Office of Pesticides
and Toxic Substances
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Office of Pesticide Programs

EPA

Environmental Fact Sheet

PESTICIDE TOLERANCES

EPA is responsible for regulating the amount of pesticide residues that may remain in or on food and animal feed. EPA's regulatory authority derives from the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

OVERVIEW OF THE PESTICIDE TOLERANCE PROCESS

Pesticide tolerances set by EPA are enforced by the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and state enforcement agencies. The U.S. food supply is monitored not only for compliance with pesticide tolerances, but also for potential contamination by aflatoxin, salmonella, and other microbial contaminants. Since surveillance resources are limited, they must be allocated on the basis of priority concerns. Pesticide residues are generally considered to be a lesser concern than microbial contamination.

Federal and state inspectors commonly sample food and feed produce for the purpose of tolerance enforcement soon after the farmer markets the treated commodity, so that any tolerance violations may be traced to their source. Thus, tolerances are intended to apply to treated raw agricultural commodities as soon as they enter into commerce, starting when the produce leaves "the farm gate."

In general, pesticide residues tend to dissipate or break down as time passes after harvest. In the majority of cases, residues are further reduced by washing, peeling, cooking, and other processing. Almost by definition, tolerances represent levels of pesticide residues that are **not** expected to occur as actual residues in food commodities that reach the consumer, or that remain in food at "the dinner plate."

The data required for a tolerance are mainly residue chemistry and toxicity data. (Such data are not generated by EPA laboratories; rather, EPA uses its data collection authorities under the law to require the pesticide manufacturer to produce these data.) All of EPA's tolerance data requirements are designed to answer three key questions. First, what is the chemical residue? Second, how much residue is there? The "what" and "how much" information, derived from residue chemistry data, is then matched by EPA toxicologists with toxicity data to answer

the third question: does the residue represent an acceptable dietary level of exposure? In other words, is there a reasonable assurance that under the prescribed conditions of use of the pesticide, no unreasonable adverse effects will result in humans even after a lifetime of exposure?

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 could 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 Plants and Animals. Plant metabolism data are required so EPA may characterize the nature of the residue that occurs on crops intended for consumption as food or animal feed. To obtain these data, the pesticide is labelled with a radioactive atom, usually carbon fourteen, and applied to the crop plant in accordance with proposed use directions. Since the pesticide molecule is radiolabelled, one or more of the metabolites or degradation products remaining in the plant at maturity 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 possibly detect residues of concern.

Plant metabolism studies are required for a minimum of three diverse crops -- for example, a root crop, an oilseed, and a leafy vegetable. If the metabolism in each of these crops is similar, then the metabolism in other crops is assumed to be similar. At the end of this process, EPA has enough information to answer the question, what is the residue in plants?

Whenever a proposed use of a pesticide may result in residues in animal feed, or when a pesticide is intended for treatment of livestock, animal metabolism studies are required in addition to plant metabolism data. Animal metabolism studies are generally carried out on ruminants (cows or goats) and poultry (chickens).

Like plant metabolism tests, animal metabolism studies use radiolabelled pesticides. The animals are dosed, and the level of radioactivity resulting in potential meat or poultry products (muscle, liver, kidney, milk, and eggs) is analyzed. If significant activity is found, then the chemical identity associated with the activity is determined. This process answers the question, what is the residue in animals?

Significant Metabolites and Tolerance Expression. Using the results of plant and animal 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."

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 crops 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. The field trial 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 each crop or crop group for which a tolerance and registration is requested. In addition, data are also required for each raw agricultural commodity derived from the crop. For example, corn residue analyses would be required for both grain and feed items--forage, silage, and fodder.

Analytical Methods. Based on plant and animal 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 field 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 residue field trials provide data for estimating tolerance levels in raw agricultural commodities, processing studies are required to determine whether residues in raw commodities may be expected to degrade or concentrate during food processing. 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 directly 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

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 non-carcinogenic effects, and a cancer risk estimate if the pesticide has carcinogenic potential. The studies begin with young (post-weanling) animals, and exposure continues through their adulthood (thereby mimicking human exposure beginning in adolescence and continuing over a lifetime).

The toxicological effects of concern here are not the severe and immediate poisoning symptoms that could result from accidental massive ingestion of a pesticide, or skin and eye irritation characteristics. Rather, these long-term feeding tests are designed to reveal potential adverse effects which may

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result from continuous low-level ingestion of a pesticide -- such as bone marrow damage, cancer, blood effects, and other chronic effects. Special test procedures also determine the potential of the chemical to cause birth defects, reproductive effects, neurotoxicity, and gene damage. In addition, the multi-generation reproduction study looks at the reproductive effects on animals exposed to pesticides in the womb and during nursing.

