Draft OPP Policy for the Use of

Anticipated Residues

of Pesticides in Foods for Use in

Chronic Dietary

Exposure Assessments

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ABSTRACT

The Food Quality Protection Act of 1996 (FQPA) (Pub. L. 104-170) was signed into law August 3, 1996. FQPA amends both the FFDCA, 21 U.S.C. 301 et seq., and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. 136 et seq. Among other things, FQPA amends FFDCA to bring all EPA pesticide tolerance-setting activities under section 408 with a new safety standard and new procedures. New Section 408(b)(2)(A)(i) of the FFDCA allows EPA to establish or leave in effect a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the tolerance is "safe." Section 408(b)(2)(A)(ii) defines "safe" to mean that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." This includes exposure through drinking water and in residential settings, but does not include occupational exposure. Section 408(b)(2)(C) requires EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing a tolerance and to "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue...." Additionally, FQPA requires more emphasis on regional pesticide analysis than previously required.

In examining aggregate exposure, FFDCA section 408 requires that EPA take into account available and reliable information concerning exposure from the pesticide residue in the food in question (the commodity for which a tolerance is being sought), residues in other foods for which there are tolerances, residues in groundwater or surface water that is consumed as drinking water, and other non-dietary, non-occupational exposures (residential and other indoor/outdoor uses).

EPA's Office of Pesticide Programs has developed the concept of

"anticipated residues" to refine dietary (food) exposure estimates to the consumer resulting from pesticide residues in foods. This document describes the OPP's approach to development of chronic anticipated residues. Exposure through residues potentially present in drinking water and exposure resulting from non-dietary, non-occupational scenarios will not be addressed in this document. Throughout this document, reference the term dietary exposure refers only to exposures resulting from pesticide residues in or on food - not including drinking water. OPP's policy for generating acute dietary anticipated residues have previously been presented to the SAP.

Dietary exposure to residues of a pesticide in a food commodity is estimated by multiplying the average daily consumption of the food forms of that commodity by the tolerance level or the anticipated pesticide residue. The Theoretical Maximum Residue Contribution (TMRC) is an estimate of the level of residues consumed daily if each food item contained pesticide residues equal to the tolerance. The TMRC is a "worst case" estimate since it is based on the assumptions that food contains pesticide residues at the tolerance level and that 100 percent of the crop is treated by pesticides that have established tolerances. If the TMRC exceeds the reference dose (RfD) or poses a lifetime cancer risk that is greater than approximately one in a million, EPA attempts to derive a more accurate exposure estimate for the pesticide by evaluating additional types of information which show, generally, that pesticide residues in most foods when they are eaten are well below established tolerances.

In determining anticipated residues, data from many sources are examined at successive stages in the risk assessment process until a conclusive statement may be made concerning the potential dietary risk of the pesticide. If the TMRC estimates indicate that the pesticide use may exceed certain threshold levels of concern, then residue field trial data, percent crop treated data, processing

studies, degradation studies, monitoring studies, and other types of data which would help provide a more accurate estimate of exposure are used to determine anticipated residues. Reliable data which are available are used prior to requiring submission of additional data by the registrant. The goal of determining the best estimate of residues "at the plate" requires weighing the usefulness of the available data sets. Because various types of data are available, and because these data may vary in quality, considerable scientific judgement is required in the assessment of dietary exposure.

Section 408(b)(2)(E) of FQPA requires that if anticipated residues are relied upon in establishing, modifying, or leaving in effect a tolerance, data will be required five years after the date on which the tolerance was established, modified, or left in effect, and thereafter at appropriate intervals, demonstrating that such residues are not above the levels so relied on.

Section 408(b)(2)(F) of FQPA states that percent crop treated data may be used is assessing chronic dietary risk only if the data are reliable, the exposure estimate does not understate exposure for any significant subpopulation group, and if data are available on pesticide use and consumption of food in a particular area, the population in such area is not dietarily exposed to residues above those estimated. This Section also provides for periodic reevaluation of the estimate of anticipated dietary exposure.

I. Purpose

Over the past ten years, the EPA's Office of Pesticide Programs has shifted its emphasis in dietary risk assessment towards generating estimates that reflect actual pesticide residue exposure to the U.S. population, and away from reliance on "theoretical upper bound" exposure estimates. To accomplish this, the concept of anticipated residues has been developed. Anticipated residues are estimates of the residues in foods nearer to the time of consumption, and more realistically reflect consumption of pesticide residues in foods than do tolerance levels.

FQPA requires that the data used in estimating anticipated residues be scientifically sound. The goal is to achieve the best possible estimate of dietary exposure to the pesticide residue. However, we realize that strict adherence to rigorous statistical criteria such as those described in the Appendices to this Policy may be extremely costly of time and of resources. The Agency will exercise its judgment in balancing the need for such statistical rigor with the costs of obtaining adequate data, and with potential hazards from consumption of pesticide residues, when assessing anticipated residues.

The purposes of this Policy are (1) to discuss the approaches currently used in dietary exposure assessment and determination of anticipated residues, (2) to discuss the limitations in these approaches and the direction the Agency is taking to overcome these limitations, and (3) to provide guidance for generating residue data which are adequate to determine anticipated residues.

Many issues regarding anticipated residues and dietary exposure assessment require further discussion and may result in a series of issue papers. These issues include, among others, the following:

(1) statistical design and evaluation of residue surveys at various levels in the chain of commerce (discussed in

Appendix 3);

(2) statistical design and evaluation of residue degradation/reduction studies (discussed in Appendix 5);

(3) a more detailed discussion of criteria for use of FDA, PDP, and other existing monitoring data for dietary exposure assessment (discussed in Appendix 4);

(4) criteria for use of existing field trial data, percent crop treated data, feeding studies, and processing studies in dietary exposure assessment (discussed in Appendix 4);

(5) use of data on pesticide usage and distribution;

(6) the strengths and weaknesses of the Dietary Risk Evaluation System (DRES), how DRES can be used to evaluate risks to more highly exposed population subgroups, and variations in risk due to geographic variability of residues or food consumption;

(7) residue estimates (e.g. average vs. 95th percentile) to use in exposure assessment considering the toxic effect and the type and quality of the available residue data;

(8) methods to estimate upper bound food consumption for chronic risk assessment;

(9) methods for obtaining a consistent set of residue data across chemicals;

(10) appropriate expression and communication of risks to the "average" consumer versus risk to most highly exposed individuals.

II. Pesticide Registration and Tolerances

A. Pesticide Registration

Pesticide products must be registered by the Environmental Protection Agency before they may be sold or distributed in the

United States. The authority of EPA to require pesticide registration is described in the Federal Insecticide, Fungicide, and Rodenticide Act, as Amended (FIFRA, 1988; Food Quality Protection Act (FQPA, 1996)). Data requirements for pesticide registration are provided in 40 CFR Part 158, and Guidelines have been developed for the data required. Required data include toxicity, product chemistry, and residue chemistry data, as well as other information (see 40 CFR 158.108 for a list of available Policies and ordering information). In addition to the required data, 40 CFR 158.690(b) contains a conditional requirement for "reduction of residue" data. Reduction of residue data are required when unreasonable risks are estimated assuming all foods contain pesticide residues at the tolerance levels. Reduction of residue data include any data which would allow a more realistic determination of pesticide residues as consumed (i.e. anticipated residues) than would assumption of tolerance level residues.

B. Tolerances

A tolerance is the legal limit for a pesticide chemical residue in or on a food. Tolerances are based on the maximum pesticide residue likely to occur in an agricultural commodity as a result of registered pesticide uses. If residues exceed the tolerance, or if no tolerance has been established, the commodity is considered to be adulterated and is subject to seizure by FDA, USDA, or State regulatory authorities. A tolerance is required before a pesticide may be registered for use on a food or feed crop. Tolerances are established by EPA under the authority of the Federal Food, Drug, and Cosmetic Act (FFDCA), and are used by the Food and Drug Administration (FDA) to regulate the movement of agricultural commodities in interstate commerce. Section 408 of the FFDCA applies to raw agricultural commodities (racs) and to processed commodities. The residue data submitted under FIFRA and described in 40 CFR 158

are used to determine tolerances.

