Statistical Issues Encountered in the Risk Assessment of Pesticides and Herbicides

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1. Introduction and overview of risk assessment

Society benefits from the development of new technologies. Many of these technologies have allowed us to increase the yield from agricultural activity. Pesticides and herbicides have been used to inhibit the loss of crop yield to insects or non-food plant species. However, the use of these chemical treatments is not without controversy as can be seen in concerns about human risk associated with consuming food that included a residue of pesticide or herbicide. One resolution to this concern is to eat only organically grown foods; however, this tends to be an expensive solution that may not be viable for feeding the ever-expanding world population. Thus, we need to understand the potential for adverse human health consequences associated with exposures to pesticides and herbicides. In the discussion that follows, a general outline is presented for risk assessment followed by a consideration of human and wildlife responses to pesticide/herbicide exposure. This is followed by a discussion of statistical techniques that have been primarily used for dose-response modeling and risk characterization.

One common framework for environmental risk assessment was described in a U.S. National Academy of Sciences publication (1983) where the process was viewed in four steps. This framework can be readily applied to pesticides and herbicides. The components of this framework include: 1) hazard identification; 2) exposure assessment; 3) dose-response modeling; and 4) risk characterization. The first step, hazard identification, identifies whether a potentially toxic substance has the potential to induce some adverse response. The second step, exposure assessment, addresses the size of the exposed population relative to the level of exposure. In addition, the pattern, amount and route of exposure are often evaluated. Third, dose-response or concentration-response modeling is used to relate increasing hazard exposure levels to the adverse response of interest. Finally, risk characterization integrates the information from the three other steps to evaluate the degree and extent to which a toxin poses a risk to the health of the environment.

2. Effects of pesticides and herbicides

Pesticides and herbicides have the potential to impact not only humans, but non-targeted flora and fauna as well. One route by which humans would have environmental exposure would be through the food supply with the consumption of food containing pesticide and herbicide residue. Another route would be through water that has been contaminated with run-off containing pesticides and herbicides. Human occupational exposure can occur in either the manufacturing or the administration of these chemicals. Generally the human health concerns associated with pesticide and herbicide exposures are not acute effects in which lethality follows shortly after
exposure. More commonly, human responses to pesticides and herbicides tend to be neurological or developmental. Neurological responses can range from short-term memory loss to more extreme reactions such as seizures may occur. Developmental responses refer to the potential of certain chemicals to impact the growth, development, and functional capacity of exposed individuals.

The effects of pesticides and herbicides on wildlife is credited in helping to inspire public awareness of the risk associated with these chemicals. Rachel Carson’s classic book, *Silent Spring*, highlighted the impact of pesticides on avian populations (Carson, 1962). These chemicals, notably DDT, were identified as being associated with a thinning of bird egg shells. These impacted eggs would not hatch out, and fears surfaced that this could lead to the extinction of certain species of birds. The impact of pesticides and herbicides also have been observed in reptiles and amphibians. The major concern today is the potential for low levels of pesticides and herbicides to induce endocrine disruption.

3. Data Sources and Statistical methods

Two basic data sources have been employed to examine the toxicity of pesticides and herbicides. Controlled laboratory-based studies employ common experimental protocols where a gradient of chemical concentrations are imposed on organisms that have been randomly assigned to experimental groups. Alternatively, observational studies have been conducted using human worker populations or field studies of wildlife populations. The human studies are conducted by epidemiologists and encompass traditional epidemiological study designs (e.g. case-control, cohort studies). The wildlife studies are conducted by field ecologists, and may involve specialized study designs (e.g. BACI, before-after-control-intervention, designs).

As noted above, risk assessment involves a number of components that are directly impacted by statistical techniques. Hazard identification depends upon responses in experimental groups receiving the pesticide or herbicide being significantly different from responses in a control group. Alternatively, an epidemiology study of workers exposed to pesticides or herbicides supports the assertion that the chemicals are hazards if exposed worker groups exhibit elevated risk of an adverse response relative to unexposed or low exposed workers which is often expressed as an odds ratios (OR).

