the registration process is restricted to the assumption that pesticides are only used for their intended function and envisages proving that such use does not promote unreasonable effects either on human health or on the environment. *Therefore, before any pesticide can be used commercially, several tests are conducted that determine whether a pesticide has any potential to cause adverse effects on humans and wildlife, including endangered species and other non-target organisms, or potential to contaminate surface waters and groundwater from leaching, runoff, and spray drift.* Effects in any non-target species may translate into ecosystem unbalance and food-web disruption that ultimately may affect human health and edible species.
The basic pathway for the registration of a pesticide is: *(1) research conducted by the manufacturer prior to its decision to pursue registration; (2) submission of data report by the manufacturer to the registration authority; (3) review of the data by the registration authority; and (4) a decision by the registration authority either to register the pesticide,* based on the merits of the submitted data, or to deny registration. The decisions of the registration authority to register a pesticide hinge on a benefit-to-risk analysis of the required data.
The registration process for a pesticide usually requires the manufacturer (registrant) to conduct, analyze, and pay for many different scientific tests. These tests define the product chemistry, risks to humans and domestic animals, the environmental fate of the pesticide, and the impact on non-target organisms. They should include the identity and physical and chemical properties of the active ingredient and formulated product, analytical methods, human and environmental toxicity, proposed label and uses, safety data sheets, efficacy for the intended use as well as residues resulting from the use of the pesticide product, container management, and waste product disposal.

3. The Process and Practice of Risk Assessment

"Risk analysis" is a systematic framework for understanding and actually managing diverse risks through the process of *risk assessment* and *risk management*. Government agencies (USEPA, European Commission, Central Insecticide Board – CIB etc) intends the *risk assessment* process to provide the pesticide industry and the public-at-large to estimate the level of risk posed by the pesticide. Ideally, risk assessment incorporates scientific knowledge with consideration of inherent uncertainties. *More specifically, risk assessment is the process of quantifying and characterizing risk, i.e. estimate the likelihood of occurrence and the nature and magnitude of potential adverse effects.*

4. Multi-Step Risk Assessment Process

Human risk assessment is best described as a 3-step process:

- *Toxicity assessment: an evaluation of intrinsic toxicity or hazard potential of the pesticide; this includes dose-response assessment*

- *Exposure assessment: an estimate of potential human exposure to the pesticide*
- *Risk characterization: an evaluation of potential risk to humans*

A. Toxicological Assessment

The potential impact of a pesticide on human health is estimated by evaluating how experimental animals—rats, mice, rabbits, guinea pigs, dogs etc responds to a range of doses. An extensive battery of toxicological studies is required for full pesticide registration.

Toxicology studies characterize animal response in a variety of scenarios ranging from acute exposure, where animals receive one relatively high dose of the pesticide, to chronic (long term) exposure where animals receive doses for up to 2-years.

Acute studies consist of a battery of 6-studies consisting of rat oral, dermal and inhalation toxicity, rabbit skin and eye irritation, and guinea pig skin sensitization. *These days, it is mandatory that one conducts in vitro skin &eye irritation and skin sensitization before taking up in vivo studies.*

Sub-chronic studies (28-, and 90 days) in rats, mice and dogs are intended to identify target organs and establishing No Observed Adverse Effects Levels (NOAEL).

It is also important to study the metabolic (oral and dermal) fate of a pesticide, including tissue distribution and metabolite identification.

Chronic studies (6-months to 1 to 2-years) in rats, mice and dogs are conducted to assess the pesticide's potential to induce toxic effects and/or cancer following long term exposure.

Other toxicological studies include testing for potential adverse effects on reproduction (including birth defects), genotoxicity, neurotoxicity, immunotoxicity, endocrine toxicity, based on chemical class. A list of such studies is listed on the website of various regulatory agencies, along with guidelines, including OECD which will not be covered in this newsletter.

