RISK ASSESSMENT METHODOLOGY FOR FISH

OFFICE OF PESTICIDE PROGRAMS

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BACKGROUND

The Environmental Protection Agency (EPA), through the Office of Pesticide Programs (OPP), is responsible for regulating pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act, as Amended (FIFRA 1988). FIFRA establishes an overall risk/benefit standard for pesticide registration, requiring that pesticides perform their intended function, when used according to label directions, without posing unreasonable risk of adverse effects on man or the environment. In addition, for any pesticide intended for use on food or feed crops, EPA is responsible under the Federal Food, Drug, and Cosmetic Act (FFDCA) for setting tolerances (maximum permissible residue levels) for pesticides in or on food and feed commodities.

EPA establishes tolerances on a national basis for residues of a pesticide in a commodity which result from application of the pesticide to that commodity. For fish, tolerances are required if the pesticide is applied to a body of water from which fish are taken for food and which travel in interstate commerce. For example, if a pesticide is applied to rice fields in which catfish or crayfish are farmed, a tolerance is required for residues of the pesticide in fish. Pesticide tolerances established by EPA are enforced by the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and state enforcement agencies. Below is a list of established tolerances for pesticide residues in fish:

Commodity	Pesticide	Tolerance (ppm)
Fish	dichlorophenoxyacetic acid	1.0
	diquat dibromide	0.1
	isopropylamine glyphosate	0.25
	simazine	12.0
	cuprous oxide	exem*
	polyoxyethylene	exem*
	fluridone	0.5
	triclopyr	0.2T**
	bensulfuron methyl ester	0.3T**
	dichlorophenoxyacetic acid	1.0
Shellfish	cuprous oxide	exem*
	dichlorophenoxyacetic acid	1.0
	diquat dibromide	0.1
	polyoxyethylene	exem*
	triclopyr	0.2T**
	isopropylamine glyphosate	3.0
Oysters	carbaryl	0.25
Catfish (meat animal)	potassium ricinoleate	exem*

*exem = exemption from the requirement of a tolerance
**T = temporary tolerance

If a pesticide has been cancelled due to health or environmental risks, it is Agency policy to revoke all food tolerances and, if necessary, to recommend action levels for pesticide residues on food and feed crops. While tolerances are established to reflect pesticide residues resulting from current pesticide uses, action levels are set for inadvertent pesticide residues, such as residues of cancelled, but environmentally persistent pesticides. Action levels, like tolerances, are established to reflect the maximum allowable pesticide residue in food or feed in interstate commerce. A policy statement issued by the EPA (Federal Register/Vol. 47, No. 189/9/29/82) describes the process of tolerance revocation for cancelled pesticides, as well as factors which must be considered when replacing these revoked tolerances with action levels. Among these factors are the extent to which the pesticide residues are unavoidable and the safety of these residues considering available exposure and toxicological data. Although action levels are established for contaminants other than pesticides, OPP is responsible for recommending action levels for pesticides only.

Based upon residue monitoring data, such as FDA surveillance data, EPA determines appropriate action levels and recommends these levels to USDA and FDA. USDA has the responsibility to establish and enforce EPA's recommended action levels in meat products, poultry, and eggs, while FDA has this responsibility in all other commodities, including fish. Current fish action levels for pesticides were established prior to the 1982 policy statement, and most were established prior to EPA's existence (1970). Information regarding how these were determined is not readily known. Below is a list of FDA action levels in fish:

Commodity	Pesticide	Action Level (ppm)
Fish	aldrin and dieldrin	0.3
	chlordane	0.3
	DDT, TDE, and DDE	5.0
	endrin	0.3
	heptachlor and heptachlor epoxide	0.3
	mirex	0.1
	toxaphene	5.0
	kepone	0.3
Fish By-products	endrin	0.3
Crabmeat	kepone	0.4
Shellfish	kepone	0.3
Fish, shellfish, crustaceans, other aquatic animals. Edible portion only Fresh, frozen, or processed.	mercury	1.0

HAZARD IDENTIFICATION AND CHEMICAL RESIDUE ANALYSIS

The Office of Pesticide Programs in EPA uses its data collection authorities under FIFRA to require the pesticide manufacturer to produce data needed to determine the hazard and chemical properties of a pesticide. The data required to set tolerances in fish and other commodities are mainly residue chemistry and toxicity data. Specific studies which are required to support a registration and tolerance petition are codified in the Code of Federal Regulations, 40 CFR, Part 158. In addition, OPP publishes Pesticide Assessment Guidelines which contain the standards and protocols for conducting acceptable tests, guidance on evaluation and reporting of data, and further guidance on when data are required. Although specific analytical method limits of detection (LODs) are not specified for these studies, OPP recommends that the LODs be sufficiently low so that the combined risk from all commodities calculated is acceptable.

