PURDUE PESTICIDE PROGRAMS

Purdue University Cooperative Extension Service

Pesticides and Human Health Risk Assessment

Policies, Processes, and Procedures

Fred Whitford, Coordinator, Purdue Pesticide Programs
Joel Kronenberg, Manager, Toxicology and Product Safety, AgrEvo USA Company
Curt Lunchick, Human Exposure Assessment Specialist, Rhone-Poulenc
Jeffrey Driver, Senior Toxicologist, risksciences.com, L.L.C. & infoscientific.com, Inc.
Robert Tomerlin, Exposure Assessment Specialist, Novigen Sciences
Jeff Wolt, Risk Assessment Leader, Dow AgroSciences
Henry Spencer, Pharmacologist, United States Environmental Protection Agency
Carl Winter, Extension Food Toxicologist, University of California, Davis
Gary Whitmyre, Senior Toxicologist, risksciences.com, L.L.C.

Arlene Blessing, Editor and Designer, Purdue Pesticide Programs

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INTRODUCTION

Health issues are the subject of lively public debate concerning pesticide use. We are exposed to pesticides in the food and water we consume and in the air we breathe; we're exposed at home, at work, and at play. Thus, questions arise as to how much risk pesticides pose. The general public and government policymakers want clear, definitive answers; and answers to questions on the relationship of pesticides and public health are based largely on information generated through risk assessment.

The goal in risk assessment is to assign risk potential on an objective basis. This publication provides background information on the risk evaluation process; it is intended to foster an understanding of how risk assessments are conducted, what assumptions are used, and how conclusions are drawn.

Initial Focus on Dietary Risks

Nearly all Americans are exposed to some level of pesticides in their diet. Thus, understanding the risk potential of pesticide residues in food is critical not only for consumers but for producers, food processors, pesticide manufacturers, and government agencies, as well; their efforts must interlink to ensure a healthful food supply.

Various health organizations, government agencies, and academic institutions first began evaluating the risk potential of pesticide residues in food and water in the 1940s. These early risk assessments were conducted in part because of increased surveillance by state, federal, and international governments.

Attention Shifts to Occupational Risks

Risk assessors in the 1950s began to question the risk posed to workers handling concentrated pesticide products (e.g., pesticide applicators) and to field workers exposed to residues on foliage (e.g., workers picking apples). This focus on worker exposure was driven by physicians' and industrial hygienists' attempts to determine how workers became overexposed and therefore ill. The advent of occupational risk assessment necessitated new methods for calculating risk—avenues previously unexplored in dietary risk assessment. Exposure from various routes at varying frequency and duration had to be considered.

Public Scrutiny Over Residential Risks

Risk assessors in the late 1980s began to focus on risks from pesticides used in and around the home and workplace. Previously, risk assessors and risk managers had thought that demonstration of minimal risk to applicators and field workers provided (by default) adequate safeguards for residential use of a given pesticide. This was based on the belief that the potential for pesticide exposure is many times lower with residential use than with occupational use; but in recent years that has been questioned.

Some suggest that occupational risk assessment conducted for pesticide handlers and field workers may not reflect risk to the young, the elderly, the sick, or other frail segments of society. Their argument is that safety standards for occupational settings are calculated for healthy workers, typically males aged 20–50. So the assumptions made, information used, and conclusions drawn via the occupational risk assessment process may not pertain to those who may be more sensitive to pesticides—children, the elderly, the sick, etc.—or to those who experience high levels of exposure.

HUMAN RISK ASSESSMENT EVOLVES AS PESTICIDE ISSUES EMERGE

The United States Congress enacted two major federal laws to manage health and environmental risks from pesticides: the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA); and the Federal Food, Drug, and Cosmetic Act (FFDCA). FIFRA gives the U.S. Environmental Protection Agency (EPA) the authority to register pesticides; to

require appropriate supporting chemical, toxicological, environmental, and residue studies; and to develop labeling requirements based on these studies. Pesticides that come into contact with food or animal feed are regulated under the FFDCA, which gives EPA the authority to establish legal limits for pesticide levels in or on food and feed.

There have been many changes in pesticide registration requirements during the last decade: what was acceptable yesterday may not be acceptable today or tomorrow! Policies and decisions on acceptable risk change, over time, as science and public policies advance. And as public awareness and concerns over potential risk change, so do registration requirements.

Early Federal Laws

The 1906 Pure Food and Drug Act prohibited unsafe substances in food. It was followed by the Insecticide Act (1910) which prohibited the interstate sale or transport of impure or improperly labeled insecticides and fungicides. Its primary focus was to ensure that products were labeled adequately and that container contents were stated precisely on the label. The Insecticide Act of 1910 contained no registration requirements and did not set safety standards.

The Insecticide Act was replaced in 1947 by a more comprehensive law called the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). FIFRA required the registration of pesticide products with the United States Department of Agriculture prior to sale or movement via interstate or foreign commerce.

Pesticide regulations were expanded again in 1954 with the Miller amendment to the Federal Food, Drug, and Cosmetic Act (FFDCA). The amendment required the establishment of tolerances for pesticide residues in or on agricultural commodities. *Tolerance* was defined as the legal limit (amount) of pesticide residue that could remain in or on a harvested food crop after application; it was established primarily on the basis of *good agricultural practices.* In 1958, an amendment to FFDCA, commonly referred to as the *Delaney Clause,* prohibited the use of any food additive shown to cause cancer in man or experimental animals. Pesticide residue concentrations in processed foods (e.g., tomato paste and tomato sauce) at levels higher than those found in the raw agricultural commodity (e.g., whole tomatoes) were considered food additives and were thereby subject to the provisions of the Delaney Clause. But pesticides that did not concentrate in *processed* foods were not considered additives and thus were *not* subject to the Delaney Clause.

Environmental Movement Changes Public Perception of Pesticides

Increasing environmental concerns in the 1960s, exemplified by Rachel Carson's *Silent Spring* (1962), changed forever how pesticides will be viewed by the American public. The most commonly used insecticides at that time were a class of chemicals called *chlorinated hydrocarbons* that included such insecticides as DDT, aldrin, and dieldrin. Environmental groups and the news media portrayed these pesticides as chemicals that bioaccumulate in the environment, disrupt links in the food chain, and poison wildlife. *Silent Spring* captured the public's attention, rallied greater public awareness of environmental issues, and called for a ban on numerous pesticides.

Government Policies Shift Toward Risk Reduction Strategies

In 1970, Congress created the U.S. Environmental Protection Agency (EPA) and shifted the regulation of pesticides from the U.S. Department of Agriculture (USDA) to EPA. Changes in FIFRA after 1970 resulted in a major philosophical shift in pesticide regulation. Originally, FIFRA required regulators to review and register pesticide products. But in 1972, Congress changed FIFRA from a labeling law to a comprehensive statute designed to regulate the manufacture, distribution, and use of pesticides. Pesticide manufacturers then were required to demonstrate that use of the product would not cause "unreasonable adverse effects on human health or the environment."

The 1972 amendment to FIFRA also created a distinction between lower-risk, unclassified pesticides (commonly called general-use products) and the higher-risk pesticides classified for restricted use. The general-use pesticides could be purchased and used by the general public, whereas the higher-risk, restricted-use pesticides could be purchased only by certified pesticide applicators and used only by certified applicators or persons under their direct supervision. By establishing the need for standards of competency for applicators of restricted-use pesticides, Congress clearly and specifically acknowledged that proper training is fundamental to the proper use of pesticides.

Risk/Benefit Considerations

Because Congress did not intend the 1972 amendment to FIFRA to be solely an environmental bill, an industry bill, or a farm bill, efforts were made to balance the needs of all stakeholders. Regulatory decisions were to be based on the balancing of potential health and/or environmental risks against potential benefits stemming from use of the pesticide; that is, decisions would depend on *risk/benefit analysis.*

Study Requirements and Scientific Testing Guidelines

Under FIFRA, EPA has issued requirements since 1975 specifying the types of toxicological, ecotoxicological, residue, and environmental fate studies that must be conducted to support pesticide registration.

EPA also has issued scientific testing guidelines specifying the methodologies that should be used in conducting these studies. The lists of required studies and recommended methodologies are updated periodically as the science advances and as new health and environmental concerns are raised.

Advances in science, new experimental tools, and new thinking have yielded more comprehensive data for review and allowed the registration and reregistration processes to improve and mature. In turn, more refined and realistic risk/benefit assessments are possible.

Good Laboratory Practices

Fraudulent practices that surfaced in one toxicology laboratory triggered concern within the Food and Drug Administration (FDA) and EPA regarding the integrity of data being submitted to support pesticide registration. As a result, Good Laboratory Practices (GLPs) were established.

The registration of a pesticide requires data from well-designed, well-documented studies conducted under GLPs by trained scientists and technicians.

GLPs are parameters within which laboratory and field studies must be planned, monitored, recorded, and reported. The resulting documentation facilitates verification that studies are properly reported; and it affords EPA reviewers a degree of confidence in the validity of the data compiled during human and environmental risk assessment.