B. Threshold Effects

With the possible effects of some types of cancer, most of the observed effects in toxicology occur only at or above specific dose (not below). These dose levels are referred to as threshold doses, and the observed effects are referred to as threshold effects. Within a full suite (above mentioned) of studies, there may be a different threshold dose for each adverse effect observed, but the precise threshold dose for each effect is rarely determined. *One of the most important aspects of toxicological studies is the definition of NOAEL, which is the highest dose that does not cause any adverse effect.*

C. Extrapolation from Animals to Humans:

Toxicological study data are used in two important extrapolations:

i. Animal to Human Extrapolations

Risk assessment has traditionally relied on laboratory animals as predictive models for humans since we share many biological characteristics. Risk assessors generally assume that adverse effects in animals may be replicated in

humans and *that humans may be up to 10 times more sensitive than the most sensitive (lowest NOAEL) effect in the most sensitive species tested.*

ii. High Dose to Low Dose Extrapolation

In general, pesticide levels to which most humans might be exposed are far lower than those used in toxicology studies. *Higher pesticide levels are used are used in animal testing to maximize the detection of potential adverse effects from overexposure.* Because of the limited number of animals that can be tested, animal studies at lower doses may not detect a subtle effect that may occur in very large human populations exposed to the pesticide. However, high doses used in animal studies may overload the metabolic processes of the animals and thus lead to adverse effects that are not predictive of those expected at lower exposure levels.

D. Tolerances

Tolerance is a legally enforceable maximum level, generally expressed in parts per million (ppm) of a pesticide and/or its metabolite(s) that can be legally present in or on a commodity at harvest (Raw Agricultural Commodity – RAC). These are usually based on results from controlled field trials in various geographies, under maximum application conditions. Similar residue levels are established for animal products (meat, milk, egg, and poultry).

E. Human Exposure

This is a science by itself, where a toxicologist is not necessarily involved, hence, I will try to cover in a cursory way to account for various aspects in assessing human exposure.

i. Dietary Exposure

Pesticide residues in the diet probably represent the primary source of pesticide exposure for the general public. The basic model for estimating dietary exposure to pesticide residues in foods is expressed as follows:

Pesticide ingested *= Residue concentration X Foods Consumed = Arrive at the Theoretical Maximum Residue Concentration* ***(TMRC)*** *or in some cases Anticipated Residue Concentration* ***(ARC)***

ii. Drinking Water, Air, Occupational Exposure – essentially the same process as dietary exposure is used to arrive at these exposures following actual experiments or in some cases by extrapolation.

F. Risk Characterization

The final step in risk assessment is risk characterization which involves the integration of toxicological data with exposure data to estimate the level of human risk.

Reference Dose (RfD) is usually calculated by the lowest NOAEL from the most sensitive effect from in the sensitive species by applying Safety or Uncertainty Factors (SF or UF). Most commonly, uncertainty factors of 10X each are applied to account for interspecies extrapolation (animals to humans) and intraspecies variation (differences among humans), for a total of 100.

i. Threshold effects

Risk assessments are conducted by utilizing a Margin of Exposure (MOE or MOS) or a Reference Dose (RfD) approach using the following formula:

$$\text{Margin of Exposure (MOE)} = \frac{\text{No Observed Adverse Effect Level (NOAEL)}}{\text{Estimated Total Pesticide Exposure}}$$

Example: If the NOAEL is 30 mg/kg/day and the estimated human total exposure is 0.2 mg/kg/day, the MOE is 150. The greater the MOE, the greater the degree of safety. In general. An MOE should be at least 100.

ii. Non-Threshold Effects (carcinogens)

These assessments provide an estimate (expressed as a probability) of the excess risk of cancer resulting from exposure to the pesticide. *For instance, a calculated risk of 1 X 10^{-6} (1 in 1,000,000) means that a person would have no more than a one-in-million chance of developing cancer in excess background incidence in the general population.* This level of excess cancer risk is considered acceptable to the general public, while a higher estimated level such as 1 X 10^{-5} (one in 100,000) may be considered acceptable for occupational exposure.