Below is a summary of the residue chemistry and toxicity studies required to support a fish tolerance request:

RESIDUE CHEMISTRY STUDIES

Residue chemistry data required for tolerance purposes include several kinds of data ranging from product chemistry information to food processing study results.

Product Chemistry Data. To characterize the pesticide substance, EPA requires data on the composition of pesticide products, called product chemistry data. In particular, these data include: (1) information on the manufacturing process, (2) chemical analysis to show the amount of the active ingredient and any associated impurities, (3) "certified limits" on the amounts of the ingredients in a product, and (4) analytical methods used to determine the composition of the pesticide.

EPA evaluates these product chemistry data to determine whether impurities constitute a significant component of the residue in food or animal feed. This is an important consideration because impurities created in the manufacture of a pesticide may become a residue problem, if they are not identified before tolerances are established.

Metabolism in Fish. Metabolism data are required so EPA may characterize the nature of the residue that occurs in fish intended for consumption as food or animal feed. To obtain these data, the pesticide is labeled with a radioactive atom, usually carbon fourteen, and applied to the water in accordance with proposed use directions. Since the pesticide molecule is radiolabeled, one or more of the metabolites or degradation products remaining in the fish will be radioactive. The carbon fourteen activity is separated into various fractions, and the

chemicals associated with the activity are identified. It is very important to identify most of the radioactivity before tolerances are established. If this is not done, previously unidentified residues may become problematic in the future as more highly sensitive analytical methods are developed which could possible detect residues of concern.

Metabolism studies are required for fish and shellfish. Fish metabolism studies use radiolabeled pesticides. The water is treated, and the level of radioactivity resulting in fish is analyzed. If significant activity is found, the chemical identity associated with the activity is determined. This process answers the question, what is the residue in fish?

Significant Metabolites and Tolerance Expression. Using the results of fish metabolism studies, EPA determines which metabolites are of concern and need to be included in the tolerance. In each case, this decision is based on (1) the toxicity of the metabolite, (2) the percent and magnitude of its residue, and (3) whether a practical analytical methodology is available or can be developed to detect and measure the metabolite. For metabolites that are toxicologically significant and occur at significant levels, a suitable analytical methodology is mandatory. Considered together, the pesticide active ingredient and any significant metabolites are called the "total toxic residue."

Fish Residue Field Trial Data. Once the metabolism data indicate what to look for, and methods are developed to measure the total toxic residue, field experiments are carried out to answer the question, how much residue is there? These are studies in which the pesticide is applied to bodies of water at known application rates, in a manner similar to the use directions which will eventually appear on the pesticide label if the tolerance and registration are approved. These trials must reflect use conditions that could lead to the highest possible residues. Generally, this means the highest permissible application rate, the maximum number of applications allowed, and the shortest pre-harvest interval permitted by the use directions. Data are normally required for a top-feeding fish, a bottom-feeding fish, and for shellfish.

Analytical Methods. Based on fish metabolism study results, EPA requires tolerance petitioners to develop analytical methods to determine all components of the total toxic residue. In some cases, it is not possible to develop a single method that can determine all components of the residue, and several methods are required. Pesticide analytical methods are used for two purposes: (1) to obtain residue data on which dietary exposure assessments and tolerances are based, and (2) to enforce the tolerance after it is established. EPA validates each new analytical method using a method trial, to ensure that the

procedures can actually be used for tolerance enforcement purposes by FDA, USDA, and state agencies.

Determining the Tolerance Level. A petitioner for a tolerance proposes a tolerance level, based on residue trial data, which reflects the maximum residue that may occur under "worst-case" conditions as a result of the proposed use of the pesticide. The tolerance must include significant metabolites and must be high enough to cover all components of the total toxic residue. If one component of the residue is significantly more toxic than other components, two levels may be included in the tolerance.

Processing Data. While fish residue field trials provide data for estimating tolerance levels in fish, studies may also be needed for fish meat derived from fish in treated water. If residues do concentrate in processing, one or more food or feed additive tolerances must be established. However, if residues do not concentrate in processed commodities, the tolerance for the parent raw commodity applies to all processed food or feed derived from it.

Feeding Studies. Whenever pesticide residues result in feed items, data on the transfer of residues to meat, milk, poultry, and eggs are required. These studies are also required if a pesticide is to be applied to water which is consumed by animals or if fish meal is fed to animals. Data from these studies tell EPA how much and what kind of secondary residues may result in meat, milk, poultry, and eggs, in cases where this question arises.