EPA Moves Toward a More Comprehensive Review of Risk

Comprehensive risk assessments were rare prior to 1980 because of insufficient scientific knowledge to interpret the data accurately. But in the late 1980s the emphasis shifted from toxicity assessment, alone, to include exposure assessment, a measure of uncertainty analysis, and an assessment of potential risk. Implementation of these additional considerations, coupled with improved scientific assessments, has improved the regulatory decision-making process.

Policy Shifts to Reduced-Risk Pesticides

EPA developed a policy in 1993 that focuses on reduced-risk pesticides and offers manufacturers the incentive of quicker registration decisions for “low-risk” products. The policy favors pesticides that have less potential to cause adverse health and environmental effects than those currently registered. Registration applications documenting low-risk characteristics are granted priority in the review process; and accelerated reviews allow low-risk pesticides to move more quickly into the marketplace, ideally in one year compared to the usual four.

Aggregate and Cumulative Risk Comes to the Forefront

On August 3, 1996, President Clinton signed the Food Quality Protection Act (FQPA), an act passed unanimously by Congress that many heralded as landmark legislation and a new beginning for food safety.

Probably the most important aspect of FQPA is that it amended FFDCA and FIFRA to create a single, health-based standard for all pesticides on all foods. FQPA mandates that tolerances for foods must be “safe,” which is now defined as “…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.” The use of a single standard for all foods eliminates inconsistencies between allowable residues on processed foods and those on raw agricultural commodities.

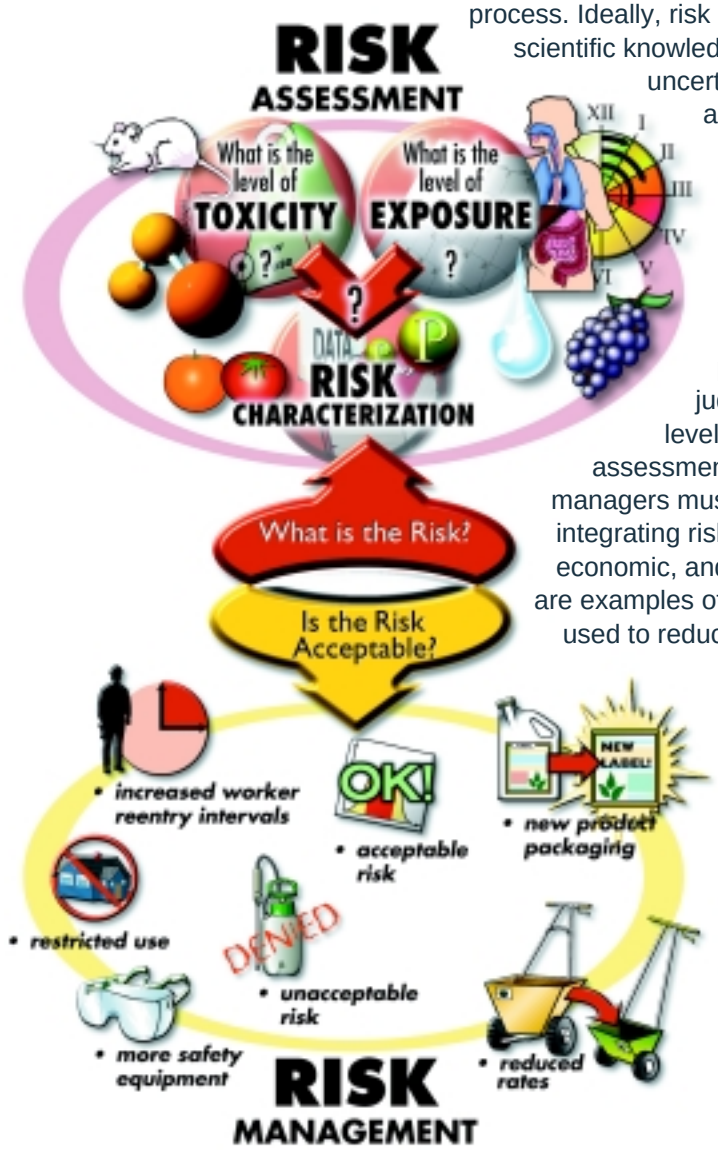
FQPA also required changes to EPA’s pesticide risk assessment process:

- Addressing aggregate exposure to a given chemical from non-occupational sources
- Combining risk assessments for groups of chemicals with common mechanisms of toxicity (cumulative risk assessment)
- Providing additional protection for infants and children
- Limiting the consideration of benefits

THE PROCESS AND PRACTICE OF RISK ASSESSMENT

"Risk analysis" is a systematic framework for understanding and actually managing diverse risks through the processes of *risk assessment* and *risk management.* It allows the incorporation of scientific and public health principles into decision-making and the setting of priorities.

EPA intends the *risk assessment* process to provide the pesticide industry and the public-at-large with methods and criteria to estimate the level of risk posed by a pesticide. It is a science-based decision-making process. Ideally, risk assessment incorporates scientific knowledge with consideration of inherent uncertainties. More specifically, risk assessment is the process of quantifying and characterizing risk, i.e., estimating the likelihood of occurrence and the nature and magnitude of potential adverse effects.



Risk management is the process by which decisions and judgments on the acceptability of levels of risk described in the risk assessment process are made. Risk managers must weigh policy alternatives by integrating risk assessment results with social, economic, and political factors. The following are examples of risk management approaches used to reduce human risk:

- Not registering the pesticide
- Restricting its use to certified applicators
- Lowering application rates
- Reducing the number of applications
- Increasing application intervals
- Providing longer intervals between application and harvest
- Using alternative application methods

These measures often take the form of label changes designed to reduce the amount of pesticide used and to lower exposure potential for farm workers and the general public.

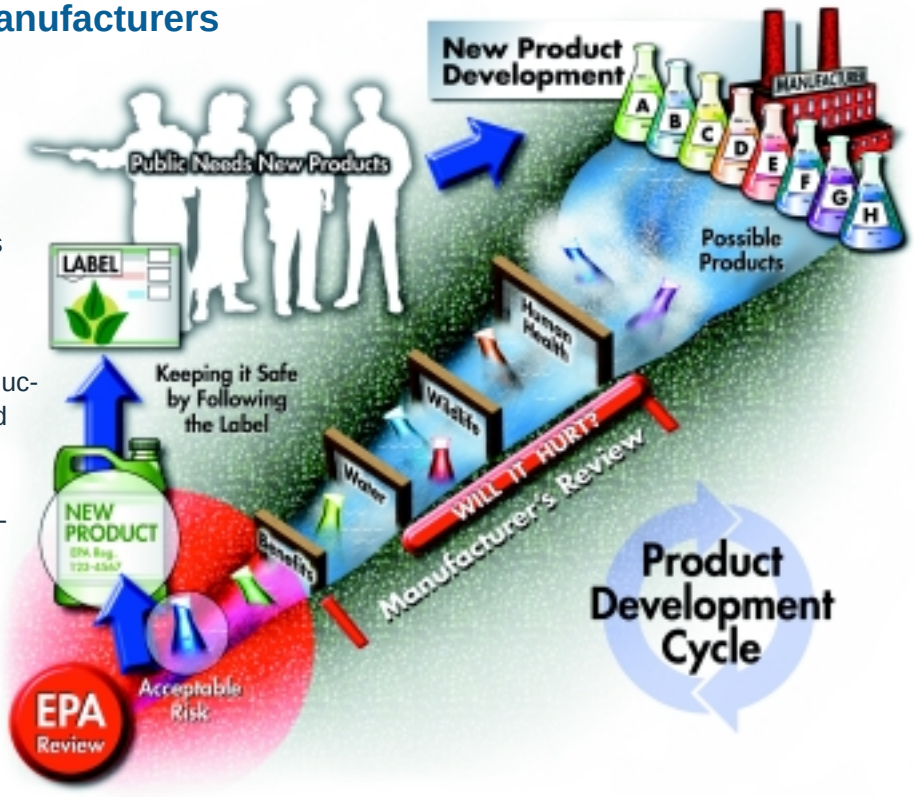
Risk Assessments Provide Multiple Benefits

EPA and the Public

The intensive regulatory assessment process benefits both EPA and the public:

- EPA's mission to protect public health from unreasonable adverse effects can be more readily fulfilled.
- The risk assessment process helps EPA make more consistent, well-informed, registration decisions.
- The risk assessment process encourages more in-depth review of technical information.
- The process provides a forum where EPA scientists and risk managers have a common basis for discussion of conclusions drawn from risk assessment.
- The process helps guide EPA decisions on whether additional data are needed to clarify potential risk.

Pesticide Manufacturers



Corporate decisions on whether or not to develop potential pesticide products are based on risk assessment, marketability, anticipated cost of production, and projected revenue. Risk assessments are conducted periodically during development and throughout the commercial life of a pesticide, often beginning with limited

preliminary data acquired very early in the development process. As toxicological properties, chemical fate, and exposure estimates are better understood, the risk assessment process is refined. Scientists working for the manufacturer develop data and serve as experts who present and interpret data for the development team. The team assesses data at various intervals to decide whether to continue research, development, and commercialization of the product or to halt the process.