Tolerances are normally established as a result of a tolerance petition which contains all of the data needed to establish the tolerance (see Section V). These data are usually generated by petitioners (usually major chemical companies) who wish to market the pesticide product. For minor uses, including small scale, infrequently needed, or specialty pesticide uses for which there is insufficient economic incentive for timely development of data by chemical companies, the U.S. Department of Agriculture (USDA) submits petitions to EPA under the Interregional Project #4 (IR-4) program.

Tolerances are required for raw and processed agricultural commodities, animal feeds, and animal products (meat, milk, poultry, eggs, and fish) in which pesticide residues could be found as a result of registered pesticide uses. Tolerances are necessary for processed commodities only if the residue concentrates significantly in the processed commodity or if the pesticide is applied directly to a processed commodity such as can occur during the fumigation of a food storage warehouse; otherwise, the tolerance for the raw commodity also applies to the processed commodity. In all cases, the tolerance represents the legal limit for a pesticide chemical residue in or on a food. However, the tolerance is not necessarily the maximum safe level since tolerances are set no higher than necessary to accomplish the intended result of representing the maximum residue likely to result from registered uses.

Many tolerances for older chemicals were established in the absence of data or were based on residue data which are no longer considered adequate due to advances in toxicology and chemical technology. For these reasons, hundreds of tolerances for older chemicals are being and have been reevaluated as part of the Agency's reregistration process. Any missing or inadequate data (data gaps) are being required of the pesticide registrant ("called-in") in order for the pesticide registrations to be continued. The Food Quality Protection Act (1996) also requires the periodic reassessment of

tolerances.

The specific uses of different types of data in determining tolerances are discussed in Section V.

III. Food Consumption

A. The Dietary Risk Evaluation System (DRES)

The Dietary Risk Evaluation System (DRES) is a computerized system which combines estimates of the level of pesticide residues on crops (and percent crop treated data) with information about how much of each crop a person eats. It then compares the resulting exposure estimate to a Reference Dose (RfD) or other toxicologically significant reference point. Information about anticipated residues for each crop is entered into DRES. An explanation of how DRES is constructed is therefore necessary to understand of how the estimates of anticipated residues are used.

DRES consumption estimates were derived from a survey conducted by the U.S. Department of Agriculture in 1977-78, which involved 3-day dietary records for 30,770 individuals and 3734 food items. DRES can handle separate residue estimates for a number of different food forms and food items for each commodity (24). For example, the different DRES food forms for apples include fresh apples and cooked apples, and food items include apple juice. Dietary exposure for DRES is expressed in terms of quantity of pesticide consumed per unit body weight per day (mg pesticide/kg body weight/day). Dietary exposure estimates for a pesticide in a specific food or food form are calculated by multiplying an estimate of the average amount of the food consumed daily by an estimate of the amount of pesticide in that food or food form. The total dietary exposure for the pesticide is the sum of these products over all foods or food forms for which there are tolerances for the pesticide in question. As a first

approximation of dietary exposure, tolerance level residues are entered into DRES. DRES can incorporate "anticipated residues" in place of tolerance level residues to generate a more realistic dietary risk assessment.

DRES can estimate dietary exposure for the U.S. population and 22 subgroups of the population as required by FQPA (1996). The 22 subgroups include groupings by season (Spring, Summer, Fall, Winter), geographical region (Northeast, North Central, Southern, and Western), ethnicity (hispanic, non-hispanic whites, non-hispanic blacks, and non-hispanic others), and age/sex (10 subgroups). DRES cannot estimate exposures for combinations across groupings such as western region/hispanics. However, DRES can account for varying residues in a commodity for subgroups within a given grouping such as by region or season.

The precision and accuracy of the exposure calculations by DRES for certain scenarios is limited in part by the 3-day time period over which the consumption data were generated. For example, the number of people who consumed certain minor commodities such as kiwi fruit or macadamia nuts during the 3-day survey period was small, and therefore, the variance of the consumption estimates for these commodities is large. If these commodities were to have significantly higher residues than other commodities, the dietary exposure estimate could be significantly affected by the imprecise consumption data for the minor commodities. An analogous situation could occur for some major commodities which are consumed by relatively few people within certain population subgroups (e.g. grapefruit consumption by infants). In these cases again, the low incidence (e.g. infants who consumed grapefruit over the 3-day survey period) may lead to relatively high uncertainty about the exposure to this subgroup. Uncertainties related to the short three-day period over which consumption data were generated are of particular concern in assessing acute toxicity.

The accuracy of extrapolating from a 3-day survey to the longer

periods of time that would be needed to cause chronic effects (weeks, months, or - in the case of carcinogenicity - a 70-year lifetime) is questionable. However, because data on long-term food consumption patterns are not available, DRES assumes that the average consumption estimates for chronic consumption by the general U.S. population and each of the 22 subgroups are equal to the average consumption estimates for the 3-day period over which the survey was taken.

EPA also uses information on the percent of a crop that is treated with a particular pesticide in carrying out a DRES analysis. The assumption that the percent of crop treated with a pesticide accurately reflects the percent of crop eaten that is contaminated with the pesticide leads to an overestimation of the risk for those people who eat a higher percentage of untreated commodity, and to an underestimation of risk for those people who eat a higher percentage of treated commodity.

In spite of the limitations discussed, DRES is currently the standard assessment system to which refinements for individual analyses are applied. The large amount of consumption information available in DRES, and its ability to incorporate and manipulate residue data, usage data, and toxicological reference values into its dietary exposure assessments, makes DRES a flexible and sophisticated dietary risk assessment tool. A detailed description of the strengths and weaknesses of the DRES are presented in references 15 through 20.

The DRES is being updated to inlcude more recent consumption data.

B. Other Food Consumption Estimates

Other means also have been used in the past to estimate consumption. Prior to the development of the Dietary Risk Evaluation System, the Food Factor System was used. The Food Factor method of

exposure analysis utilized two types of data to determine food consumption nationally. First, food consumption was estimated from the retail weights calculated from agricultural production figures (from USDA) adjusted for loss during distribution. Secondly, household surveys (USDA 1955, 1965/66, 1976/77) were conducted (personal interviews with household members) to determine food consumption measured at the level at which food enters the kitchen. In the household surveys, food consumption was expressed as lbs. commodity/week/household, and a food factor was determined by dividing the consumption estimate for a particular commodity by the total food consumption (97.85 lbs./week /household, 3.27 meal equivalents per person per household per day.) Total residue intake was determined by multiplying the food factor by the residue for each commodity, and then summing the resulting residues for the individual commodities. This system is no longer being used because it does not account for processed forms of foods or differences in consumption by population subgroups (regional, age or ethnic subgroups), and for other reasons. (21, 22)

IV. Types of Risk and Exposure Scenarios

For the purpose of determining the residue estimate to be used in a dietary risk assessment, risk is broadly categorized into carcinogenic risk, non-carcinogenic chronic risk, and acute risk. This document addresses only carcinogenic and non-carcinogenic chronic risks.

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. Therefore, the anticipated residue estimates used for quantitative

carcinogenic risk assessment are estimates of average residues in foods at the time of consumption. This estimate could be an average residue from field trials conducted at a typical use pattern or an average from monitoring data. Although some regional variability in the average residue is likely due to variations in environmental conditions and agricultural practice as well as distribution of commodities in commerce, this has not been considered by the Agency in past risk assessments because of the lack of adequate regional residue data, use information, and food distribution information, all of which would be required for an estimated average residue at the time of consumption. Regional variations in residue levels may be increasingly incorporated into risk assessment as better regional residue, use, food distribution, and consumption data are available and as directed by FQPA.