TOXICOLOGY STUDIES

Pesticides having tolerances in fish are considered aquatic food crop pesticides under CFR 158.340. The toxicity data base (as described below) required for this use includes the following: acute, subchronic feeding in rat and dog, chronic feedings in rat and dog, teratology (developmental toxicity) in rats and rabbits, reproduction study in rats, cancer evaluation usually in rats and mice), metabolism and a mutagenic battery. Other studies may be required on a case-by-case basis.

Acute Studies. Determination of acute oral, dermal, and inhalation toxicity is usually the initial step in the assessment and evaluation of the toxic characteristics of a pesticide. These data provide information on health hazards likely to arise soon after, and as a result of, short-term exposure. They also provide information used in establishing the appropriate dose levels in subchronic and other studies and provide initial information on the mode of toxic actions(s) of a substance.

Subchronic Studies. Subchronic tests provide information on health hazards that may arise from repeated exposures over a limited period of time. They provide information on target organs and accumulation potential. The resulting data are also useful in selecting dose levels for chronic studies and for establishing safety criteria for human exposure. These tests are not capable of detecting those effects that have a long latency period for expression (e.g., carcinogenicity).

Chronic Studies. Chronic toxicity (usually conducted by feeding the test substance to the test species) studies are intended to determine the effects of a substance in a mammalian species following prolonged and repeated exposure. Under the conditions of this test, effects which have a long latency period or are cumulative should be detected. The purpose of long-term oncogenicity studies is to observe test animals over most of their life span for the development of neoplastic lesions during or after exposure to various doses of a test substance by an appropriate route of administration.

Teratogenicity (Developmental Toxicity) and Reproduction Studies. The teratogenicity study is designed to determine the potential of the test substance to induce structural and/or other abnormalities to the fetus as the result of exposure of the mother during pregnancy. Two-generation reproduction testing is designed to provide information concerning the general effects of a test substance on gonadal function, estrus cycles, mating behavior, conception, parturition, lactation, weaning, and the growth and development of the offspring. The study may also provide information about the effects of the test substance on neonatal morbidity, mortality, and preliminary data on teratogenesis and serve as a guide for subsequent tests.

Mutagenicity Studies. For each test substance, a battery of tests are required to assess potential to affect the mammalian cell's genetic components. The objectives underlying the selection of a battery of tests for mutagenicity assessment are: (1) to detect, with sensitive assay methods, the capacity of a chemical to alter genetic materials in cells; (2) to determine the relevance of these mutagenic changes to mammals; and (3) when mutagenic potential is demonstrated, to incorporate these findings in the assessment of heritable effects, oncogenicity, and possibly other health effects.

Metabolism Studies. Data from studies on the absorption, distribution, excretion, and metabolism of a pesticide aid in the valuation of test results from other toxicity studies and in the extrapolation of data from animals to man. The main purpose of metabolism studies is to produce data which increase the Agency's understanding of the behavior of the chemical in its consideration of the human exposure anticipated from intended uses of the pesticides.

For tolerance purposes, the toxicology data obtained from studies in which test animals are exposed to the pesticide chemical, mainly through oral exposure, are used to determine a lifetime "no observed effect level" (NOEL) for noncarcinogenic effects, and a cancer risk estimate if the pesticide has carcinogenic potential. The studies begin with young (postweanling) animals, and exposure continues through their adulthood (thereby mimicking human exposure beginning in adolescence and continuing over a lifetime). Using the NOEL, an acceptable daily intake (ADI) level -- which EPA scientists now call a reference dose (RfD) -- can be proposed for humans by applying a suitable uncertainty factor.

Three studies (rat reproduction, chronic rat feeding, and chronic dog feeding) generally form the basis for determining the RfD or ADI. The lowest dose causing no adverse effects from these three studies is divided by a safety factor to determine the RfD or ADI. The safety or uncertainty factor is intended to allow an extra margin of safety to compensate principally for (1) the scientific uncertainty inherent in the process of extrapolating human risk projections from animal data, and (2) the possibility of differing sensitivities to the pesticide in individuals or subgroups (such as children) among the general population. The magnitude of this factor may vary, depending on the toxicological effects observed in laboratory animals, and the amount of toxicity data available, but a 100-fold uncertainty factor is used in most instances.

In general, the reference dose can be defined as an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of adverse effects. The RfD is peer reviewed in the Office of Pesticide Programs prior to discussion by the Agency and is incorporated into the EPA Integration Risk Information System (IRIS).