Risk Assessment Is a Multi-Step Process

Human risk assessment is best described as a 3-step process:

- Toxicity assessment: an evaluation of intrinsic toxicity or hazard potential of the chemical
- Exposure assessment: an estimation of potential human exposure to the chemical
- Risk characterization: an evaluation of potential risk to humans

An Assessment of Toxicity: What Are the Effects from the Chemical?

The purpose of assessing the toxicological properties of a pesticide is to determine whether it has the potential to produce adverse effects on human health. Carefully controlled experimental studies on animals form the basis for distinguishing the toxicological properties of a pesticide. The animal studies employ a wide range of pesticide doses, including levels far above those to which humans are generally exposed.

An Assessment of Exposure: What Are the Routes and Levels of Human Exposure?

Human exposure to pesticides usually occurs via ingestion of pesticide residues in food and water. However, dermal and inhalation exposure and the incidental ingestion of residues stemming from residential or occupational pesticide use also are recognized as potential routes of exposure. The extent of exposure depends on the type of use (e.g., crop, lawn, or garden applications; mosquito control; indoor pest control), application rate, method and frequency of application, and the breakdown and movement of the chemical in the environment.

Risk Characterization: What Is the Relationship Between Exposure and Toxicity?

Risk is a function of both toxicity and exposure, and risk characterization is the integration of pesticide toxicity and exposure data to predict the likelihood of adverse human health effects. Though toxicity data and

exposure data are evaluated separately, the resulting assessments are used together to characterize risk. A highly toxic chemical may not pose significant risk if exposure is minimal; on the other hand, a slightly toxic chemical may pose unacceptable risk at high doses or prolonged exposure.

TOXICOLOGICAL ASSESSMENT

The potential impact of a pesticide on human health is estimated by evaluating how experimental animals—rats, mice, rabbits, guinea pigs, dogs, etc.—respond to a range of doses. An extensive battery of toxicology studies is required for full pesticide registration.

Toxicology studies characterize animal response in a variety of scenarios ranging from acute exposure, where animals receive one relatively high dose of the pesticide, to chronic (long-term) exposure where animals receive lower doses daily for up to 2 years.

Acute studies are conducted to estimate exposure levels that are likely to produce mortality and other acute effects, as well as to determine whether the pesticide is likely to irritate the eyes or skin.

Subchronic studies are intended to identify effects on organs (liver, kidneys, spleen, etc.) following daily exposure for several weeks or months.

Chronic studies are conducted to assess the chemical's potential to cause toxic effects and/or cancer following long-term exposure.

Other toxicological studies include testing for potential adverse effects on the reproductive health of adults; on the growth, development, and reproductive abilities of offspring; and on changes in the genetic content of cells. A list of studies routinely conducted to support pesticide registration in the United States is shown in Table 1 (p. 13).

Two Major Types of Toxicological Tests

Scientific inquiry into the toxic properties of a pesticide requires studying how an organism reacts to the pesticide and what internal changes it incurs. Toxicology is an interdisciplinary science; that is, it requires input from numerous disciplines, including pathology, biochemistry, hematology, genetics, endocrinology, and physiology, in order to deduce cause-and-effect relationships. No single study provides all of the information necessary to identify the toxicological properties of a pesticide; rather, a series of studies generally classified as either *phenomenological* or *mechanistic* must be conducted.

Phenomenological Studies

Phenomenological studies form the basis of toxicology where "dose makes the poison." The most important aspect of toxicological evaluation is the determination of the *dose/response* relationship between amount of exposure and incidence or severity of observed effects. Effects may

Table 1. Toxicology Studies Generally Conducted for Pesticides in the U.S.

Phenomenological Studies

Acute Toxicity

- Acute oral toxicity (rat)
- Acute dermal toxicity (rat or rabbit)
- Acute inhalation toxicity (rat)
- Eye irritation (rabbit)
- Skin irritation (rabbit)
- Skin sensitization (guinea pig)

Subchronic Toxicity

- 28-day feeding* studies in rats, mice, and dogs
- 90-day feeding studies in rats, mice, and dogs
- 21-day and/or 90-day dermal studies in rats or rabbits

Chronic Toxicity and Carcinogenicity

- 1-year dog feeding study
- 18-month mouse feeding study
- 2-year rat feeding study

Reproduction/Developmental Toxicity

- Rat and rabbit developmental toxicity (teratology) studies
- 2-generation rat reproduction studies

Neurotoxicity

- Acute rat neurotoxicity
- 90-day rat neurotoxicity
- Acute and subchronic hen delayed neurotoxicity
- Rat developmental neurotoxicity

Genetic Toxicology

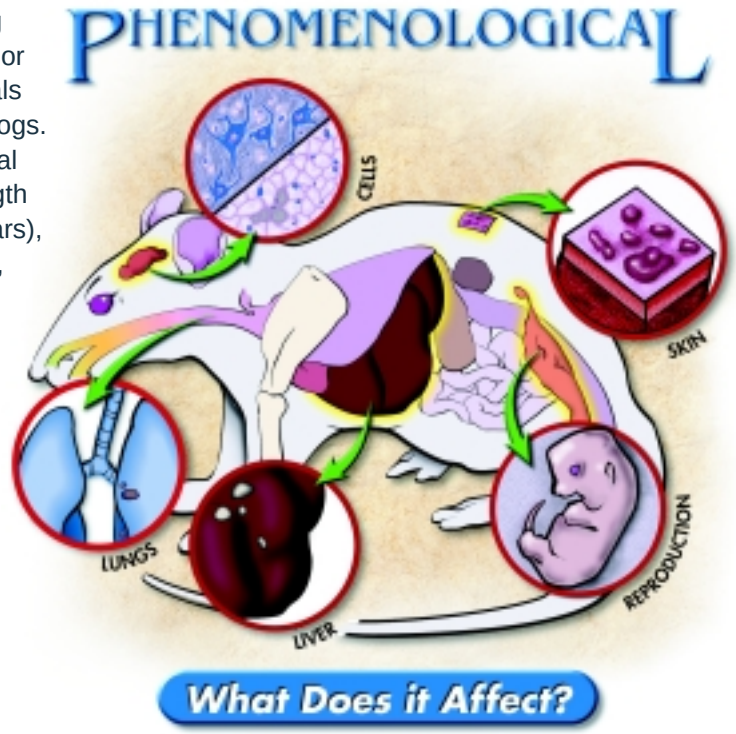
- Ames Salmonella bacterial point mutation assay
- Mouse micronucleus assay
- *In vitro* mammalian point mutation assay (mouse lymphoma)
- *In vitro* and/or *in vivo* chromosomal aberration assays
- *In vitro* and/or *in vivo* unscheduled DNA synthesis assays

Mechanistic Studies

- **Absorption**
- **Distribution**
- **Metabolism**
- **Excretion**
- **Pharmacokinetics**

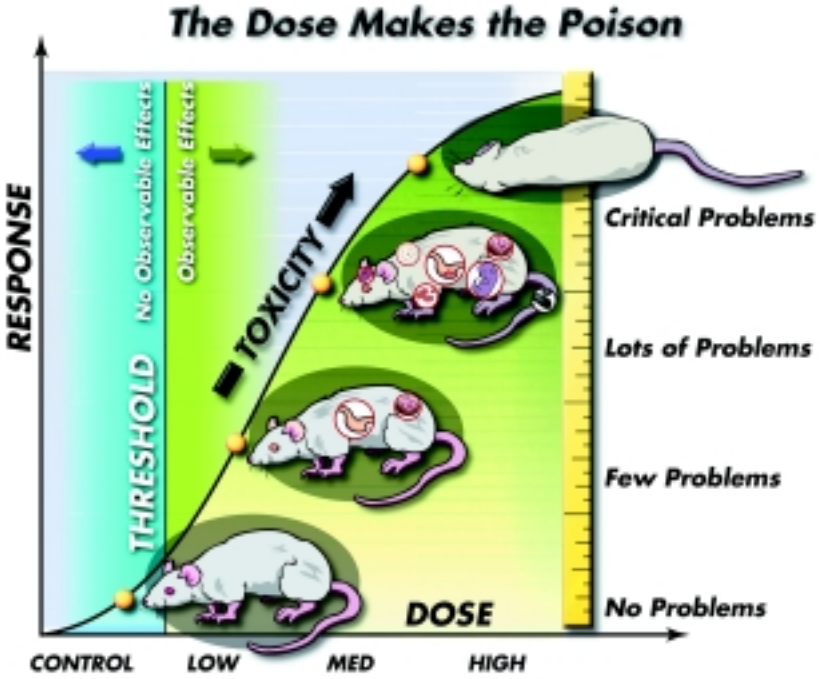
*In some cases, the pesticide may be administered via drinking water, gavage (stomach tube), or capsule (for dogs) instead of being mixed into the animal's diet.

be observed from studies using isolated cells or tissue cultures or from those using small mammals such as rodents, rabbits, and dogs. The design of phenomenological studies varies according to length of exposure (days, months, years), route of exposure (dermal, oral, inhalation), and toxicological measurements (e.g., reproductive toxicity, cancer, organ toxicity, developmental toxicity, neurotoxicity, and immunotoxicity).