In determining exposure for non-carcinogenic chronic effects, the Agency currently uses either the average residue from field trial data reflecting the maximum use pattern (maximum amount applied, maximum number of applications, minimum retreatment interval, and minimum pre-harvest interval[PHI]), or the average residue from monitoring data. Since most of the field trial data available are for applications at the maximum application rate, maximum number of applications, and minimum PHI, the average residues found in these commodities will likely exaggerate the average residue actually present in foods at the time of consumption. In practice, pesticides are commonly applied at application rates less than the maximum rate, less than the maximum number of applications are made, and crops are harvested at PHIs which are longer than those registered, all leading to lower residues. Additionally, pesticides may degrade between the time of harvest and consumption. As in the case of carcinogenicity, regional exposure analyses may be performed if adequate regional data are available. Anticipated residues for pesticides in/on foods are revisited periodically.

V. Types of Data

In Section V.A. through V.G. below, the major types of residue data are discussed and how these data are used to establish tolerances. Use of these data in determining anticipated residues and dietary exposure is discussed in Section VI.

A. Metabolism Studies in Plants and Animals

Plant and animal metabolism studies are designed to characterize the chemical composition of the pesticide residue in plants and animals. In plant metabolism studies, the plant is treated with the pesticide, usually radiolabelled with ^{14}C, in a manner similar to the proposed use. For example, if corn were to be treated with a pesticide using foliar spray applications, foliar applications of the radiolabelled pesticide would be made to corn in the metabolism study. Following pesticide treatment, the plant is managed as closely as possible to the way the plant would be managed in the field and samples of important plant commodities are obtained (e.g. corn grain, forage, and stover). The samples are collected at times which correspond to normal harvest times. The samples then are analyzed to determine the chemical structures and quantities of metabolites present in the total radioactive residue.

Two types of animal metabolism studies normally are conducted. If an animal is to receive dermal pesticide treatments (sprays, dips, etc.), the radiolabelled pesticide must be applied to the animal dermally. If the animal will consume the pesticide or pesticide residue orally, oral administration is required. Following pesticide treatment for a sufficient length of time, animal tissue, milk, and egg samples are obtained and analyzed to determine the chemical structures and quantities of metabolites present in the total pesticide residue.

The tolerance expression which is published in 40 CFR Part 180 for each pesticide, describes which chemical components of the pesticide must be regulated. The HED Metabolism Committee determines the residue to be regulated (tolerance expression) and the residue to be considered in various risk assessments. Metabolites are included in the tolerance expression depending on their toxicological significance, their percentage of the total residue, and whether analytical methodology can be developed to measure residues of the metabolite in agricultural commodities. Methodology is essential for metabolites which are both toxicologically significant and present at significant levels. The active ingredient and toxicologically significant metabolites are called the total toxic residue. If one component of the residue is significantly more toxic than the other components, two levels may be necessary in the tolerance expression.

More detailed information regarding how to conduct and evaluate metabolism studies can be found in the OPPTS Test Guidelines, Series 860 (EPA 712-C-96-169), available from the U.S. Government Printing Office (http://fedbbs.access.gpo.gov; 202-512-0132).

B. Analytical Methodology

Chemical components of the pesticide residue which are included in the total toxic residue are determined by the HED Metabolism Committee. Once the total toxic residue has been determined, analytical methods must be developed to allow determination of residues of these components in agricultural commodities (raw, processed or animal) for which tolerances are required. These analytical methods are necessary to provide residue data in residue field trials and as a means of enforcement of the tolerances. Detailed information regarding analytical methods may be found in the OPPTS Test Guidelines, 860.1340 (EPA 712-C-96-174).

C. Residue Field Trials

After the metabolism studies have indicated what to look for and analytical methods have been developed to measure the total toxic residue, the actual residue field trials are carried out. These are studies in which the pesticide is applied to crops in a manner similar to the directions for use which will eventually appear on the label; then, samples are obtained and analyzed for total residues. The purpose of residue field trial studies is to determine the appropriate tolerance level which is the maximum legally allowable pesticide residue and is used to regulate the commodity as it travels in interstate commerce. Data normally are required for each crop (or for representative commodities in a crop group as defined in 40 CFR 180.34(f)(9)) for which a tolerance and registration is requested. Data also are required for each raw agricultural commodity (rac) derived from the plant (for example, corn residue data would be required for the grain and the forage, and stover). Samples generally are placed in frozen storage immediately after collection to minimize loss or dissipation of the pesticide residue prior to analysis. The field trial data must reflect the use conditions that could lead to the highest residues and must represent the highest application rate, the maximum number of applications, and the shortest time intervals between applications and between the last application and harvest to be included on the label. The residue data also must be representative of major growing areas and seasons, major types or varieties of the rac, the general types of pesticide formulations for which registration is requested, and the types of applications to be made (e.g. ground applications and ultra-low volume aerial applications.) Further information regarding field trial data are available in the OPPTS Test Guidelines, 860.1500 (EPA 712-C-96-183). Additional information regarding the use of field trial data in determining tolerances and anticipated residues is

included in Appendices 1 and 4.

D. Processing Studies

Processing studies are designed to determine the concentration (or reduction) of residues when the raw agricultural commodity is processed commercially. Typically, a raw agricultural commodity containing weathered residues, frequently resulting from field applications at exaggerated (higher than maximum label) pesticide application rates to assure obtaining quantifiable residues, is processed using a method which closely simulates commercial processing. Important processed fractions are obtained at various points in the process and analyzed for the total toxic residue. The ratio of the residue in the processed commodity to the residue in the raw commodity is the concentration (or reduction) factor. If the average ratio for all processing studies is greater than 1, the residue is said to concentrate upon processing. If the average ratio from all processing studies is equal to or less than 1, there is no concentration of residues. These ratios, if greater than 1, are then multiplied by the highest average field trial residue (HAFT) for the raw agricultural commodity to determine if tolerances are required for the processed commodities. Tolerances are not required for processed commodities unless the residue concentrates significantly (concentration factor multiplied by the HAFT is greater than the rac tolerance) upon processing. Additional information regarding processing studies can be found in the OPPTS Test Guidelines, 860.1520, EPA 712-C-96-184.

E. Feeding Studies

In animal feeding studies, pesticide residues which may be found in meat, milk, poultry, and eggs as a result of ingestion of treated feeds by animals are determined. The maximum residues in animal

commodities likely to result from ingestion of animal feeds treated at the maximum application rates (and shortest PHIs) are used to determine tolerances for animal commodities (except in cases where dermal applications are also made to the animal in which cases residues from dermal applications also would have to be incorporated into the tolerance level).

In general, animals are dosed with the pesticide for a period of time, and the resultant residues in eggs, milk, and animal tissues are measured (the total toxic residue as determined by the HED Metabolism Committee). If metabolism studies show that there are plant metabolites of toxicological concern which are not also animal metabolites, the animal may need to be dosed with the metabolites which are plant metabolites and not animal metabolites, as well as with the parent compound.

The livestock theoretical dietary burden (residue intake from treated feeds) is determined by multiplying the tolerance level for livestock feed items by the maximum fraction of each feed item (corrected for percent dry matter for ruminants) in the livestock diet (found in OPPTS Test Guidelines, 860.1000, Table 1; EPA 712-C-96-169). Then the residue contributions from each commodity are summed to obtain the total dietary burden of the animal. The feeding levels to be used in the livestock feeding studies are based on the estimated dietary burden of the pesticide in the livestock feed. The levels used should be approximately 1x, 3x, and 10x of the estimated dietary burden, where 1x is the worst case estimate of potential livestock dietary exposure based on the assumption that all components of the feed contain tolerance level residues. The exaggerated feeding levels are particularly important if non-quantifiable residues are reported at the 1x feeding level; they help show whether residues in tissues vary linearly with the feeding level. Additionally, exaggerated feeding levels will allow for future tolerance requests (the animal dietary residue burden must be less than the maximum feeding level used in the feeding studies or

additional feeding studies may be required).

The dietary burden is compared to the levels fed in the livestock feeding study, and the residue in each tissue, in milk, and in eggs is determined from a graph or linear regression analysis. Sometimes a simple ratio is used if the estimated dietary burden is close to one of the levels in the livestock feeding study or is significantly lower than the lowest level in the feeding study. The residue estimated in this manner for meat and poultry tissues, milk, and eggs is rounded upward and becomes the tolerance level. However, as required by FQPA, the tolerance level is not set at a level lower than the limit of quantification (LOQ) of the analytical method.

