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# Workshop 5.4

# General process for the risk assessment of pesticides that interact with or affect the endocrine system*

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*Abstract*: The U.S. Environmental Protection Agency's Office of Pesticide Programs evaluates human health risk associated with exposure to pesticide chemicals. Chemical hazard and exposure assessment are components of the risk assessment process. For the risk assessment of single chemical conventional-type pesticides, there may be multiple exposure scenarios depending on the use pattern. Examples include acute and chronic dietary, and short-, intermediate-, and long-term occupational/residential exposures. For hazard assessment, available toxicity data and a weight-of the-evidence approach are used in the process of selecting appropriate toxicity endpoints for relevant exposure scenarios. The pesticide registration process requires that certain types of supporting toxicity data be submitted by the registrant depending in part on the chemical use pattern (e.g., food use). Types of toxicity data that might be submitted and used in hazard assessment include acute, subchronic, chronic, carcinogenicity, mutagenicity, metabolism, reproduction, developmental, neurotoxicity, and mechanistic studies. There may be data from multiple exposure routes (e.g., oral, dermal, inhalation) and from the scientific literature to consider. Dose–response information is also taken into account. In endpoint selection for a chemical, endocrine system-related effect(s) and dose–response relationship(s) are assessed in context of other types of effects, toxicities, and dose–response relationships noted. Endocrine system-related endpoints may include frank effects (e.g., endocrine organ hyperplasia or cancer) or precursor events (blood hormone level elevations). Endocrine system-related endpoints are generally treated like other cancer or non-cancer toxicity endpoints (e.g., hepatic cancer, neurotoxicity) in the risk assessment process. For chemicals with evidence of endocrine system interaction(s), an endocrine system-related effect may or may not be the most sensitive or relevant endpoint for a particular risk assessment exposure scenario. Some chemical examples will be presented. In the final risk assessment, hazard assessment information is integrated with exposure information. The assessment may be adjusted, at some point, for uncertainties in hazard or exposure data. An aggregate risk assessment, in which multiple sources or routes of exposure are considered, is typically performed for occupational and residential exposure scenarios. A cumulative risk assessment may be considered for groups of chemicals with a common mechanism of toxicity.

The U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) evaluates risks associated with exposure to pesticide chemicals. This paper presents examples of some of the consid-

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erations that might be used in the process of assessing risks of pesticide exposure to human health, including risks from chemicals that interact with, perturb, or affect the endocrine system. In order to further narrow down a broad topic for purposes of the symposium, the perspective of the presentation is taken primarily (although not exclusively) from general experience with the single chemical risk assessment of conventional pesticides such as insecticides, fungicides, rodenticides, and herbicides. This paper should not be considered as a comprehensive review of the subject and is not intended to convey what has been, should be, or will be done in the risk assessment of any particular substance. It should be noted that the agency conducts risk assessments on other types of materials and exposure scenarios. In addition, modifications in the current approaches to the assessment of chemical risk are possible with advances in information or technology or changes in policy.

Chemical hazard and exposure assessments are components of the risk assessment process. There may be numerous factors and conditions to be considered in these steps. For instance, the type of chemical to be evaluated (e.g., conventional pesticide) and the type of risk assessment to be performed (e.g., single chemical) are identified. In order to assess hazard for particular exposure scenarios, the use pattern of the chemical is ascertained. Examples of use patterns include food uses in which a chemical is used agriculturally and residues might be found in the diet and non-food uses in which a chemical might be used in swimming pools or on turf or roadside weeds. Many different exposure scenarios are possible. For example, dietary exposure to pesticides may be acute and occur singly or within one day or may be chronic and occur repeatedly over periods of time up to a lifetime. Other possible situations are short, intermediate, or long-term occupational exposures to workers that mix, load, or apply pesticides or pick crops in the field and residential exposures through household uses of chemicals. Consideration is also given to which population groups might be susceptible to certain pesticide exposure scenarios. One possible group is the general population. Another is females, age 13 years and older, representing females that might experience pesticide exposure during the child-bearing years.