Threshold Effects

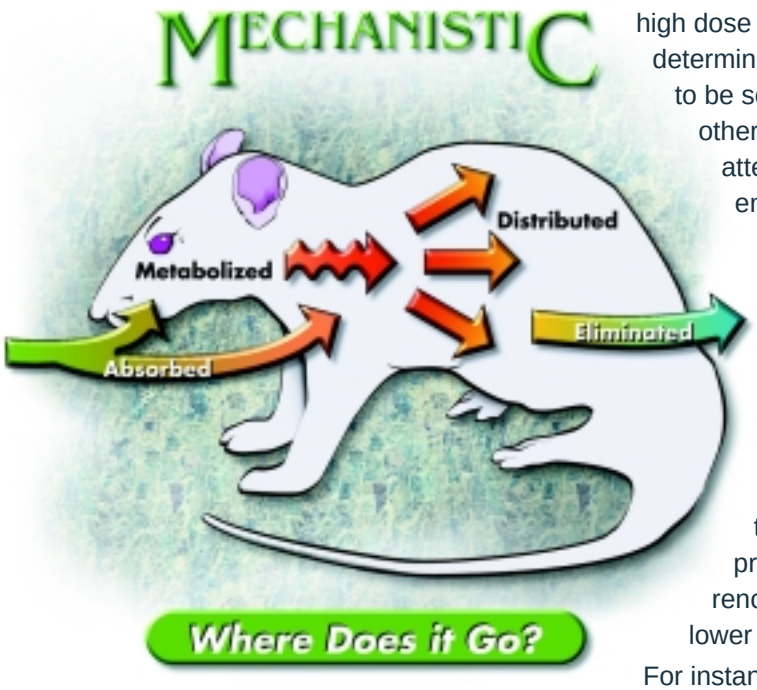
With the possible exception of some types of cancer, most of the phenomena observed in toxicology occur only at or above specific dose levels (not below). These dose levels are referred to as *threshold doses,* and the observed effects are referred to as *threshold effects.* Within a full suite of studies, there may be a different threshold dose for each adverse effect observed, but the precise threshold dose for each effect is rarely determined. One of the most important aspects of toxicological studies is the identification of the *No Observed Adverse Effect Level* (NOAEL), which is the highest dose that does not cause any adverse effect. The lowest dose level that results in an adverse response is called the *Lowest Observed Adverse Effect Level* (LOAEL). The threshold dose, while not precisely determined, lies somewhere between the NOAEL and the LOAEL.



Mechanistic Studies

Mechanistic studies detail the processes by which an adverse effect is manifested. Some are conducted to determine how a pesticide is absorbed, distributed, metabolized, and eliminated. Others attempt to identify the underlying physiological processes and/or biochemical pathways that are affected by the pesticide, i.e., to determine the mechanism responsible for producing adverse effects.

Scientists need to determine if tumors identified in animal studies actually result from pesticide/DNA interaction or if they are secondary to other toxicity. Many pesticides induce cancer in rodents at high dose levels, but not all doses induce genetic changes. While the precise mechanism for carcinogenic response at high dose levels cannot always be determined, many tumors are thought to be secondary responses to some other toxic effect, such as an attempt to replace dead cells via enhanced cell proliferation. The secondary response of cell replacement leads to more opportunities for genetic mistakes that may lead to cancer. An increased incidence of cancers of this type presumably would occur only at or above a threshold dose for cell proliferation; increased occurrence would not be expected at lower dose levels.



For instance, bladder tumors were reported in animals exposed to high doses of a chemical in a chronic study. Without additional detailed information, it would be assumed that the cancers resulted from a non-threshold effect. However, in this case the pesticide was shown to cause cell proliferation in the bladder at high dose levels, only; thus, a threshold for the tumors can be assumed. The type of tumor and mode of action of the carcinogenic response noted in animals is very important for other reasons, as well. In some cases, the tumors observed in animal studies may not occur at all in humans. For example, some chemicals produce kidney tumors in male rats through a process involving a protein that is found in male rats but not in humans. Similarly, due to physiological and biochemical differences, rats (particularly males) are far more susceptible to thyroid follicular tumors than are humans. Thus, the development of data to understand the mechanism by which the chemical induces a carcinogenic effect in animals is extremely valuable in determining the potential of the chemical to cause cancer in humans.

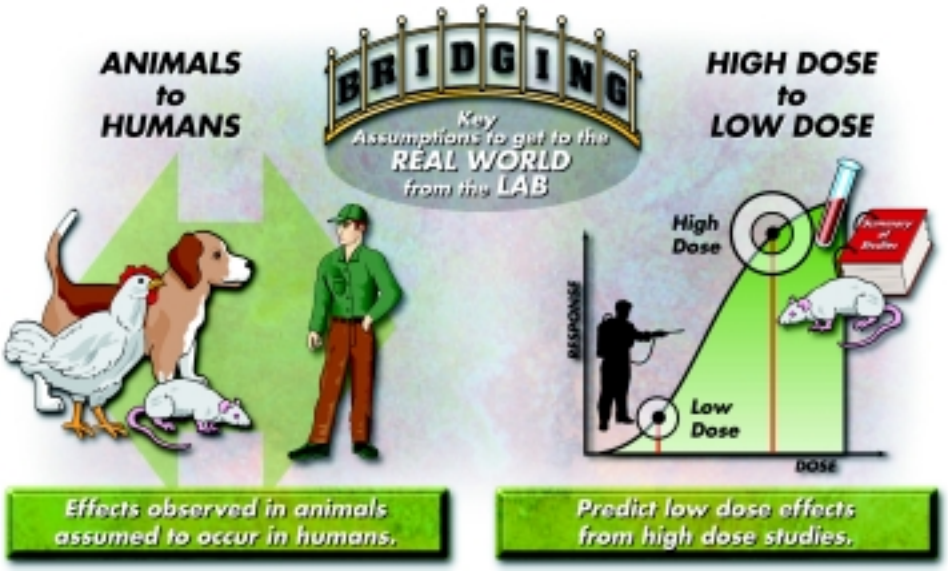
Extrapolation from Animals to Humans

The phenomenological and mechanistic studies are used in two important extrapolations:

- Animal to human extrapolations
- High dose to low dose extrapolations

Animal to Human Extrapolations

Risk assessment has traditionally relied on laboratory animals as predictive models for humans since we share many biological characteristics. Risk assessors generally assume that adverse effects in animals may be replicated in humans, and that humans may be up to 10 times more sensitive than the most sensitive animal species tested. This is assumed unless there is sufficient information to indicate otherwise.



High Dose to Low Dose Extrapolations

In general, pesticide levels to which most humans might be exposed are far lower than those used in animal toxicity studies. Higher pesticide levels are used in animal testing to maximize detection of potential adverse effects from overexposure. Because of the limited number of animals that can be tested, animal studies at lower doses may not detect a subtle effect that may occur in very large human populations exposed to the chemical. However, high doses used in animal studies may overload the metabolic and/or physiological processes of the animals and thus lead to adverse effects that are not predictive of those expected at lower exposure levels. This dilemma leads to one of the major challenges for toxicologists and risk assessors today: determining whether the effect is real or artificial.

Studying the Human Experience

As previously indicated, most of the toxicology data used in human risk assessment is derived from animals; and questions are sometimes raised as to the relevance of these data. But in some cases there are several ways to evaluate the likelihood of similar effects occurring in humans.

Human Cell Research

New approaches to cell and tissue culture studies allow the use of isolated human cells and tissues in evaluating pesticide toxicity. Isolated human cells and tissue can be obtained (from persons who have died in accidents or undergone surgery) and placed in a nutrient solution that allows the cells to continue their normal metabolic processes. Once tissue and cell cultures are established, a pesticide can be introduced and its effect studied for varying lengths of exposure. If metabolism of the chemical is similar between human cells and animal cells, validity for using the animal model is assumed.

Clinical Studies

Although rare, human volunteer studies are conducted with some pesticides, but only after thorough review and approval by an ethics review board. Such studies are conducted under carefully controlled conditions, with many safeguards to protect human health. Volunteers are carefully monitored by physicians before, during, and after the studies to verify no adverse effects. The comparison of data generated from human volunteer studies to those generated in animal studies leads to more accurate human risk assessment. In some studies, absorption, metabolism, and excretion are studied by exposing volunteers to a small, nontoxic dose. On rare occasions, clinical trials using human volunteers may be conducted to help validate a predicted no-effect level in humans.

Epidemiological Investigations

Epidemiology studies can be used to corroborate predictions and extrapolations from animals to humans. Individuals working in pesticide manufacturing facilities are ideal subjects for epidemiological studies. In these particular work situations, much is known about the workers' medical history, work history, and exposure levels. Thus, an association between chemical exposure and a particular chemical can be evaluated by comparing the health of an individual exposed to a pesticide to that of someone not exposed.