Further information regarding animal feeding studies is available in the OPPTS Test Guidelines, 860.1480, EPA 712-C-96-182.

F. Monitoring Data

In a pesticide residue monitoring study, samples of agricultural commodities are obtained at various times and from various locations and analyzed for pesticide residues. The specific commodities sampled, sampling locations and times, numbers of samples, sample sizes, and many other sampling parameters depend on the purpose of the study. Purposes for which pesticide residues are commonly monitored in foods include enforcement of tolerances and effluent discharges, trend analyses, assessment of environmental contamination and dietary exposure assessment. Although our focus here is on chronic dietary exposure assessment, monitoring data obtained specifically for this purpose are not always available for many commodities and pesticides. Therefore, monitoring data designed for other purposes commonly are used taking into account the uncertainties or bias introduced because of the different purposes for which the data were generated. Further discussion of the use of monitoring data in dietary exposure assessment is included in Section VI and in Appendix 4. Below we discuss some of the major existing

monitoring programs and the factors which determine their usefulness in dietary exposure assessment.

The most widely available monitoring data are those from the FDA and USDA. The Food and Drug Administration (FDA), as part of their enforcement program for pesticides, collects four types of monitoring data: domestic surveillance, domestic compliance, import surveillance, and import compliance. Compliance data generally are the result of targeting collection towards commodities suspected of containing illegal residues, while surveillance samples are collected without any suspicion that a particular shipment contains illegal residues. They are, however, selected partly on the basis of volume of production of a commodity and partly on the basis of prior residue problems with a certain food commodity and growing region. In their surveillance monitoring program, FDA monitors a wide variety of agricultural and processed commodities for numerous contaminants, including pesticides, using primarily multiresidue methods of analysis which are capable of determining a variety of contaminants from a single sample analysis. In its surveillance monitoring program, FDA also conducts incidence/level monitoring to acquire information on specific pesticides, commodities, or pesticide/commodity/country combinations. Among recent incidence/level monitoring conducted by FDA are monitoring for residues of aldicarb (potatoes), captan (cherries), benomyl (apples, grapes, peaches), captafol (apples, cherries, rice), an aquaculture survey, a milk survey, and a processed food survey. Although routine monitoring and incidence/level monitoring provide data for many pesticides, other pesticides are not monitored by FDA or only limited data are available. Domestic samples are collected as closely as possible to the point of production in the food distribution chain since the prime objective is to monitor fresh food being shipped in interstate commerce for compliance with EPA tolerances. Therefore, additional degradation which could occur between the collection point and the "dinner plate" is possible. Information which would allow

determination of the location at which a sample was grown is not readily available. Import samples are collected at the point of entry into U.S. commerce (12, 13, 14).

A major objective of the FDA monitoring program is to prevent foods that contain illegal residues from entering interstate commerce. Although the overall program is not designed to provide truly representative sampling of commodities for the purpose of dietary exposure assessment, FDA's FY '92 program included a trial effort to provide statistically based monitoring data in pears and tomatoes. Bias may enter if the compound of concern was targeted for FDA monitoring and higher than typical residues were seen. If the compound being assessed were not given priority in sample collection, and monitoring were directed towards other competing compounds, the FDA surveillance data for the first compound may show infrequent "detects" and artificially low average residues.

FDA also conducts the Total Diet Study, also called the Market Basket Survey, in which pesticide residues are determined in food prepared for consumption. The Total Diet Study is designed to estimate dietary intake of selected pesticides by various U.S. age-sex groups. Foods are collected four times per year in retail markets at 12 locations throughout the U.S. and are prepared as table-ready (cooked) before analysis. Each market basket consists of 234 foods that represent at least 90% of the items in the American diet (14). These data are useful to the FDA for making trend analyses; however, since so few samples of each commodity are obtained, these data have limited use for risk assessment.

FDA monitoring includes few samples of meat and poultry (these commodities commonly are included only in the Total Diet Study). Monitoring data may be available for animal commodities from USDA for chemicals included in their routine monitoring programs. Pesticide monitoring data from USDA's Food Safety and Inspection Service (FSIS) primarily include analyses for chlorinated pesticides in animal fat, and other selected pesticides in liver samples. USDA's FSIS monitors

shelled eggs and egg products for pesticides (formerly done by USDA's Agricultural Marketing Service (AMS)), while FDA monitors for pesticide residues in in-shell eggs.

The USDA, in cooperation with the EPA and FDA, established (1991) the Pesticide Data Program (PDP). This program is designed to provide actual residue monitoring and usage data to help form the basis for conducting more realistic risk assessments. Briefly, EPA provides USDA with pesticide/commodity combinations for which the EPA desires data; and the PDP generates these data (including residue monitoring and usage data) in cooperation with the States. Over 700 samples of each commodity are collected in a year and analyzed for pesticides of interest to EPA. These data are then provided to EPA. The PDP monitors residues in those fresh fruits and vegetables most prevalently consumed by the US public. To date, PDP has tested 25 food commodities, 17 of which were fresh fruits and vegetables, six were processed commodities, and the remaining two were milk and wheat.

An important aspect of this program is that it is designed to meet the data quality and random sampling criteria required for monitoring data used for risk assessment. The majority of the sampling sites are either terminal markets or large chain store distribution centers. These are typically the last points before distribution to retail sites. Samples are prepared by practices that emulate those of the consumer, for example, bananas are peeled.

Monitoring data also may be generated by other sources including states, registrants, and other interested parties such as food processors and consumer or environmental groups. Monitoring data generated by the states (CA, FL, NJ and others) are available; some of these data are incorporated into a data base acquired through an FDA contract. FDA has coordinated with several states to coordinate data collection and compile the data to increase their availability and usefulness (FOODCONTAM project).

EPA has the authority to require pesticide registrants to

generate market basket surveys of pesticide residues and recently has exercised this authority in issuing "Data Call-Ins" requiring statistically based national surveys for residues of specific pesticides. Appendix 3 provides guidance on the design and evaluation of pesticide residue surveys. A discussion of the use of existing monitoring data in dietary exposure assessment is presented in Appendix 4.

G. Residue Degradation-Reduction Studies

Residue degradation/reduction describes any change in the amount and composition of the total toxic residue from harvest to the point of consumption. Therefore, many types of processes are grouped under degradation-reduction studies including storage, commercial transport, commercial processing, washing, peeling, trimming, cooking, and others. In the case of post-harvest pesticide applications, degradation/reduction describes the changes from pesticide application to consumption. Pesticides may degrade to form less toxic products or, less commonly, to form more toxic products.

Two general mechanisms are responsible for the degradation/reduction of pesticide residues in a commodity: physical processes and chemical processes. Physical processes include washing, volatilization, and removal of parts of a commodity such as peels, hulls or outer leaves. The pesticide also may react chemically in the presence of moisture, heat, light, acids, bases, enzymes, oxidizing or reducing agents, metal ions, or under other conditions which may decrease or modify the residue. The major chemical degradation pathways are oxidation and hydrolysis, both of which can occur by enzymatic or non-enzymatic mechanisms. Most enzymes responsible for pesticide degradation would lose their activity permanently after being heated to 100°C or above.

The kinetics of pesticide degradation generally are assumed to

be pseudo first order for a particular degradation process depending only on the pesticide residue (which would be very low relative to other chemicals involved in the degradation process such as water). However, many degradation processes can occur at the same time. Therefore, in order to determine the overall kinetics of degradation, a mean half-life (obtained by averaging half-lives calculated from a series of sets of points along the curve of log (residue concentration) vs. time) may be used cautiously as an estimate of the half-life of the composite degradation process.

After harvest, commodities can be stored (sometimes for extended periods of time), transported, commercially processed, waxed, washed, peeled, cooked, and treated in other commodity-specific ways. Time and temperature considerations are important when examining the effects of storage, transportation, commercial processing, and cooking. Humidity may be important when examining storage and transportation. The point at which wax (with or without pesticides) is applied to some commodities must be considered (e.g. apples, cucumbers). The typical way(s) commodities are washed, peeled, and cooked (e.g. boiled, fried, roasted, etc.) are important considerations. Other processes also may be important for specific commodities (e.g. shelling nuts, removal of the outer leaves from lettuce and cabbage, removal of the thick part of the stem from broccoli and asparagus). Residue degradation/reduction studies for representative commodities within a crop group may be sufficient to characterize residue degradation/reduction within the entire crop group if commercial and home preparation practices are similar for the different commodities.