An important part of hazard assessment is the selection of appropriate toxicity endpoints for relevant chemical exposure scenarios, such as acute and chronic dietary exposures. In the endpoint selection process, the available toxicity data and dose–response information for a chemical is evaluated in a weight-of-the-evidence (WOE) approach to determine pertinent effects and dose levels (e.g., no observable adverse effect levels, NOAELs; points of departure) for use in performing risk assessments. With the WOE approach, toxicity endpoints are not necessarily chosen from the toxicity study with the lowest NOAEL. Rather, the WOE approach involves evaluation and consideration of all of the available relevant data for a chemical and aids in providing an overall picture of a chemical's effects and dose–response relationships. Therefore, individual studies are looked at in the context of other available information for the chemical and not in isolation. The WOE approach can be used in assessing both noncancer effects and the carcinogenicity potential for a chemical. Sound science and rationally based scientific judgments should be used in implementing the WOE approach to select toxicity endpoints. Some points to consider in the WOE assessment include evaluating whether a selected endpoint makes sense in the context of the all of the available data, whether an endpoint has human relevance, whether the species in which a potential endpoint is observed is an appropriate model for human disease, and whether the potential endpoint has toxicological significance. Other examples of information that might be considered in a WOE analysis are the shape of the dose–response curve, dose-spacing issues and evidence for progression of events leading to a lesion or particular type of toxicity.

There may be several sources of toxicity data available for the evaluation of a given chemical using the WOE approach. First, the pesticide registration process has requirements for certain types of toxicology data that are submitted to the agency for analysis. Requirements depend in part on the use pattern (e.g., food use, non-food use) for a particular chemical. Examples include acute, subchronic, chronic, carcinogenicity, mutagenicity, metabolism, dermal absorption, reproduction, developmental, and neurotoxicity studies. Mechanistic or special studies to focus in on a particular issue may also be performed (although not necessarily required). Toxicity data may be obtained from studies using different routes of exposure (e.g., oral, dermal, inhalation) and from different species. Data from the open

literature may also be used in the WOE evaluation. In addition, toxicity data may be available from structurally related compounds or compounds with other types of similarities to the chemical under review.

Some pesticides affect or interact with the endocrine system. Available toxicity data from the types of toxicology data sources noted above may provide evidence of direct effects on endocrine organs, tissues or cells or of indirect effects on the endocrine system, including such phenomena as perturbation of endocrine system homeostasis leading to hypertrophy and/or tumor formation in an endocrine tissue. In general, endocrine system-related effects and dose–response relationships are assessed in context of other types of effects, toxicities, and dose–response relationships noted for a chemical. Endocrine system-related effects considered for use as endpoints in risk assessment may include frank effects (e.g., endocrine organ hyperplasia; cancer), or precursor events (e.g., sustained blood hormone level elevations). Sometimes, observed effects are relatively nonspecific in nature such that it is difficult to judge whether the effects are really endocrine system-related.

For use in hazard assessment incorporating a WOE approach, endocrine system-related endpoints, cancer or non-cancer, are generally treated like other cancer (e.g., hepatic cancer) or non-cancer (e.g., splenic necrosis) endpoints. However, for Food Quality Protection Act (FQPA) considerations, it is possible that some kinds of endocrine system-related endpoints as well as other types of endpoints (such as some types of reproductive and neurotoxicity findings) might have particular relevance in evaluating the relative susceptibility of infants and children vs. adults to an agent. It should be noted that an endocrine system-related effect may or may not be the most sensitive or relevant endpoint for a particular risk assessment exposure scenario. For example, a chemical may have more than one toxic effect (e.g., testicular atrophy and neurotoxicity) with the neurotoxic effect perhaps occurring at a dose lower than that of the testicular atrophy.