DIETARY EXPOSURE ASSESSMENT

Pesticide residues in the diet probably represent the primary source of pesticide exposure for the general public. Dietary exposure is a function of the type and amount of food consumed and the pesticide residues in or on that food. The total dietary intake of a single pesticide for any population is calculated by summing the potential pesticide intake from all food items that potentially contain its residues.

The basic model for estimating dietary exposure to chemical residues in food is very simple:

Pesticide Ingested =
Residue Concentration x Foods Consumed

There are numerous dietary exposure models ranging from single (point) exposure residue estimates to complex simulation analyses using probabilistic approaches. But all models, however complex, are based on the basic relationship: Exposure depends on the residue concentration in the food and on the amount of food consumed.

Two types of dietary exposure are generally considered: chronic and acute.

Chronic exposure occurs over a long period of time. It is calculated for typical exposure levels and therefore uses mean consumption and mean residue values.

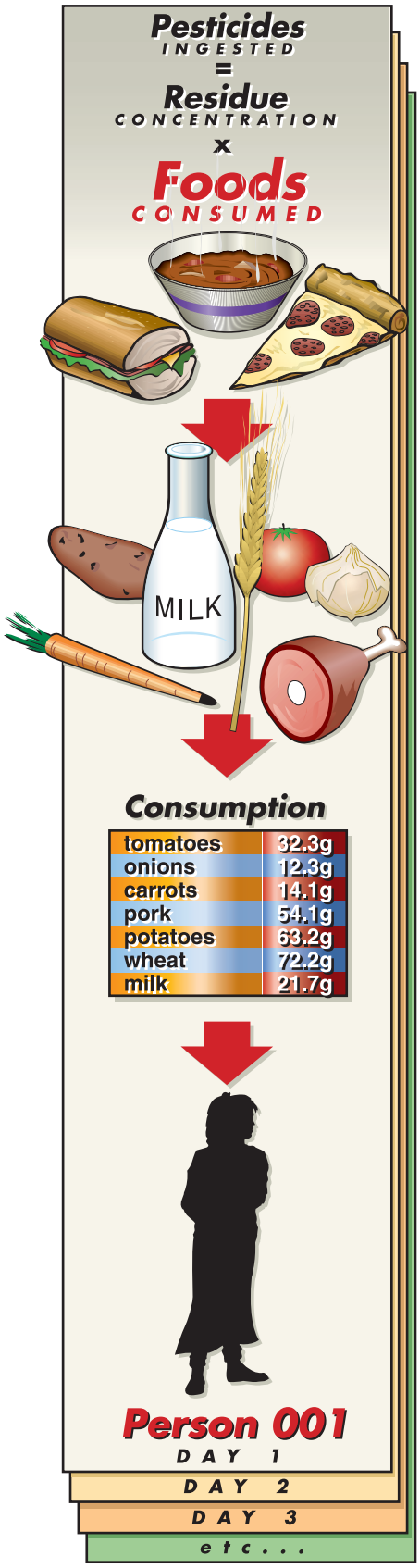
In contrast, acute exposure considers extreme exposure. Acute dietary exposure is calculated using individual consumption data. The residue values used are tolerances (maximum values) from previous studies, or the entire range of residue values from probabilistic assessments.

How Much Food Do We Consume?

USDA Estimates Food Consumption

The United States Department of Agriculture is the primary agency that collects information on food consumption by the American public. Nationwide Food Consumption Surveys were conducted by USDA in 1977–78 and in 1987–88. In 1989, USDA began an annual survey: Continuing Survey of Food Intake by Individuals (CSFII).

CSFII surveys are important because food consumption patterns change, with time, and impact estimations of pesticide exposures. For example, overall fruit consumption has remained unchanged, but children are drinking more fruit juices. People are eating leaner cuts of meat, more chicken and fish, and less beef than they did ten years ago. We are



eating more restaurant meals, both dine-in and carry-out, and more ready-to-heat microwave meals.

USDA food consumption surveys are intended to measure daily consumption patterns for households across the U.S. at various times throughout the year. The surveys ask participants to complete questionnaires that deal with the total household food intake over two or three consecutive days. Each participant is asked to describe the type and quantity of each food eaten, the time of day it was consumed, and its origin (home or restaurant).

Completed questionnaires are submitted to USDA nutritionists who convert the foods eaten to corresponding raw agricultural commodity ingredients. This determination is based on generic or product-specific recipes and food label ingredient statements. For instance, if a person eats two slices of a supreme pizza, they actually consume tomato paste, bell peppers, onions, wheat, olives, sugar, milk products, pork, vegetables, and oil.

The total amount of each raw agricultural ingredient consumed is calculated by adding the contribution from each food eaten. For instance, the daily dietary intake of wheat is calculated by adding the total amount of wheat consumed in bread, bakery goods, cereals, pasta, and other wheat-containing food items.

The final calculation is to divide the weight of each agricultural ingredient eaten by the weight of the individual. The food consumption estimate is expressed as grams of raw agricultural commodity per kilogram of body weight per day.

If a 69-kilogram (150-pound) woman consumes 100 grams of wheat per day, her consumption is expressed as 1.45 grams of wheat per kilogram of body weight:

$$100 \text{ g} \div 69 \text{ kg} = 1.45 \text{ g/kg}$$

A 113-kilogram (250-pound) man who eats 100 grams of wheat per day consumes approximately 1 gram of wheat per kilogram of body weight:

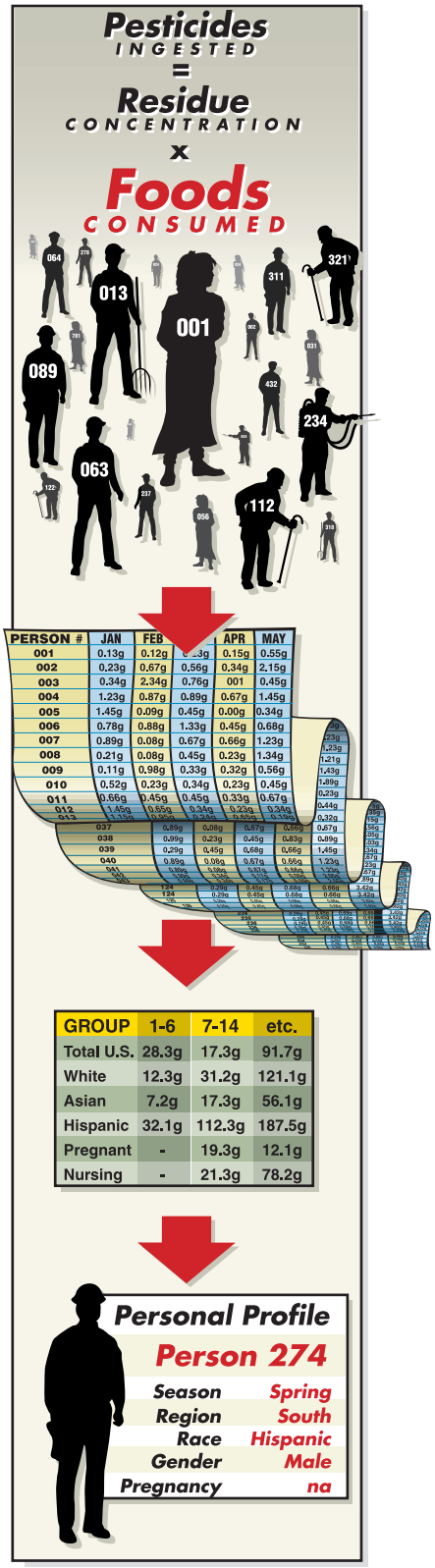
$$100 \text{ g} \div 113 \text{ kg} = 0.88 \text{ g/kg}$$

A 27-kilogram (60-pound) child who eats 100 grams of wheat per day consumes approximately 4 grams of wheat per kilogram of body weight:

$$100 \text{ g} \div 27 \text{ kg} = 3.7 \text{ g/kg}$$

Understanding Consumption Patterns by Subpopulations

USDA dietary consumption surveys are designed to represent the entire United States population as well as specific subpopulations. Each person in the survey is classified according to demographic characteristics: age, sex, ethnic group, pregnancy and lactation status, and household income. Based on individual responses, food consumption patterns are established for the populations and subpopulations as listed in Table 4 (p. 29).



How Much Pesticide Is on Food?

The amount of a food commodity consumed is only part of the equation for estimating total pesticide consumption in the diet. The other critical measurement is the amount of residue in or on those foods. Pesticide residues can be estimated by many methods, each with its own strengths, limitations, and assumptions.