A residue degradation/reduction study should take a treated sample through all of the processes from harvest to consumption and should simulate typical commercial and home practices as closely as possible. Subsamples should be removed at each important point for residue determination in the edible portion of the commodity. In all cases, but particularly when degradation products are more toxic than

the parent, application rates should be chosen which are close to the maximum registered rates so that metabolite ratios which approximate those likely to result from typical applications can be determined. Residues in the raw commodities should be well above the analytical method limit of quantitation (LOQ) at the beginning of the study so that the decline in residues can be measured accurately. Analytical methods must have sufficiently low limits of quantitation (LOQs) so that an acceptable risk can be estimated using the LOQ, considering combined risk from all foods.

Design of studies to measure residue degradation/reduction in commodity storage is presented in Appendix 5. Additional discussion of the integration of field trial, storage, processing, cooking, and other data are required.

H. Pesticide Usage Data

Pesticide **usage** data describe the amount of pesticide applied per unit time (lbs.a.i. per year, for example), the number of acres of each crop treated (or the percentage of the crop treated), and similar information. This is to be distinguished from **use** data which describe the specific way the pesticide is used on a crop such as the type of application ("in-furrow", for example) or the timing of applications. Pesticide usage data are collected by the Agency for use in human risk/benefit analyses, environmental exposure/risk analyses, and serve as an input for design and planning activities for monitoring and enforcement efforts (25).

Usage data are available from many sources. Proprietary sources of usage information include those from Doane Marketing Research, Inc., Maritz Marketing Research, Inc. and Technomic Consultants. Doane and Maritz provide current estimated use and usage data for major crops and some small acreage crops. Doane also provides livestock usage data. Estimates generally are based on surveys/panels and may include some expert opinion, especially

Technomic. Survey data are available from USDA covering major field crops, and more recently, other crops. Usage information are available from many states, but the usefulness of these data frequently are limited for many reasons including pesticide usage not being reported by crop, sporadic collection of data, the availability of only older data (5-10 years old), and collection of data only for "major crops". The Census Bureau estimates usage by pesticide classes, not specific pesticide, and can conduct special surveys for selected states when funds are available. Battelle provides primarily foreign pesticide usage data. Information sometimes is obtained through phone calls to cooperative extension personnel, but the information usually is based on opinion rather than on hard data. Finally, registrants provide data under Section 7 of FIFRA giving the amounts of pesticide that are produced and distributed, but the amounts used on specific crops are not provided.

These data are most useful for estimating ranges of percent of crop treated on a national and regional basis for major chemicals on major crops (major crops as defined here include field corn, wheat, soybeans, peanuts, cotton, sorghum, barley, oats/rye, alfalfa, and perhaps rice, plus a few specialty crops such as potatoes, tobacco, and citrus as a group.) Data are limited for specialty (minor) crops, postharvest applications (except apples, oranges, grapes, and some grain fumigants), and livestock (while there are data on percent of crop treated for feed, there is little information on which animals are fed the treated feed.)

The use of percent crop treated information in dietary exposure assessment is described in Sections VI.A. and VI.A.2. The usefulness of pesticide usage data for dietary exposure assessment has been limited to national estimates of percent crop treated because of the reasons discussed above, and because there has been no information connecting the treated crop to its distribution in commerce and processing. Tolerance multiplied by percent crop treated yields an anticipated residue estimate. FQPA requires reconsideration of the

dietary exposure assessment (anticipated residue) after five years if percent crop treated data are utilized.

VI. Use of Data

The following sections discuss how various types of data are used in dietary exposure assessment. First an overview of the sequence of events in determining dietary exposure is presented, followed by a more detailed discussion of how the various types of data are used.

A. Anticipated Residue Determination: Sequence of Events in Determining Dietary Exposure

Tolerances, as explained, often do not accurately reflect actual residues likely to be found in ready-to-eat foods. However, an accurate prediction of likely crop residues is vital when estimating dietary exposure to pesticide residues for the purpose of risk assessment so that realistic risk estimates can be obtained. To this end, "anticipated residues" are determined. An "anticipated residue" is simply the best estimate of the pesticide residue likely to be consumed.

The sequence of events normally followed in developing dietary exposure/anticipated residue estimates for pesticide chemicals is the following:

(1) Exposure assessment based on tolerance level residues

(2) Reassessment of exposure using adjustments for the percent of crop treated

(3)(a) Reanalysis of the residue field trial data to determine

averages or upper limits on the residue, depending on the toxic effect

(b) Adjustment of the residue for the effects of washing, cooking, processing, storage and other factors depending on the available data

(c) Use of existing monitoring data from FDA, USDA, the States, etc., when available and reliable

(d) Reassessment of anticipated residues and comparison of anticipated residues estimated from monitoring data and field trial/degradation data (if both are available) to determine consistency between the data sets, and if inconsistent, which anticipated residues to use

(e) Reassessment of exposure based on anticipated residues determined in (3a) to (3e) above

(4) Requiring monitoring or other studies to be carried out by the pesticide registrant

Exposure assessment is carried out in a step-wise manner in order to assure that no unreasonable risk results from use of the pesticide while not requiring the registrants to generate unnecessary data. In performing the sequence of events above, the process is stopped if the exposure estimate does not exceed OPP's level of concern. Examples of some of the calculations used in determining anticipated residues are presented in Appendix 1.

As a first step in estimating the dietary exposure to pesticides, the Agency traditionally has assumed that residues would be at the tolerance level. This conservative assumption leads to unrealistically high estimates of dietary exposure (for chronic

exposure) for a number of reasons. For example, pesticides are not always applied at the maximum rate or minimum PHI, not all crops are treated, and residues on food at the time of consumption often are significantly lower than the residue on the rac. The latter is due to breakdown of the pesticide during shipping and storage, and other processing procedures such as peeling, trimming, cooking, and canning which may reduce the pesticide residue.

If the dietary exposure analysis conducted using tolerance level residues leads to an estimate of dietary exposure which is considered to be acceptable, then the Agency does not attempt to further refine the dietary exposure assessment. However, if the exposure estimated using tolerances is of concern, tolerance levels would be adjusted for percent crop treated and the exposure would again be estimated. Risk management decisions based on anticipated residues corrected for percent crop treated are made considering potential changes in the percent crop treated as well as on the available pesticide alternatives.

If estimations using tolerances and percent crop treated data show exposure to result in risk levels of concern, anticipated residues would be determined.

Prior to requiring submission of new data, all available data would be examined for its usefulness in determining anticipated residues. This would include field trial data, processing studies, monitoring data, feeding studies, percent crop treated data, information regarding typical application rates and methods, and any other type of data which would provide a more realistic estimate of residues "at the plate". If these data were determined to be adequate, a more accurate exposure estimate would be made based on the anticipated residues estimated from these data. Otherwise, additional data would be required of the registrant to maintain registration of the pesticide. If the available data were considered adequate to determine anticipated residues, and if exposure estimated from these anticipated residues were still of concern, it then would

be determined whether additional data could provide a still more accurate anticipated residue estimate which might indicate acceptable risk. If so, these data would be required of the registrant in order to maintain the pesticide registration. Otherwise, methods other than improving the accuracy of the anticipated residues would be utilized to mitigate the risk.

For a typical exposure assessment consisting of one pesticide and many commodities, anticipated residues are determined for each commodity using either monitoring data or field trial/degradation studies, depending on the data which are available for each individual commodity (both monitoring and field trial data may be used for different commodities in a single exposure assessment for a pesticide).