In addition to residue chemistry and toxicology studies, the Agency requires data on environmental fate, reentry protection, spray drift, and effects on nontarget organisms for establishing tolerances. All of these studies are used to assess exposure and toxicity to humans and the environment.

RISK ASSESSMENT

Risk Assessments for tolerances and action levels in fish and other commodities are determined by integrating toxicological, consumption, and residue data according to the following formula:

$$\text{risk} = \text{toxicological value } (q_1^* \text{ or RfD}) \times \text{residue value} \times \text{consumption}$$

For carcinogenic pesticides such as DDT, chlordane, and aldrin/dieldrin, the toxicological value is determined by using both the cancer potency factor (q_1^*) and a reference dose (RfD) or acceptable daily intake (ADI). The q_1^* is expressed as a human q_1^* derived by multiplying a surface area conversion factor by the animal q_1^*. If the pesticide does not cause cancer or causes such a weak carcinogenic response that the q_1^* calculation would be inappropriate, the risk would be determined by comparing the exposure to the reference dose. Both the q_1^* and reference dose can be found on the Agency's Integrated Risk Information System (IRIS).

Consumption information is taken from OPP's Dietary Risk Evaluation System (DRES) -- formerly known as the Tolerance Assessment System (TAS). DRES is a computerized data management system which can estimate dietary exposure for the U.S. population and 22 subgroups. The consumption data in DRES is based on USDA's Nationwide Survey of Food Consumption. (Currently, EPA is using data from USDA's 1977-78 survey since these are the most recent comprehensive survey results available. USDA is in the process of analyzing results from its 1987-88 Nationwide Survey, and EPA will use these more recent survey results when they become available.)

DRES is composed of data files for food consumption estimates, toxicology summaries for each chemical and residue concentrations for each chemical in specific foods. DRES is capable of breaking fish consumption down by season (4), geographical region (4), ethnic group (4), and age-sex (10 subgroups), and can be used to estimate separate consumption of freshwater finfish, saltwater finfish, dried saltwater finfish, shellfish, and caviar. The average fish consumption value in DRES is 0.25 fish/kg body weight/day. To estimate consumption of fish by high fish consumers, conservative estimates of red meat replacement by fish (2.24g fish/kg body weight/day) and red meat and poultry replacement by fish (3.00g fish/kg body weight/day) have been assumed using DRES consumption for red meat and poultry.

The residue value used in the risk assessment will vary depending on the nature of the toxic effect. For acute effects, an upper bound residue value will be used, while for carcinogenic effects, an average residue level is appropriate. The residue level used in calculating dietary exposure is the tolerance or maximum permissible residue level.

Although the Dietary Exposure Branch in OPP does not have a routine procedure for calculating action levels, the Branch has used the following method for recalculating action levels which may be potentially recommended to FDA. The residue value used in calculating dietary exposure for action levels is the composite average residue of all fish species consumed nationally, weighted

by the percent of national consumption for each species. The composite average residue is calculated assuming all fish above a specified maximum level (action level) are removed from the market (i.e., residues in these fish are not included in the calculations). Other factors which could influence the residue value chosen include the variability of the residues within or among species, the quality of the available monitoring data, the required confidence in the risk assessment, and many other factors. Deciding on the appropriate residue level to use for risk assessment depends on these many factors and is done on a case-by-case basis for specific pesticides and exposure scenarios.

While the residue level used for risk assessment varies as described above, the residue level recommended as an action level must represent the maximum allowable pesticide residue. It should be noted that the residue level used for risk assessment and the residue level used for an action level need not be the same, and for carcinogenicity and other chronic effects, they are usually not the same. For example, the Agency's current models of carcinogenesis relate the frequency of carcinogenesis to the amount of pesticide exposure over a long time period. At any one meal, lower or higher levels of pesticide residue may be consumed, but over a period of time, residue consumption will likely approach an average residue level which can be used for risk assessment. For calculating an action level, the maximum allowable residue (which reflects a specific average residue) should be used.

Residue data are normalized to reflect the total residue (including metabolites) in the edible portion of the fish. Nondetectable residues may be incorporated into the calculations as the LOD, 1/2 LOD, or a more complicated analysis may be done depending on the toxic effects and on the quality of the available residue data. Depending on the toxicological effect, either average or upper bound residues are determined from these data. When performing risk assessments for contaminated fish as part of an action level evaluation, consumption of commodities other than fish is not considered. Also risk from each pesticide chemical is considered separately since use of the mixtures approach, which would require some knowledge of the relative quantities of pesticides in fish, is not feasible because of the large variability in relative pesticide levels.