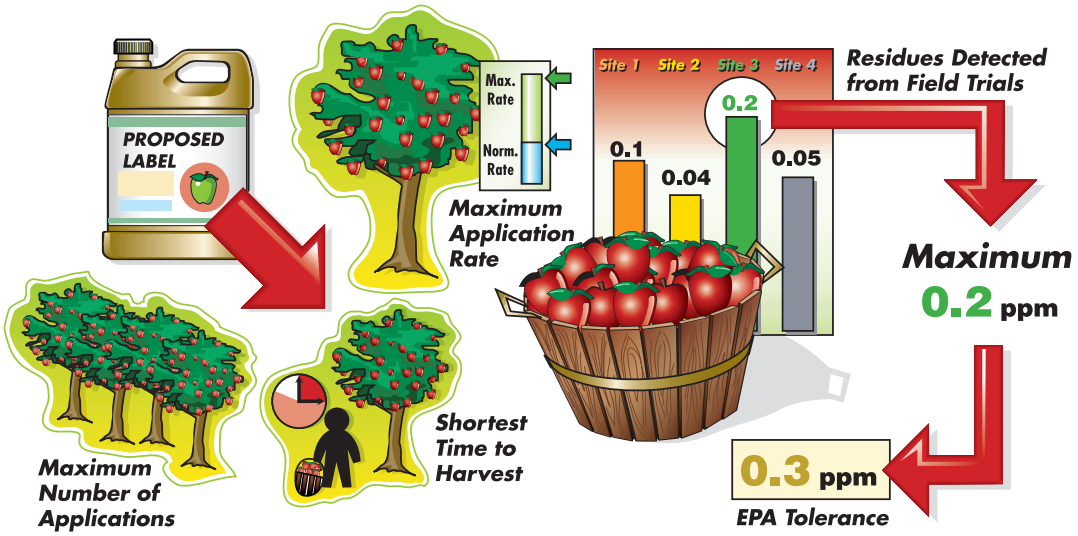
Tolerances

A tolerance is a legally enforceable *maximum* level, generally expressed in parts per million (ppm), of a pesticide and/or its metabolites that can be legally present in or on a commodity such as fresh or processed foods, animal feed, meat, milk, and eggs. International tolerances are referred to as maximum residue levels.

Tolerances for Crops and Products Derived from Crops

Crop tolerances are based on results from controlled field trials conducted in various geographical locations. The trials are designed to identify the highest concentrations expected on a crop, often referred to as a raw agricultural commodity (RAC), using good agricultural practices, maximum application rates, maximum number of applications, and the shortest application-to-harvest interval. And because they are conducted under maximum conditions, they yield maximum residue levels.

The registrant petitions EPA to set a pesticide tolerance for each crop that appears on a product label. As a general rule, EPA requires a slightly higher tolerance than the highest found in the field tests. The higher tolerance allows for the occurrence of slightly higher residues that may occur under environmental conditions not tested, and under differing production or agricultural practices.



Tolerance Development: Crops

Table 2 (p. 22) shows residue levels in samples taken from three crops for the purpose of setting a tolerance for Insecticide X. The registrant conducted 16 residue studies, as mandated by EPA residue chemistry guidelines. Since the maximum residue observed in the apple field trials was 0.27 ppm, the registrant might petition EPA for a pesticide tolerance of 0.3 ppm, which is slightly above the highest residue detected on the apples in any of the 16 trials.

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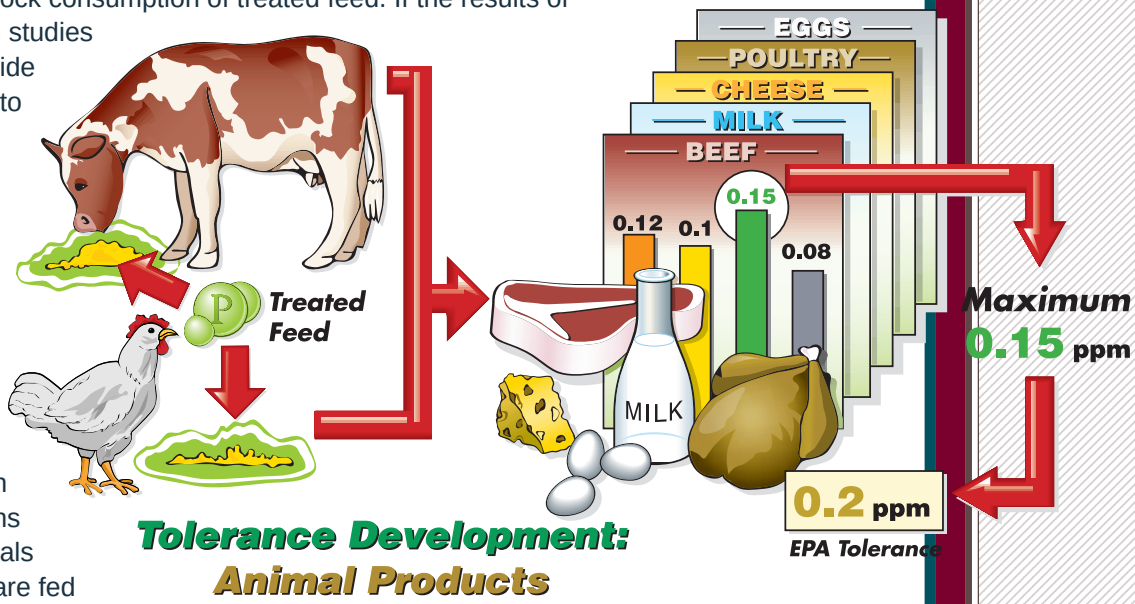
Table 2. Residue levels (ppm) from field trials for Insecticide X

Sample	Apples	Oranges	Tomatoes
1	0.27	1.20	0.44
2	0.24	1.10	0.42
3	0.21	1.00	0.39
4	0.19	0.94	0.33
5	0.18	0.93	0.31
6	0.14	0.91	0.27
7	0.13	0.83	0.27
8	0.13	0.81	0.24
9	0.11	0.80	0.20
10	0.09	0.77	0.19
11	0.09	0.75	0.18
12	0.08	0.73	0.17
13	0.07	0.66	0.16
14	0.06	0.64	0.14
15	0.04	0.63	0.11
16	0.04	0.54	0.09
Mean	0.13	0.83	0.24

Tolerances for Animal Products

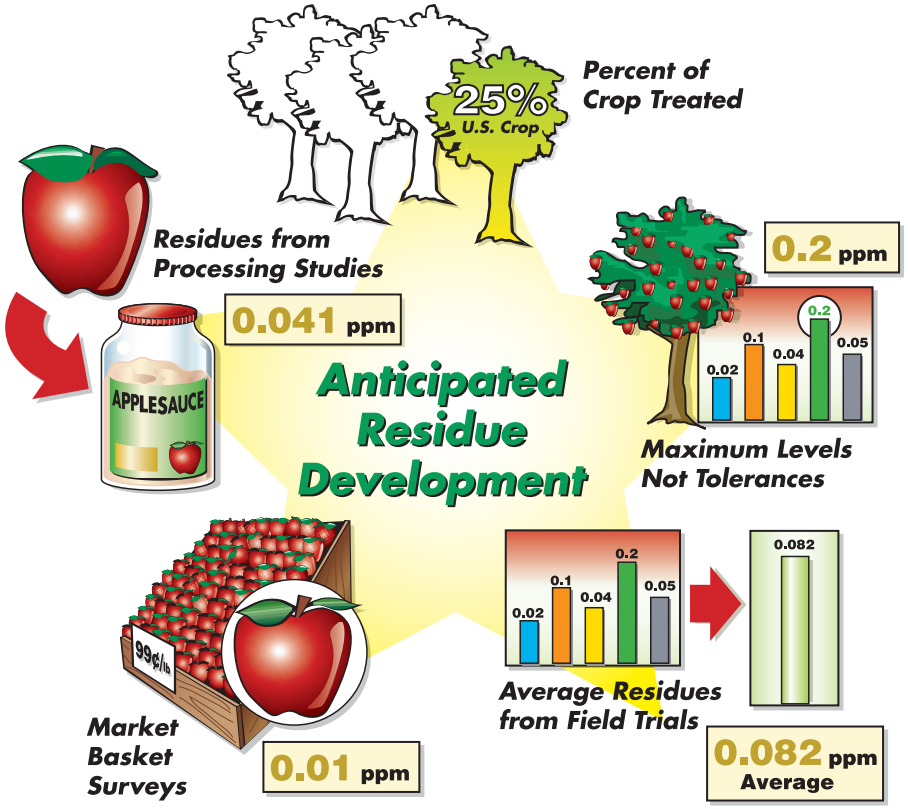
Direct application of pesticides to livestock can leave residues in meat, as can livestock consumption of treated feed. If the results of animal metabolism studies indicate that pesticide residues are likely to be found in animal products from livestock that has fed on crops treated with pesticides, tolerances for products such as meat, milk, and eggs must be established. To establish tolerances, chickens and ruminant animals (goats and cattle) are fed



diets containing various levels of the pesticide for 28 days. Eggs, meat, and milk from these animals are then analyzed for pesticide residues. The registrant would petition EPA for individual tolerances for beef, poultry, eggs, and milk, depending on the residues detected.