In some cases, anticipated residues determined from monitoring data which are considered sufficiently precise, representative, and free from bias, and which were generated in a manner such that the residues seen are likely to reflect actual residues "at the plate", are substantially different from anticipated residues determined using other types of data. This difference frequently can be attributed to a lack of sufficient information regarding pesticide degradation between harvest and consumption and the resulting inaccuracy in the anticipated residue estimate based on field trial/degradation data. In these cases, the anticipated residue estimate from monitoring data is considered more accurate and is used. If both the monitoring and field trial/degradation data are considered adequate but give conflicting results which cannot be attributed to some uncertainty in one of the data sets, the more conservative estimate of the anticipated residue is used.

When data necessary to determine anticipated residues are required of the registrant, it is the registrants' responsibility to develop an acceptable protocol, although the type of data needed may be specified by EPA. Registrants are encouraged to submit protocols to the Agency for review prior to the initiation of studies.

Additionally, to help assure that the registrants' resources are not wasted on studies which will not be acceptable to the Agency, OPP has drafted "Acceptance Criteria" for all types of residue studies. These documents were prepared as part of the Phase 3 Guidance of FIFRA 88. These criteria must be met before the studies will be accepted (the studies may still be rejected for other reasons even though they meet the minimum requirements described in the "Acceptance Criteria").

The approach to estimating the anticipated residue generally is governed by the type of data available for a given pesticide/crop combination. The types of data utilized are illustrated in Figure 1 by a series of concentric circles in which the outer boundary represents the highest permissible legal residue, and the center reflects the actual residue intake by the consumer. As one nears the center of the circle, the anticipated residue more realistically estimates the actual residue intake. Residue field trial and processing data are available for most pesticides in the tolerance petitions. Monitoring data, cooking studies, and studies of the change in residues during transport and ambient storage generally are not available in tolerance petitions. Monitoring data typically are available from FDA for pesticide chemicals which are capable of being analyzed by FDA multiresidue or single-residue methodology. These include most chlorinated hydrocarbons, N-methyl carbamates, phenolic, organophosphate and carboxylic acid-containing pesticides. Monitoring data sometimes are available from other sources including the USDA, State agencies, and registrants. Monitoring data are available from PDP for requested crop/commodity combinations.

The choice of the appropriate data bases to use for estimating dietary exposure and the manner in which these data bases are treated are issues which require considerable scientific judgment and are decided on a case-by-case basis. In general, the database selected must have sufficient information to determine the desired anticipated residue with reasonable reliability. This is discussed further in

Sections VI.A.(1) and (2).

A flow diagram depicting some of the ideas discussed is shown in Figure 2. Also shown are generalized equations for determining anticipated residues in plant and animal commodities.

1. Monitoring Studies

Monitoring data are the preferred source of data for anticipated residue estimates, assuming sampling is representative and sufficiently extensive, because these studies measure the residue that actually is present in foods in the chain of commerce. The closer to the "dinner plate" the data are obtained, the more likely the data will reflect realistic residue consumption. Many factors must be considered and weighed when determining the usefulness of available monitoring data, and in designing a monitoring program; formulation of a "cookbook" process for these purposes, which includes all contingencies which might be encountered, is not feasible. Below we discuss some factors which must be considered when determining the adequacy of monitoring data in determining dietary exposure.

Descriptions of the FDA Surveillance and Compliance Monitoring Programs were provided in Section V.F. and are discussed in more detail in Appendix 4. As discussed, these programs were designed for purposes other than dietary exposure assessment. However, reliable dietary exposure information can be obtained from these data in many cases provided the limitations in the data base, which are discussed below, are considered.

An important consideration in determining the usefulness of any monitoring data in dietary exposure is the geographical representativeness of the data. Determination of geographical representativeness must be made on a case-by-case basis since crops grown and pesticides used vary with location. Since the location in

which a crop sample was grown generally is not available with FDA

Figure 1: Approach to Targeting Realistic Residues to Use in Dietary Risk Assessment

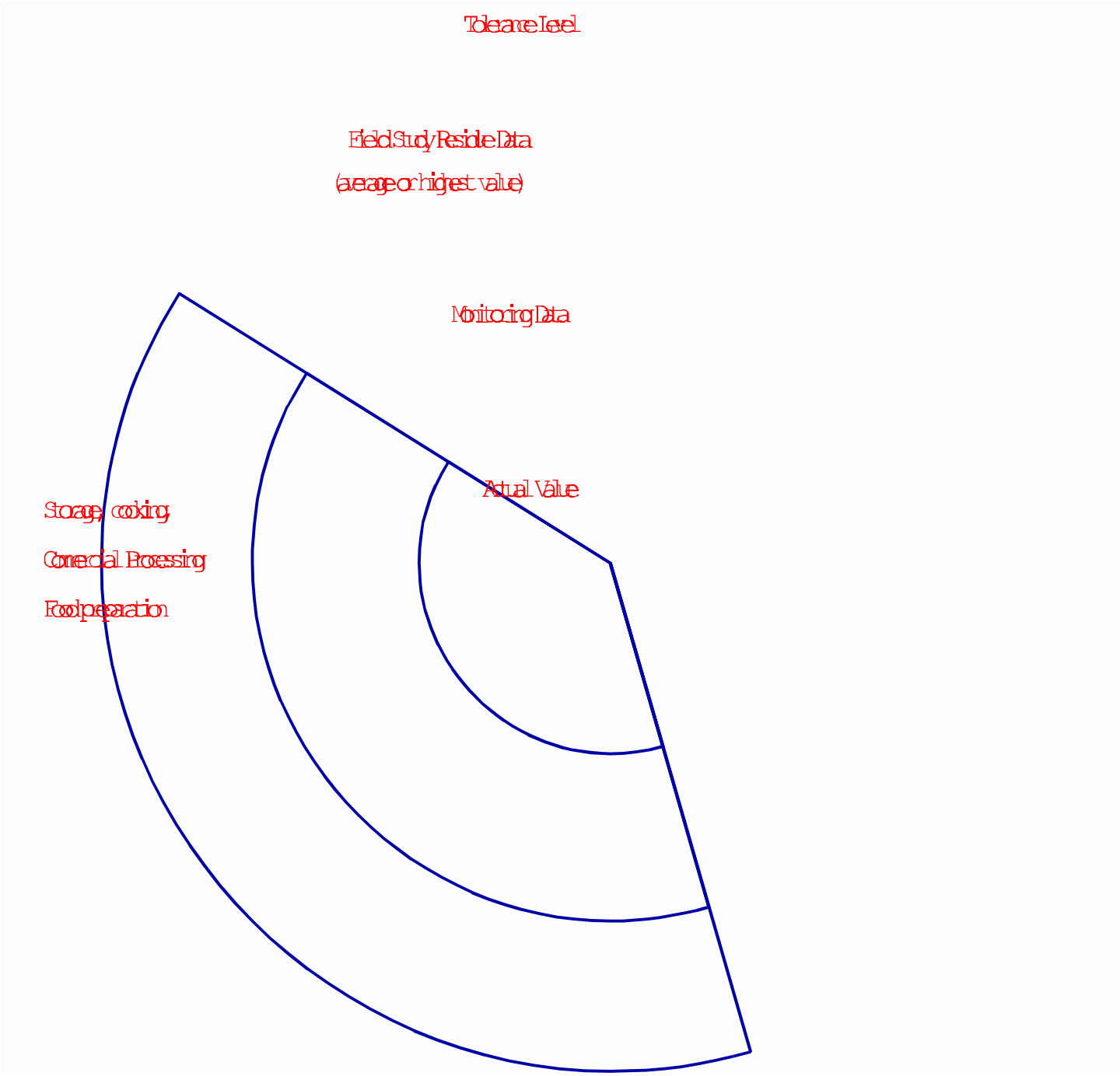
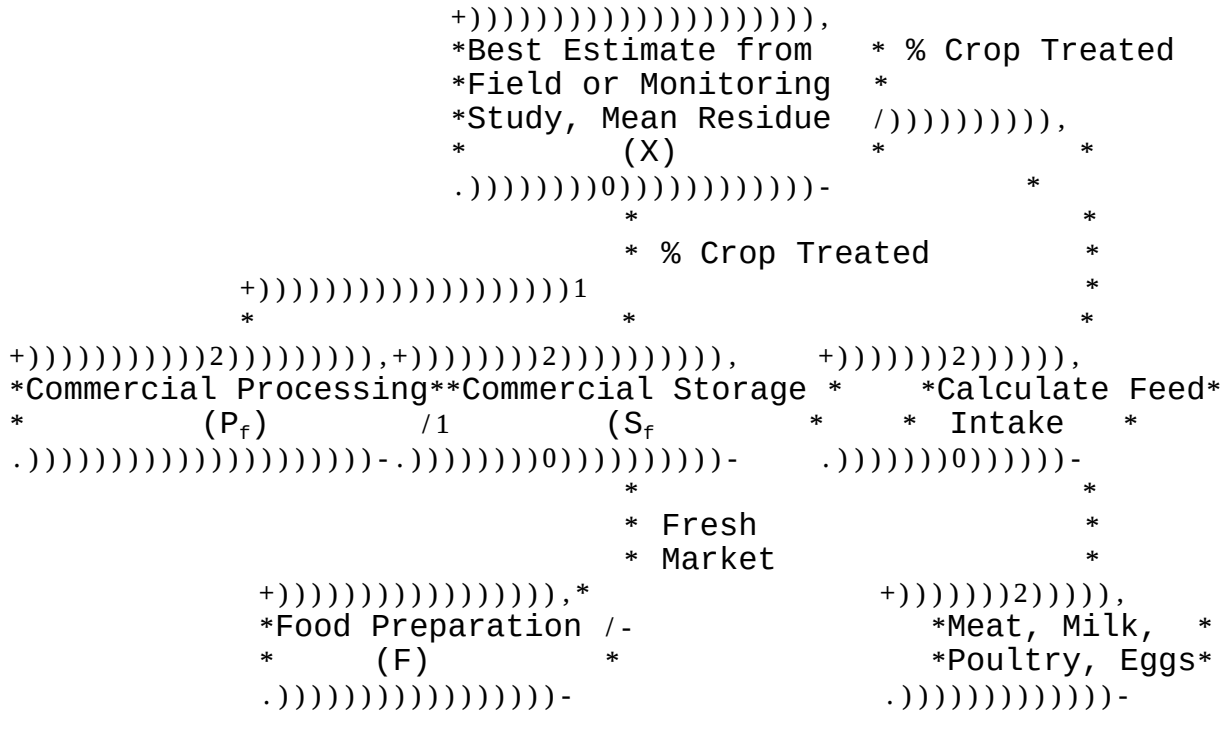