The Reference Dose, or Acceptable Daily Intake (ADI) Level.

Using the NOEL, an acceptable daily intake (ADI) level -- which EPA scientists now call a reference dose -- can be proposed for humans by applying a suitable uncertainty factor. The 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.

TOLERANCE DECISIONS

Traditionally, in making tolerance decisions, EPA has compared the reference dose with the Theoretical Maximum Residue Contribution (TMRC) of the pesticide to the daily diet. The TMRC is a mathematical construct obtained when the proposed tolerance(s) is added to any other tolerances that have already been established for the pesticide, and multiplied by average food consumption estimates based on USDA data from its 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.) As a rule of thumb, where basic data requirements are satisfied, EPA has routinely established a proposed tolerance if the TMRC is less than the reference dose.

However, as a routine practice, before making tolerance decisions on a pesticide, EPA uses the Dietary Risk Evaluation System (DRES) -- former known as the Tolerance Assessment System -- to calculate TMRC and risk estimates for the general population and a number of subgroups including the two most sensitive subgroups identified by the system. In some cases,

peak exposures to certain subgroups, such as infants and children, may exceed the reference dose by some percentage even though this is not the case for the composite average of the population. Since the reference dose is not a precise indicator of risk, exceeding the reference dose by a small factor is not necessarily a cause for concern. However, if the DRES analysis indicates that exposure and thus estimated risk to such a subgroup is so high that adverse effects are likely to occur, the Agency will not approve a tolerance even if the estimated risks to the average population are acceptable.

Examples of cases where dietary concerns for infants and children in particular have been the overriding consideration include:

> A decision bu EPA in 1985 not to approve tolerances for the pesticide pydrin for proposed new uses on alfalfa and sorghum, due to risks to children from secondary residues in milk.

> An action level for the occurrence of heptachlor epoxide in milk from cows fed pineapple greens that had been treated with heptachlor. Based on the potential for short-term liver toxicity in non-nursing infants and small children, EPA recommended and FDA issued a lower action level than would have been required to protect adults from adverse effects.

> EPA's announcement in early 1989 to expedite a notice of cancellation for all uses of Alar (daminozide), meanwhile extending a temporary tolerance for Alar residues in apples and urging voluntary restraint on its use. In the case of Alar, EPA was particularly concerned about the upper-limit cancer risk for Alar exposure to infants and toddlers for the first year and one-half of childhood.

It is important to note that the TMRC is a very rough-hewn tool of the tolerance process. Taken out of context, and applied literally, the TMRC can be used to make calculations that misrepresent risks from pesticides as artificially high. It is necessary to go beyond the TMRC approach, using real data on pesticide usage rates and anticipated residue levels, in order to evaluate actual dietary exposure and risk to consumers from pesticide residues in the food supply. Certain standard TMRC assumptions tend to greatly exaggerate the dietary risks attributable to pesticides; for example: (1) that 100% of each crop that may legally be treated with a pesticide is in fact treated with the pesticide, and (2) that pesticide residues in each commodity that may be treated with the pesticide are always present at tolerance levels at the time of consumption. Studies have shown that either is rarely the case, and that therefore the amount of residues on foods when they reach the consumer is

typically well below the established tolerance level.

There is an important exception to the reference dose approach described above. EPA has not used the reference dose concept, which implies a threshold level of risk, in considering tolerances for pesticides that induce cancer in test animals. Instead, the Agency takes a more conservative approach, based on widely used quantitative risk assessment models, which projects upper-bound (worst-case) estimates of additional risk above the background cancer risk in the general population of 1 in 4 or 0.25 (2.5×10^{-1}). Basically, the approach involves determining a quantitative estimate of a pesticide's carcinogenic potency, called a "Q star," and comparing the Q star to dietary exposure estimates. Dietary exposure estimates are based on the tolerance level of residues unless verifiable data on actual residues of the pesticide in agricultural commodities and consumer products are available.

In regulating pesticides that induce cancer in laboratory animals, EPA applies the "negligible risk" concept recommended by the National Academy of Sciences (NAS) to the extent possible in making registration and tolerance decisions under FIFRA and FFDCA.

In sum, the tolerance process is highly protective in that it is based on the most sensitive animal test results available and a combination of highly conservative assumptions and risk assessment practices. Tolerances are set at the lowest level necessary to accommodate the maximum application rate and frequency being proposed for the pesticide use, even when higher levels would be safe for human consumption.