Next, two simplified hypothetical applications of the WOE approach to toxicity endpoint selection will be presented using toxicology data that include indications of possible endocrine system-related interactions. Both examples are artificial in nature and are composites drawn from experience with toxicology data on numerous chemicals over the years. The examples are for illustrative purposes only, over-simplify a more complex process, and do not represent an evaluation by the agency of any particular pesticide nor of how the agency would definitely use such data in a hazard or risk assessment.

The first hypothetical example concerns a fungicide with food uses. Five developmental toxicity studies were performed by the oral route with the chemical. In a rabbit study, no effects were observed in offspring. Four rat studies were available in which similar dose levels of the test material were administered. Although effects on sexual differentiation in male offspring only were observed in all of these studies, they occurred at lower doses in two of the studies that had been conducted using a modified dosing regimen. Maternal effects were observed only at doses higher than those at which effects in offspring were noted. Findings in a rat reproductive toxicity feeding study included endocrine organ weight changes and developmental delays and feminization of male offspring at doses at which parental toxicity was observed but which were much higher than those at which effects were seen in the rat developmental toxicity studies. The effects on male development in the rat studies were consistent with proposed antiandrogen activity of the chemical. This interpretation was supported by other submitted toxicity data on the fungicide (e.g., subchronic, chronic, cancer, metabolism, and mechanistic studies) and information from the literature on this and similar chemicals (e.g., antiandrogen pharmaceuticals, other pesticides with antiandrogen activity). One possible use of these data might be to establish a toxicity endpoint and NOAEL based on the in utero effects noted in male offspring in the developmental toxicity studies. This type of endpoint has relevance for a risk assessment conducted for the population group of human females of child-bearing age (13 years and older). Since the developmental effects noted could possibly occur after a single dose of the chemical, the endpoint could be appropriate for an acute exposure scenario.

The second hypothetical example concerns a herbicide with food uses. It is structurally related to other chemicals known to induce thyroid tumors in rats. Two rat chronic/carcinogenicity feeding stud-

ies were available. Thyroid hyperplasia was observed in one and thyroid tumors were noted in the other but only at doses considered to be excessive. Thyroid effects were not found in other species. No developmental or reproductive effects were observed in the developmental and reproductive toxicity studies. Although no obvious endocrine-related effects were noted in a dog chronic feeding study, hemosiderosis and anemia were observed at the lowest dose tested. Ovarian atrophy was found in one long-term mouse feeding study, along with uterine tumors, and was also noted in one long-term rat feeding study, along with prostate atrophy. The results of both of these rodent studies were confounded by the presence of a chemical additive and the effects were not seen in other long-term feeding studies in these species conducted without the additive. However, two other nonendocrine organ tumor types were observed in both rat long-term feeding studies performed with and without the additive present. From these data, an endpoint for chronic toxicity (for possible use in a chronic dietary exposure scenario and risk assessment) could be supported based on nonendocrine system-related effects (e.g., on the hemosiderosis and anemia observed in the dog study) rather than on endocrine system-related findings. Ovarian and prostate atrophy were only seen in the presence of the chemical additive and thyroid hyperplasia was observed only at excessive doses of the chemical. The two nonendocrine system-related tumor types could be considered as more feasible candidates for the cancer risk assessment. Uterine tumors were only noted in the presence of the chemical additive and thyroid tumors occurred only at an excessive dose in the rat and there were no signs of thyroid effects in other species.

In preparing the final risk assessment for an individual chemical, hazard assessment information is integrated with exposure information. The assessment may be adjusted, at some point, for uncertainties in hazard or exposure data. FQPA considerations are factored in, as necessary. Examples of other types of risk assessments conducted in OPP are aggregate and cumulative risk assessments. In aggregate risk assessments, multiple sources or routes of exposure may be combined. Cumulative risk assessment may be considered for groups of chemicals determined to have a common mechanism of toxicity. Ideally, final risk assessments will provide useful information for chemical risk management.