Figure 2: Determination of Anticipated Residues for Quantitative Carcinogenic Risk Assessment



$AR_{crops} = X_F \times \%CT \times S_f \times P_f \times F$

$AR_{crops} = X_M \times P_f \times F$

AR_{meat} = Feed intake (corrected for %CT) x residue transfer (obtained from feeding studies)

AR = Anticipated Residue
X_F = Average residue from field trial or farmgate monitoring
X_M = Average residue in monitoring studies, including non-quantifiable residues
%CT = Percent crop treated
S_f = Storage factor - corrects for change in residues during storage
P_f = Processing factor - corrects residue in raw agricultural commodity for concentration or dilution of residues in processed foods/feeds
F = Food preparation factor - corrects for changes in residues during food preparation (e.g. cooking, trimming, etc.)

monitoring data, absolute assurance of geographical representativeness is not possible. However, in many cases, the Agency has concluded that FDA data were likely to be reasonably geographically representative of pesticide residues in a commodity. These conclusions were made considering the FDA collection districts and states from which the samples were obtained. First, the collection districts must represent those in which the commodities are known to be grown and could be treated with the pesticide. If major growing areas are not included, the data would be used only if pesticide usage data indicated that either the pesticide was not used in those areas or that pesticide use in those areas was similar enough to use in other represented areas so that the residue information could be translated to the non-represented area. Secondly, a sufficient number of samples from each collection district must be available to assure the reliability of the anticipated residues determined. Again, the number of samples required depends on the crop being considered, as well as on the percent of that crop treated. The number of samples needed also will depend on the toxicological effect of concern since the number of samples required for reliable assessment of chronic exposure will differ from the number required for acute exposure. In general, the Agency requires analysis of a pesticide in at least 100 samples of a particular commodity in FDA monitoring data before use of the data will be considered. Thirdly, consideration must be given to the season or collection times of samples in each collection district. If samples were collected only at times when pesticide residues were not likely to be found in a commodity, the data would have limited usefulness. Also, if a large number of samples were obtained from a specific local study, the data might not be representative of residues throughout the collection district.

Another important consideration in determining the usefulness of FDA or other monitoring data in determining dietary exposure is the analytical methodology used. Two factors are important: the limit of

quantitation (LOQ) and the chemical components which are measured by the method. The analytical method LOQ must be sufficiently low to allow unambiguous determination that the risk is acceptable. In many cases in which no quantifiable residues were found in a commodity, risks estimated assuming non-quantifiable residues at the LOQ, or even at 1/2 the LOQ, would be of concern. Also, the method must measure all of the components of the total regulated residue. If only the parent compound is determined, as is the case with some pesticides monitored by FDA, a significant portion of the total residue may not be measured and the data will have limited usefulness.

If FDA or other monitoring data are determined to be adequate to determine anticipated residues based on the considerations discussed above, anticipated residues could be determined for raw commodities, processed commodities, animal products, or animal feeds. Anticipated residues are determined directly from the monitoring data for raw commodities. For processed commodities or animal feeds, anticipated residues can be determined directly if adequate monitoring data for the processed commodity or animal feed are available, or by multiplying the anticipated residue for the raw commodity by the concentration/reduction factor from processing studies available in the tolerance petitions. For animal products, anticipated residues can be determined directly if adequate monitoring data are available for these commodities or they can be determined by using anticipated residues for animal feeds (determined from monitoring studies) in conjunction with animal feeding studies (see Section V.E.). Consideration must be given to possible different pesticide treatments of a commodity destined for the fresh market versus the same commodity destined for processing.

Descriptions of the USDA Pesticide Data Program (PDP) were provided in Section V.F. The PDP was designed to provide objective residue data that can be used for anticipated residue determinations. To date, PDP has tested 25 food commodities, 17 of which were fresh

fruits and vegetables, six were processed commodities, and the remaining two were milk and wheat. Most of the samples are collected at the terminal market or distribution center locations. Samples are prepared as if for human consumption, e.g., apples are washed and cored. Pesticides determined are those of interest to EPA. More detail is provided in Appendix 4.

For a limited number of pesticides, monitoring data are available from the U.S. Department of Agriculture (USDA) for animal fat (or liver) and certain forms of eggs. If a sufficient number of samples are available, these data can be used to determine anticipated residues in animal commodities in a manner similar to the way FDA data are used to determine anticipated residues for raw and processed agricultural commodities.

Monitoring data from sources other than the FDA and USDA have been used by EPA for dietary exposure assessments. In some cases, data generated by the registrants have been used.

For monitoring to reflect real-world exposure it is important that significant market disruptions have not occurred (8,11). A case where market disruption occurred was Alar® (N-dimethylaminosuccinamic acid). Longer term monitoring will be necessary in these situations, and monitoring should be continued until some time after normal use resumes, i.e., the market disruption is over, in order to obtain the most accurate estimate of the anticipated residue. It may be possible, however, to correct the data for the effect of the market disruption, if the percent of crop treated is accurately known both before and after the market disruption.

The discussion presented above of the Agency's use of pesticide monitoring data for dietary exposure assessments provides general information and guidance. However, it must be emphasized that the adequacy of the available data in dietary exposure assessment must be determined on a case-by-case basis and requires considerable scientific judgment. The process of dietary exposure assessment and use of monitoring data has evolved over the years and is continuing

to evolve as additional degradation, monitoring, usage, and consumption data become available. Recent changes include the move towards determining anticipated residues rather than using tolerance levels, and towards the development of more statistically sound approaches to use of these data. Statistical issues in the use of existing monitoring data and in the design of monitoring studies for the purpose of dietary exposure assessment are presented in Appendices 4 and 3 respectively.