ISSUES RELATED TO INFANTS AND CHILDREN

Several points should be highlighted regarding the tolerance process that relate to the protection of children:

> As mentioned above, in animal studies used for human risk assessment purposes, chemicals are administered to test animals beginning with young animals (post-weanling) and continuing through adulthood (mimicking human exposure that begins in adolescence and continues over a lifetime). The body dose received by the young animals may be double that of the adult animals, due to changes in their consumption patterns. However, the lower (adult) body dose is typically used in reference dose estimates. This results in a <u>lower</u> (and more protective) reference dose than would otherwise be the case.

> In setting reference doses, EPA generally uses a 10-fold uncertainty factor to compensate for the uncertainty inherent in the process of extrapolating human dietary risk

projections from animal data and, in addition, another 10-fold factor to compensate for the possibility of differing sensitivities in individuals or subgroups -- such as children -- among the general population.

> In cases where carcinogenicity is the potential effect of concern, EPA considers the upper limits of risk that may result from a lifetime exposure. Where these upper limit risks are not unreasonable from lifetime exposure, EPA concludes that the risk from a portion of lifetime exposure (e.g., between ages 1 and 12 or between 1 and 21) is likewise not unreasonable -- regardless of changes in eating habits expected to occur between infancy and adulthood. This practice is consistent with EPA's published cancer risk assessment guidelines and with current, mainstream thinking in the scientific community. EPA does not at this time have data to support specific modifications to this approach with respect to infants and children. However, at the request of the Agency, the NAS is currently examining issues surrounding pesticides in the diets of infants and children. When the NAS concludes its report, EPA will consider whether its present approach should be adjusted in light of the Academy's findings.

> Data on the comparative toxicity of pesticides in adult versus young weanling mammals are very limited and principally pertain to acute toxic effects only. A series of acute studies show mixed results. In studies of 37 chemicals administered to adult and weanling rats, weanlings demonstrated greater sensitivity in 8 cases. Adults showed greater sensitivity than weanlings in 23 cases. In 6 cases the sensitivity of adult and weanling rats was roughly the same.

> When estimating dietary exposure to infants and children, EPA's DRES uses milligram-per-kilogram body weight (rather than body surface) comparisons with dietary intake levels for risk assessment purposes. As the FIFRA Scientific Advisory Panel has pointed out, this practice is likely to overstate dietary risk to infants.

OTHER AREAS OF CONCERN

Pesticide Residues in Imported Foods and the "Circle of Poison". The tolerances established by EPA and enforced by FDA apply equally to domestically grown and imported food commodities. FDA monitors food crops imported from other countries to ensure that they do not contain pesticide residue levels higher than those determined acceptable for food crops grown in the U.S. Imported food crops may be denied entry into the U.S. if they are found to contain pesticide residue levels that exceed the established U.S. tolerances.

Also, to ensure that U.S. consumers are not eating residues of pesticides that have been banned in this country, EPA revokes the tolerances for pesticides that are cancelled. Once tolerances are revoked, neither domestic nor imported foods may lawfully contain residues of the banned pesticides. By revoking tolerances for banned pesticides, EPA prevents a "circle of poison" situation from occurring since pesticides banned in the U.S. are prevented from reentering the U.S. food supply through foods grown in other countries where the pesticide still may be lawfully used.

Neurotoxicity testing. EPA is in the process of upgrading its guidelines for neurotoxicity testing requirements. On this initiative, EPA's Office of Pesticide Programs (OPP) is working in concert with the Office of Toxic Substances (OTS), in publishing and reviewing public comment on neurotoxicity testing guidelines. These guidelines have been revised in light of public comments, and were recently submitted to the FIFRA Scientific Advisory Panel for review. EPA will incorporate the guidelines into its data requirement regulations under 40 CFR Part 158 and will require such data on a case-by-case basis until the revisions become final and effective.

Inert Ingredients. EPA published a Federal Register notice on April 22, 1987, describing a policy of increased scrutiny of inert ingredients. New inerts are subject to data requirements and registrants were urged to replace existing "inerts of toxicological concern" with less toxic chemicals. Registrants who failed to substitute were required to label their products to reveal the identity of the toxic inert, and will be required to submit the extensive data necessary for a product-by-product risk/benefit evaluation.

Data Gaps. Although a large number of active ingredients are registered for pesticide use on food, fewer than half of the active ingredients account for approximately 90 percent of the poundage of agricultural pesticides used. However, some of these products were first registered after 1984, and EPA has very extensive information on these pesticides. Other pesticides have been registered for some years and are undergoing reregistration. Since EPA has concentrated its reregistration efforts on reviewing these large agricultural use pesticides, EPA either has now, or will have in a very few years, a more complete data base on the pesticides contributing most heavily to dietary exposure.