Both the experimental and observational studies can be used in the dose-response modeling and risk characterization stage of risk assessment. Dose-response modeling in epidemiology reflects the nature of the data gathered. For example, logistic regression techniques are commonly used with case-control studies while Poisson regression and other relative or additive risk regression models are used with cohort studies. Dose-response modeling for data from controlled experimental studies reflects the nature of the response being measured (e.g. continuous or dichotomous responses) and the correlation/independence of the responses being measured. Not surprisingly, multiple regression or anova models (Neter et al. 1996) are commonly employed for continuous responses such as measures of growth or development. Developmental responses are often based upon experiments where a dam is exposed to a pesticide or herbicide and then pups within a litter are observed to determine if they exhibit the adverse response of interest. Thus, litter
is a natural clustering variable in such analyses and must be considered because of the expectation that littermates would be correlated. Random effects in anova models can be employed to address this for continuous responses while generalized estimating equations are often used for addressing this for dichotomous responses such as cleft palate in a fetus (Ryan et al. 1992). Finally, dose-response modeling for development toxicity must reflect the hierarchical nature of responses. An adverse response may be a resorbed embryo, dead fetus, malformed fetus or reduced birth weight. Statistical models that reflect this structure have been developed and are frequently applied (Catalano et al. 1994). This continues to be an area of active statistical inquiry.

Most of the illustrations mentioned above address mammalian models that have been used to examine the dose-response patterns for pesticides and herbicides. Other experimental models are commonly employed to examine aquatic or environmental toxicology of pesticides and herbicides. Studies using larval minnows or invertebrate species are often employed for regulatory testing of water quality – a common target of concern when examining pesticide and herbicide run-off or discharge. Survival, reproduction and growth are among the responses examined in such studies. Regression models reflecting these different response scales such as generalized linear models have been recommended (Maul 1992). One particularly interesting feature of these data is that non-monotonic patterns in which low levels of exposure produce beneficial effects such as enhanced growth before toxicity is manifest at higher levels of exposure. This pattern is often referred to as “hormesis” and suggests that, at minimum, polynomial predictors must be considered while nonparametric regression options such as generalized additive models (Hastie and Tibshirani, 1990) could also be examined.

Historically, the highest concentration at which organism response is not significantly different from the control condition is identified. This no-observed-adverse-effect level or NOAEL is then adjusted by uncertainty factors (species to species extrapolation factor and others) to obtain an acceptable exposure level. Criticism that the NOAEL is sensitive to experimental design properties (e.g. high variability leads to high NOAEL) led to considerations of other analytical strategies. Most notable is the development and promotion of the so-called benchmark concentration/dose (Crump 1984). Other regression-based estimators that involved estimating the concentration associated with a specified inhibition in responses relative to the control responses have also been suggested (Bailer and Oris 1997). These methods can also be modified when non-monotonic dose-response patterns are present to address inhibition relative to maximal estimated responses as well as control responses (Bailer and Oris 2000). Future methods that might be examined in this context include ideas from Bayesian Model averaging where the risks from different models are effectively weighted by the posterior support the data provide to each of these models.

Two additional subjects that deserve special mention in the risk assessment of pesticides and herbicides are exposure assessment and evaluating mixtures. Humans may well be exposed to pesticides and herbicides via a number of different routes. Residue on foods may be eaten while contamination in water may result in dermal exposures from showering or from drinking contaminated water. There is a distribution of the residue in food, in water, in the length of
showers, and in the amount of water consumed. These distributions along with uncertainty in the rates of dermal absorption and gastro-intestinal absorption are evaluated in probabilistic risk assessments (USEPA 1998). These are often Monte Carlo simulations where a representation of exposure that captures both uncertainty and variability is generated. Humans and wildlife are usually exposed to a mixture of chemicals in their environments. Most laboratory experiments are focused on single chemical toxicity assessments. Integrating separate studies with multiple chemicals into a single picture is a challenge. Multiple chemicals with similar modes of toxicity may act in an additive fashion while other scenarios where chemicals “compete” for the same binding sites. This may lead to a less than additive response. In the case of acute exposures to organophosphate or carbamate pesticides, the interactions between combinations of chemicals can be more complex. In addition to inhibition and additivity, synergism and potentiation have also been observed (Keplinger and Deichmann 1967).

In summary, pesticides and herbicides are of special concern for risk assessment given the possible broad impact of such chemicals on humans and wildlife. The full array of statistical modeling tools developed in epidemiology and toxicology are all required for these exposures. Finally, the characterization of these chemicals is made significantly more difficult because of the challenge identifying exposures and addressing the risks associated with mixtures.

REFERENCE


RESUME

Pesticides and herbicides have been used to inhibit the loss of crop yield to insects or non-food plant species. The quantitative tools to evaluate the potential for these interventions to cause adverse human and wildlife responses are described in the context of a risk assessment framework. A review of past practice, a summary of current methods and speculation related to future trends are all mentioned. No-observed-effect concentrations have been used for establishing regulatory levels for these chemicals. The shortcomings of this endpoint has promoted the development of regression-based endpoints such as the benchmark doses which are commonly used today.