Anticipated Residues

Using the tolerance as a maximum estimated amount of pesticide residue acceptable in or on food or feed presents a "conservative" worst-case scenario. More realistic estimates would result from data generated under "normal" use patterns. For example, pesticides are not always applied at the maximum rate and frequency permitted by the label; and crops are not always harvested as soon as legally allowed following pesticide application. Also, residue levels may decrease, over time, as a result of storage, washing, trimming, and cooking.



The assumptions and data used to calculate anticipated residue estimates generally depend on the crop and/or whether acute or chronic risks are being evaluated. Depending on the exposure scenario and the degree of refinement or accuracy necessary, anticipated residues may be derived as follows.

- *Take into account the percentage of a crop treated with the pesticide.* Only a portion of any crop in the United States is likely to be treated with a given pesticide, and only the treated portion is expected to yield pesticide residues.

- *Use the maximum residue from field trials, rather than the tolerance; it is often used when assessing potential acute risks from consuming whole foods such as apples, potatoes, tomatoes, etc.* The *maximum residue* generally is slightly lower than the tolerance. For instance, in Table 2 (p. 22) the highest pesticide residue found on apples is 0.27 ppm.
- *Use the average residue from field trials when considering chronic dietary risk or acute risk from blended commodities.* A blended commodity generally is not eaten intact; instead, it is mixed with like crops from other farms, such as wheat that is ground into flour for myriad uses, and apples for juice, pie filling, etc. In the example shown in Table 2, the mean residue value of 0.13 ppm for apples could be used instead of the tolerance (0.3 ppm) or maximum residue (0.27) in assessing potential chronic exposure to apples or acute exposure to apple juice.

Adjusting for the fact that only 15 percent (0.15) of the apple crop is treated (Table 3, p. 27), the average residue would be 0.02 ppm (0.15 x 0.13 ppm); with oranges, adjusting for 20 percent of the crop treated, the average residue would be 0.17 ppm (0.20 x 0.83 ppm); and with tomatoes, adjusted for only 10 percent of the crop treated, the average residue would be 0.02 ppm (0.10 x 0.24 ppm).

- *Use factors from processing studies.* Registrants often conduct studies to evaluate the effect of processing on residue levels. Depending on the physicochemical properties of the pesticide (e.g., solubility in fat and water) and the nature of the crop, residues in processed fractions (e.g., corn oil, tomato paste) may be higher or lower than in the raw agricultural commodity.
- *Use residues based on monitoring data.* FDA, USDA, and the states routinely collect and analyze foods such as fresh produce, meat, milk, and eggs to determine the levels of pesticide residue present. EPA prefers that monitoring or market basket data (rather than residue data from field testing) be used for dietary exposure assessment.

  Food may be monitored by collecting samples at or near the farm, at the point of entry into the United States (for imported foods), and at close-to-consumer locations (e.g., at produce markets or grocery distribution centers). Such monitoring programs typically show much lower average residues than those from field residue studies.
- *Use residues based on market basket surveys.* On occasion, registrants measure actual residues present in food at the time of purchase by the consumer. These studies are conducted by sampling and analyzing fresh and/or processed products at retail locations throughout the country.

In addition, FDA conducts a Total Diet Study that uses a market basket approach to analyze pesticide residues after food has been prepared for eating. Over 200 food items are selected and purchased in grocery stores in four geographical areas, four times a year, and prepared in institutional kitchens. The foods are analyzed for pesticide residues after they are table-ready or in final form for consumption. These studies provide more realistic estimates of pesticide residue concentrations *actually consumed* because they take into account changes that result during storage, cleaning, processing (e.g., apples into applesauce), and cooking.

One of the most useful residue databases for exposure assessment is USDA's Pesticide Data Program (PDP), which is designed to provide residue data for risk assessment. Several features distinguish it from typical monitoring databases such as those compiled by FDA, whose objectives are enforcement.

Tolerances are established on the raw agricultural commodity (RAC), i.e., the harvested crop. When enforcement programs (e.g., FDA's

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monitoring programs) collect and analyze food samples, the RACs are tested. For example, FDA analyzes pesticides in whole oranges, including the peel. USDA's PDP, on the other hand, analyzes residues in the meat of the fruit, only, excluding the peel. Therefore, PDP provides residue information on foods "as eaten." Such data are more suitable for risk assessment than those collected during enforcement program studies.

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PDP sampling is based on a rigorous statistical design. Samples are collected from large distribution centers that account for approximately 60 percent of the nation's food supply. Often, regulatory agencies such as EPA want to evaluate potential dietary exposure to foods consumed in relatively large quantities. PDP focuses on fresh fruits and vegetables, although milk and processed foods such as canned green beans, grape juice, and corn syrup sometimes are sampled, as well. EPA and USDA collaboratively select specific foods to be sampled and analyzed in each study. The Pesticide Data Program typically uses methods 5–10 times more sensitive than those used in enforcement program studies.

How Much Pesticide Do We Consume, Long-Term?

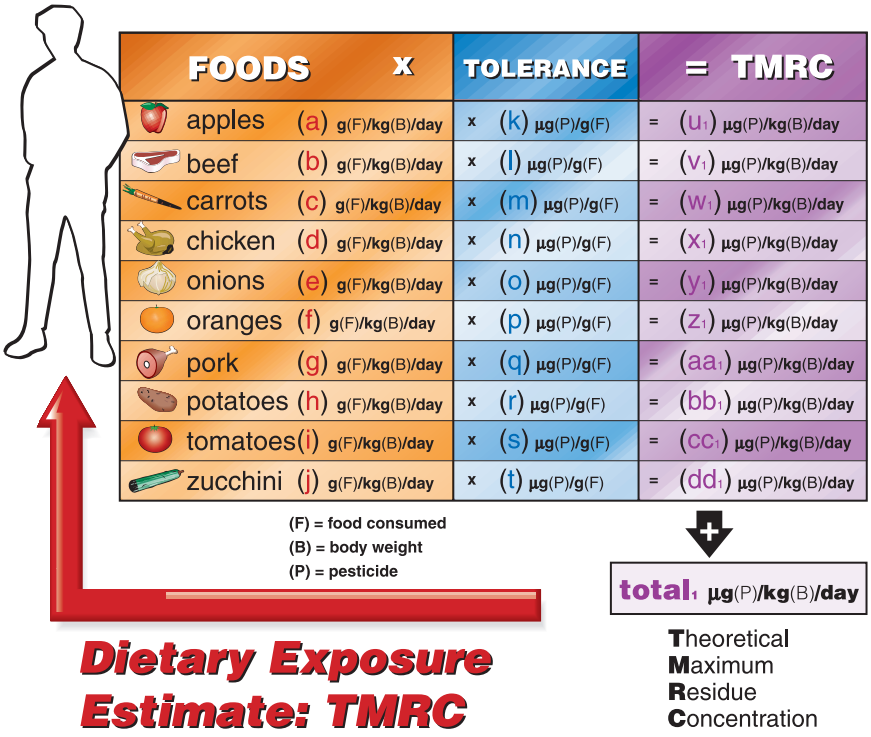
There are two basic techniques for estimating long-term exposure to pesticides in food:

- Use of tolerance levels to calculate the Theoretical Maximum Residue Contribution (TMRC), also referred to as the Theoretical Maximum Daily Intake
- Estimation of the Anticipated Residue Contribution (ARC), also called the Estimated Daily Intake

Theoretical Maximum Residue Contribution

TMRCs for a pesticide are calculated individually for the entire list of crops on the label. They are calculated for each agricultural commodity by multiplying the amount consumed by the corresponding tolerance

level. The theoretical maximum amount of pesticide consumed is then calculated by summing the TMRCs from each individual commodity. The estimate of total exposure developed via this method represents the theoretical, worst-case, maximum legal amount that an individual might consume.



TMRCs are calculated on the assumption that 100 percent of the crops for which the pesticide is registered are treated, and that pesticide residues are present at tolerance levels. TMRC analysis further assumes that post-harvest storage, handling, processing, or cooking does not reduce residues. For example, Insecticide X is registered and has tolerances as listed in Table 3.