2. Residue Field Trial and Degradation/Reduction Studies

As stated earlier, residue degradation/reduction describes any change in the amount and/or composition of the total toxic residue from harvest to consumption. Numerous factors must be considered including field preparation, storage and transport (which can occur at several points between harvest and consumption), commercial processing (bottling, canning, cooking, drying, shelling, fractionation, extraction, deodorizing, and many other processes), and home preparation (peeling, washing, various types of cooking, etc.). A commodity may follow any of several pathways between harvest and consumption.

Residue degradation/reduction, as defined here, has been considered in a few instances in possible designs for a single study to determine anticipated residues. Data for the separate components (e.g. commercial processing) are used frequently to determine tolerances and anticipated residues. Descriptions of the major residue degradation/reduction processes used in determining anticipated residues have been provided in Section V.D. (Commercial Processing Studies), V.G. (Residue Degradation/Reduction Studies), and VI.A. (Anticipated Residue Determination: Sequence of Events in Determining Dietary Exposure). Specific information regarding use of these data, as well as a preliminary discussion of the design of

degradation studies, are presented below.

The data the Agency uses most frequently in determining anticipated residues are field trial data, commercial processing studies, and feeding studies, as well as percent crop treated data.

The first step in anticipated residue determination by this method is analysis of field trial data to determine an average or residue (see Section IV) reflecting the registered use which would lead to the highest residues. These residue estimates are determined for each crop/commodity. More than one residue estimate may be obtained for a particular crop if the crop is known to be treated in different ways and if sufficient information is available to relate the different pesticide use patterns and residues to different residue consumption by population subgroups. As discussed for monitoring data, the analytical method limit of quantitation (LOQ) can limit the usefulness of the residue data, particularly if all or a large portion of the residues are not quantifiable. If the limit of quantitation (LOQ) is too high, estimated risks may be unacceptable even assuming non-quantifiable residues are at the LOQ (or at 1/2 the LOQ).

The second step in this process is the incorporation of percent crop treated data (for chronic risks only). The average residue determined from the field trial data generally is multiplied by the percent crop treated for each commodity to obtain a residue estimate which reflects an aggregate population exposure. Using percent crop treated in a dietary exposure assessment artificially "spreads" the exposure over the entire U.S. population. Higher consumption of treated commodities by some population subgroups is addressed separately in the Dietary Risk Evaluation System (DRES), if adequate data are available to make these evaluations. Chronic dietary exposure analyses generally are done using percent crop treated data for two reasons. First, adequate pesticide usage data and consumption data rarely are available which would allow determination of dietary exposure to highly exposed subgroups. Secondly, since the

registered uses leading to the highest residues are used to determine average residues, conservatism already is incorporated into the anticipated residue determination. Compounding the conservative assumptions already incorporated into the toxicological reference values and residues with the additional conservative assumption of 100% crop treated would lead to risk estimates which exaggerate the aggregate U.S. population risk and would also likely exaggerate the risks to many of the more highly exposed population subgroups. Percent crop treated data are used for raw and processed agricultural commodities as well as for animal feeds (prior to determining the dietary burden for the animal). Two dietary burdens frequently are calculated for dairy cattle reflecting animal consumption of (1) feed items which contain high residues but are fed only in limited geographical areas ("local milk shed" diet), and (2) major feed items consumed in many parts of the country ("typical national diet"). Two sets of average residues in milk are calculated which show average residues which might be found in particular localities as a result of feeding high-residue, locally-grown animal feeds which have limited importance on a national basis, and national average residues likely to be found in animal commodities resulting from feeding cattle major national feed items. This approach is important for fresh milk since milk generally is shipped short distances prior to consumption.

When a range of percent crop treated estimates is provided, the highest estimate (most conservative) is used.

The use of field trial/percent crop treated data does not account for exposures from imported commodities. However, monitoring data are available from FDA and PDP for many commodity/pesticide combinations. The issue of anticipated residue determination for imported commodities requires further discussion.

Storage stability data (frozen storage) are required in tolerance petitions in order to assure that the pesticide residues in crop samples from residue field trials are stable for the length of time that the samples are stored prior to analysis. Some change in

the quantity or composition of the pesticide residue frequently is seen during frozen storage. These data are used to correct the results of the residue field trials for any possible degradation during frozen storage.

Commercial processing studies also are required in tolerance petitions if residues could concentrate in processed fractions (see Section V.D.). The average concentration/reduction factors are used. The average factor is multiplied by the average of field trial residues to estimate an anticipated residue for chronic risks.

Other types of studies have been used in determining anticipated residues. The effects of washing, peeling, and trimming have been incorporated into some dietary exposure assessments. The effects of fresh market processing (e.g., wax dips) have been considered. In some cases, conversion of residues during cooking has been an issue as in the cases of alar (UDMH) and EBDCs (ETU). When the degradation product is more toxic than the parent compound, the Agency has used 100% conversion as the first approximation of residues of the degradation product on cooking. Reduction of residues on cooking has also been considered for some commodities for which processing studies were available such as apples and tomatoes.

Part of the difficulty in arriving at an accurate dietary exposure estimate for pesticide residues at the time of consumption is the variety of methods that may be used in food preparation and the fact that very few commodities are eaten individually. For example, soup and cake consist of a mixture of commodities. Nevertheless, information on the effect of trimming, peeling, washing, cooking (boiling, baking, frying) may be used in arriving at anticipated residues. The information is most useful if the studies correspond to the appropriate DRES food forms.

For additional guidance regarding field trial, residue degradation/reduction, and processing studies see OPPTS Test Guidelines, Series 860 (EPA 712-C-96-169) and Appendices 4 and 5.

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9. Introduction to the Tolerance Assessment System, D. Stephen Saunders, Ph.D., EPA and B. Petersen, Ph. D., Petersen and Associates, March, 1987.

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860.1000	Background	EPA-712-C-96-169
860.1100	Chemical Identity	EPA-712-C-96-170
860.1200	Directions for Use	EPA-712-C-96-171
860.1300	Nature of the Residue-plants, livestock	EPA-712-C-96-172
860.1340	Residue Analytical Method	EPA-712-C-96-174
860.1360	Multiresidue Method	EPA-712-C-96-176
860.1380	Storage Stability Data	EPA-712-C-96-177
860.1400	Water, Fish, and Irrigated Crops	EPA-712-C-96-178
860.1460	Food Handling	EPA-712-C-96-181
860.1480	Meat/Milk/Poultry/Eggs	EPA-712-C-96-182

860.1500	Crop Field Trials	EPA-712-C-96-183
860.1520	Processed Food/Feed	EPA-712-C-96-184
860.1550	Proposed Tolerance	EPA-712-C-96-186
860.1560	Resonable Grounds in Support of the Petition	EPA-712-C-96-187
860.1650	Submittal of Analytical Reference Standards	EPA-712-C-96-016
860.1850	Confined Accumulation in Rotational Crops	EPA-712-C-96-188
860.1900	Field Accumulation in Rotational Crops	EPA-712-C-96-189

Hazard Evaluation Division (or Health Effects Division) Standard Evaluation Procedures:

Product Chemistry (EPA-540/09-86-143)
Directions for Use (EPA-540/09-86-144)
Qualitative Nature of the Residue: Plant Metabolism (EPA-540/09-88-102)
Metabolism in Food Animals: Qualitative Nature of the Residue (EPA-540/09-89-061)
Analytical Method(s) (EPA-540/09-89-062)
Magnitude of the Residue: Crop Field Trials (EPA-540/09-85-021)
Magnitude of the Residue: Processed Food/Feed Studies (EPA-540/09-86-145)
Residues in Meat, Milk, Poultry and Eggs: Feeding Studies/Feed-throughs
Residues in Meat, Milk, Poultry and Eggs: Dermal Treatments (EPA-540/09-092)
Specialty Applications: (1) Classification of Seed Treatments and Treatment of Crops Grown for Seed Use Only as Non-Food or Food Uses (2) Magnitude of the Residue: Post-Harvest Fumigation of Crops and Processed Foods and Feeds (3) Magnitude of the Residue: Post-Harvest Treatment (Except Fumigation) of Crops and processed Foods and Feeds (EPA-540/09-86-142)

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