G. Tiered Approach to Risk Assessment

Following is an example of a multi-tiered approach to dietary risk assessment; a similar approach can be used in occupational and residential pesticide risk assessment.

A.Tier 1:

In an initial risk assessment using conservative default assumptions of 100 percent crop treated and all residues present at the tolerance level, the TMRC's of fine pesticides are calculated to be:

i. 0.001 mg/kg/day for pesticide A
ii. 0.01mg/kg/day for pesticide B
iii. 0.1 mg/kg/day for pesticide C
iv. 1.0 mg/kg/day for pesticide D
v. 3.0 mg/kg/day for pesticide E

Although most pesticides have different chronic RfD's, for simplicity it is assumed that the RfD for each of the five pesticides is the same: 1 mg/kg/day. The 1.0 mg/kg/day chronic reference dose is compared to the total amount of each pesticide consumed. *Individual dietary consumption of pesticide A, B, and C is substantially below the chronic RfD; thus it is assumed that dietary consumption of these pesticide residues will not cause adverse human health effects.*

Pesticide D results are borderline, so it does not pass Tier 1 risk assessment. The possibility that pesticide E may pose a dietary risk to humans cannot be excluded since Tier 1 estimated consumption exceeds the chronic RfD. Therefore, both pesticides D and E are candidates for Tier 2 risk assessment.

B.Tier 2:

In Tier 2, only the percentage of crops actually treated is assumed to contain residues. In this example, TMRCs for pesticide D and E are 1.0 and 3.0 mg/kg/day, respectively. However, if data were available to indicate that not more than 50% of labeled crops are in fact treated, the assumed Anticipated Residue Contribution (ARCs) would be 0.5 and 1.5 mg/kg/day, respectively. Thus, the anticipated dietary exposure to Pesticide D (0.5 mg/kg/day) is clearly below the chronic RfD of 0.1 mg/kg/day, and no further refinement of the risk assessment process is needed. Pesticide E is a candidate for Tier 3 assessment, however, since its potential exposure (1.5 mg/kg/day) exceeds the RfD.

C.Tier 2:

In Tier 3 risk assessment, anticipated residues are even further refined using residue data from fields, processing studies, and/or monitoring studies.

In this example, data indicates that Pesticide E readily degrades during storage and that much of the residue is removed during handling or washing of fruits and vegetables prior to distribution to grocery stores. Based on these data, the ARCs from pesticide E are further reduced to 0.14 mg/kg/day, which is well below the RfD. Thus, the use of ARCs that incorporate better data allows risk assessors to conclude that there is no unreasonable risk from consuming foods from crops treated with this pesticide.

6. Conclusion

The risk of pesticide exposure to human health is a function of both exposure and toxicity. Since both measurements involve a degree of uncertainty, risk assessments generally use very conservative assumptions to assure adequate margins of safety. *The risk assessment process generally proceeds in a tiered manner from assessments based on very limited data with very conservative assumptions through assessments with extensive data and a solid understanding of the pesticide and its human exposure effects.* The tiered approach allows for low-risk pesticides with large margins of exposure to be screened out of risk assessment process at a very early stage.

Despite the public desire for zero risks, the world is not risk-free. Recognition of the risks associated with pesticide use leads to informed decision-making in identifying those levels of risk acceptable to society. Responsible management of pesticide risks and benefits allows optimal benefits in terms of public health, safety, and prosperity.

Questions

1. *Discuss on Pesticide Registration and Safety?*
2. *Write about the basic pathway for the registration of a pesticide?*
3. *Write on Multi-Step Risk Assessment Process?*
4. *How is the Reference Dose (RfD) calculated?*
5. *Write about Threshold effects and Non Threshold effects?*
6. *What are the Tiered Approaches to Risk Assessment?*

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ToxGurukul is a group of professionals in the field of toxicology who are in search of a platform to learn and share the vast knowledge in this area. This syndicate belongs to independent professionals from different backgrounds of toxicology who share their knowledge to un-puzzle the Rubik's cube that each face in their daily work routine.

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