As previously mentioned in the Background of this paper, most action levels for pesticides in fish were established by FDA prior to EPA's existence. At the request of Region V, OPP has initiated a study to reassess fish action levels for chlordane, DDT, aldrin/dieldrin, heptachlor, and mirex. OPP's analysis considered several possible options for assessing fish action levels, ranging from maintaining the status quo to lowering

action levels to the limit of detection (LOD). Intermediate options were based on 90th and 95th percentile residue determinations weighted to account for variations in the consumption of different species of fish. OPTS management has been briefed on these options, and a decision concerning the appropriate methodology should be forthcoming.

ECONOMIC IMPACT ANALYSIS

In general, OPP performs economic analyses for chemical-specific regulatory actions (i.e., Special Reviews), as well as for major policies and regulations. For the most part, OPP does not perform economic analyses for the registration of a pesticide or for the establishment of a tolerance, with the exception of minor use exemption waivers and tolerance fee waivers. Modification of action levels for fish or other commodities, however, would require an analysis and comparison of the risk reduction and economic costs associated with various policy options during regulatory development. The results of these analyses would be used to determine the trade-off between costs and risks for each option under consideration. In this fashion, OPP can identify and propose the most cost-effective option (i.e., the option which has the lowest cost-to-risk ratio).

In the options paper (mentioned above) in which OPP analyzed the impacts of reducing action levels for certain pesticides, the program completed a risk assessment and an economic impact assessment for each option under consideration (as required under E.O. 12291). Because the uses for these pesticides have been cancelled, modifications to existing action levels would not affect their use or environmental loading. In addition, pesticide users (i.e., farmers, homeowners, and commercial applicators) would not be directly affected. Instead, the Agency expects that most of the regulatory costs would be borne by commercial and recreational fisherman and that some of these impacts would be passed down to the consumer level in the form of higher prices for fish. The following sections identify the implications of lowering fish action levels and outline the Agency's analytical methodology.

As previously mentioned, EPA recommended action levels are usually adopted by the FDA. FDA inspects food for the presence of contaminants exceeding its established action levels, and has the power to seize contaminated shipments which are intended for interstate commerce. When the Agency lowers the action levels (i.e., becomes more stringent), the amount of fish that can be seized by FDA increases. Eliminating fish with relatively high levels of contamination reduces the average amount of pesticide residues in marketable fish. This reduction in residues lowers dietary exposure and subsequent risks to human health. To determine the most cost-effective approach, the economic costs are compared to the risk reduction achieved under each regulatory

option. The methodology used to determine regulatory costs is outlined below.

While EPA action levels for fish have no binding effect on the regulation of commercial fish in interstate commerce, either for fish inspection programs or fishing restrictions, some states have developed their own maximum residue levels which trigger regulatory and/or nonregulatory actions. Changes in EPA action levels may cause a state to re-evaluate its own risk assessments for fish consumption, which may, in turn, result in some type of policy action intended to restrict fish consumption. These actions include seizing intrastate shipments, prohibiting shipments, closing fisheries, issuing "catch and release" restrictions, and issuing consumption advisories.

The impacts of seizing shipments are fairly straight forward to estimate. However, predicting the response of state and local government agencies, consumers, and the fishing industry is more difficult to determine. In response to restrictions on fishing in certain areas or for certain species, fisherman may simply fish other areas or species. Similarly, consumers may change their fish consumption patterns rather than reduce total consumption of fish in response to consumption advisories. Given these uncertainties, the Agency quantified only the economic impacts on commercial fisherman for the RIA on fish action levels. A qualitative discussion of impacts on the sports fishing industry was also included.

The value of economic impacts is based on residue data regarding pesticide concentrations in fish. These data enable the Agency to determine the percentage of each fish species that would exceed current action levels (baseline), and the action levels proposed under the regulatory options. Based on these results, OPP estimated the volume and value of fish that would not be marketable under each option. These estimates assume perfect enforcement of the assumed action level under each regulatory scenario (i.e., all fish contaminated above the action level are inspected and seized, and no fish below the action level are included in seized shipments).

As mentioned earlier, changes in pesticide action levels in fish have no direct effect on sports fishing. However, changes may trigger states to issue new or revised consumption advisories or issue "catch and release" restrictions. Since these responses are difficult to predict, and the resulting changes in behavior of sports fishermen are even more difficult to predict, OPP has not attempted to estimate the (monetary) impacts on the sports fishing industry. To address this issue, OPP economists have presented information regarding the value of sports fishing (i.e., direct cash outlays as well as downstream benefits to local economics), and a qualitative discussion of the possible impacts associated with changing action levels. In particular,

examples of economic impacts resulting from known fish contamination have been cited. OPP believes this type of information will help frame the level of impacts that could result in affected areas.