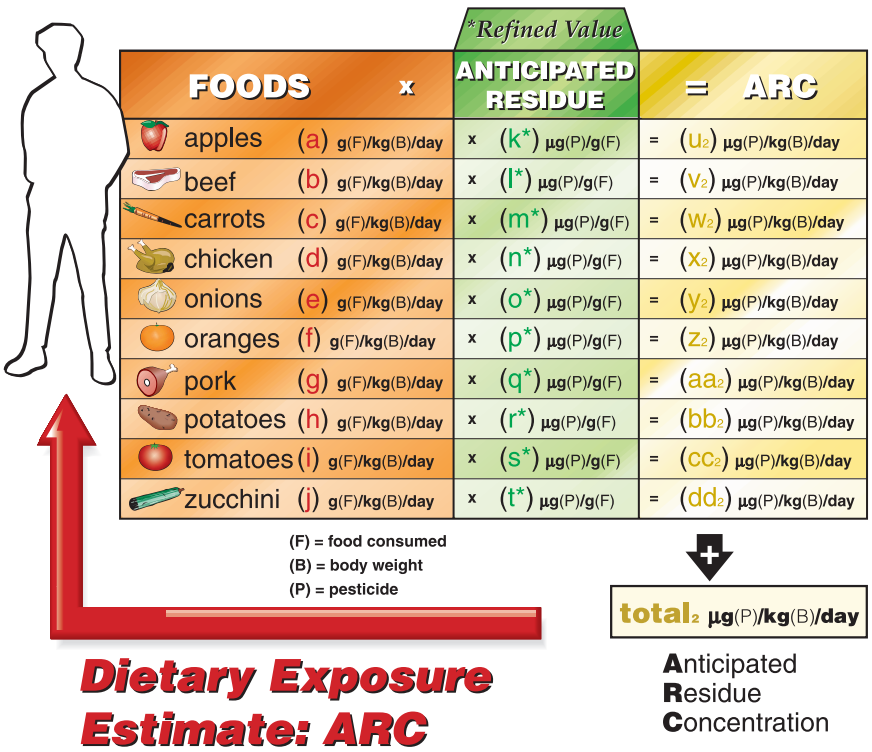
Table 3. Established Tolerances for Insecticide X

Commodity	Tolerance (ppm)	Crop Treated (%)
Apples	0.30	15
Corn	0.02	5
Oranges	1.50	20
Tomatoes	0.50	10
Wheat	0.02	100
Meat	0.02	100
Milk	0.02	100
Poultry	0.02	100
Eggs	0.02	100

Tolerances established for raw agricultural commodities are valid for all forms of the crop consumed unless scientific experiments indicate the need for different tolerances for different forms of the food. For example, if a tolerance of 0.3 ppm is established for apples, that is the legal pesticide limit on fresh apples, apple juice, apple juice concentrate, dried apples, etc. But if an experiment shows that the tolerance on dried applies should be 1 ppm, that tolerance would be assigned to dried apples, only, while the tolerance for all other apple products would be 0.3 ppm. A sample TMRC calculation using tolerances shown in Table 3 and consumption data from the 1994–1996 CSFII is given in Table 4 (p. 29).

Anticipated Residue Contribution

More realistic estimates of dietary exposure can be obtained by considering pesticide use patterns and/or residue levels anticipated rather than the TMRC. The methodology and assumptions used to estimate anticipated residues vary somewhat, depending on whether short- or long-term risk is being evaluated.



Anticipated residue estimates are further refined by considering residue data from field trials, food processing studies, and monitoring. Reduced residues are expected when data from processing and monitoring studies are incorporated. Such studies analyze residues in crops not immediately after harvest, as in field trials, but after storage, handling, and processing. They provide a more realistic estimate of potential human exposure.

The ARC values in Table 4 were calculated using more detailed information:

- Mean residue values from field trials (instead of tolerance)
- Percentage of crop treated (instead of assuming that 100 percent is treated)
- Adjustment for the effects of processing (instead of default concentration factors

In addition, theoretical residues in edible animal tissues were calculated by using data from animal metabolism and livestock feeding studies (instead of simply using tolerance values). As shown, even relatively simple refinements have tremendous impact on the results of exposure estimation. It is expected that the procurement of monitoring data would reduce exposure estimates even further.

Table 4. Estimates of Chronic Dietary Exposure (mg/kg/day) Using Theoretical Maximum Residue Contributions and Anticipated Residue Concentrations

	TMRC Exposure (mg/kg/day)	ARC Exposure (mg/kg/day)
U.S. population (total)	0.005408	0.000152
U.S. population (spring)	0.005299	0.000150
U.S. population (summer)	0.005122	0.000146
U.S. population (autumn)	0.005544	0.000157
U.S. population (winter)	0.005677	0.000156
Northeast region	0.006741	0.000185
Midwest region	0.005245	0.000152
Southern region	0.004740	0.000135
Western region	0.005453	0.000151
Hispanics	0.006858	0.000180
Non-Hispanic whites	0.005011	0.000145
Non-Hispanic blacks	0.005957	0.000162
Non-Hispanic/non-white/non-black)	0.006957	0.000185
All infants (<1 year)	0.003911	0.000103
Nursing infants (<1 year)	0.001463	0.000041
Non-nursing infants (<1 year)	0.004627	0.000122
Children 1–6 years	0.015889	0.000418
Children 7–12 years	0.008507	0.000239
Females 13–19 (not pregnant or nursing)	0.005341	0.000147
Females 20+ (not pregnant or nursing)	0.003555	0.000104
Females 13-50 years	0.003976	0.000115
Females 13+ (pregnant/not nursing)	0.005251	0.000144
Females 13+ (nursing)	0.004984	0.000143
Males 13–19 years	0.005864	0.000165
Males 20+ years	0.003638	0.000108
Seniors 55+	0.003329	0.000098

How Much Pesticide Do We Consume, Short-Term?

Acute analysis does not calculate a single estimate of exposure as with TMRC and ARC. Like the TMRC and ARC calculations for chronic exposure, however, acute distributional analysis may be worst-case or refined. The first level of acute analysis assumes that 100 percent of all registered crops contain tolerance level residues, and exposure distribution is calculated from individual daily consumption data. Since there is no variation in residue data, variation in consumption forms the basis for distribution. So, in the initial acute analysis we can evaluate safety at the extreme end of exposure distribution because all consumption data are included in the analysis—even those on individuals who consume large quantities of food. In contrast, chronic analysis uses mean consumption data to estimate typical exposure over a relatively long period of time.

Table 5 summarizes the results of a Tier 1 acute dietary exposure analysis for Insecticide X, using tolerance levels shown in Table 3 (p. 27). Thus, the entire U.S. apple supply was assumed to contain 0.3 ppm, milk supplies were assumed to contain 0.02 ppm, etc.

Table 5. Acute Dietary Exposure Estimates (mg/kg/day) for the Upper 95th, 99th, and 99.9th Percentile for Selected Subgroups

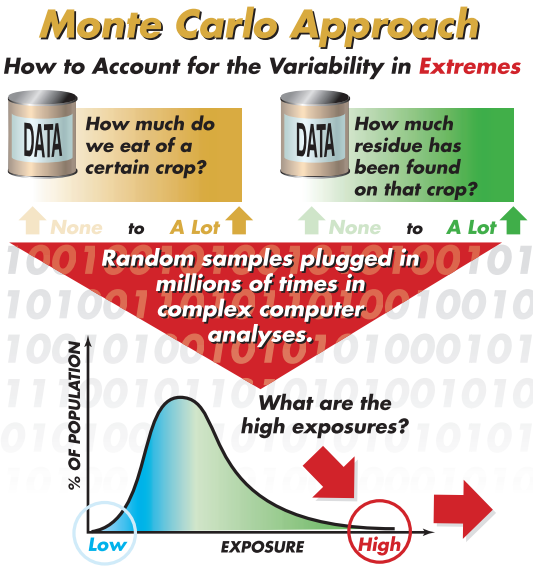
	95%	99%	99.9%
U.S. Population (all seasons)	0.022468	0.049183	0.103411
Non-nursing infants (<1 year)	0.015741	0.035950	0.061152
Children (1-6 years)	0.055713	0.101169	0.201126
Children (7-12 years)	0.032254	0.058032	0.088462

In Table 4 (p. 29), the TMRC estimate for the U.S. Population is a simple point estimate of 0.005408 mg/kg/day. In contrast, exposures for the Tier 1 acute analysis shown in Table 5 are summarized for the 95th, 99th, and 99.9th percentiles of the exposure distribution. In fact, the acute analysis yields a complete exposure distribution whereas Table 5 reports only the high-end exposure estimates. Comparison of the two tables clearly demonstrates the difference between chronic and acute assessment.

The estimated exposure in the upper 95th percentile is 0.055713 mg/kg/day for children 1–6 years old; the other 5 percent of children in that age group would witness exposures above 0.055713 mg/kg/day. Ninety-nine percent (99%) of children 1–6 years old would be exposed to 0.101169 mg/kg/day or less, and one percent would be exposed to 0.101169 mg/kg/day or more.

Monte Carlo Analysis

The Monte Carlo approach is a popular statistical technique used to refine exposure estimates for acute dietary risk assessment. Repeated sampling from the complete distribution of food consumption and the entire spectrum of pesticide residue data (from field trials, monitoring data, and market basket surveys) are used to predict the amount of pesticide likely to be consumed by one individual on a given day. Percentage of crop treated also can be included in the Monte Carlo analysis, but differently than for chronic exposure.



Some individuals do not consume fresh apples, whereas others consume several apples per day; and Insecticide X residues on fresh apples may vary from no residue (apples not treated) up to 0.27 ppm, as shown in Table 2 (p. 22). The residue distribution on apples (from which the Monte Carlo analysis would sample randomly) initially would consist of the 16 residues from field trials (Table 2). But since only 15 percent of the apples were treated with Insecticide X, 90 zero-residue samples would be added to the distribution so that the 16 Insecticide X residues would comprise 15 percent of the total (106). Thus, the entire residue distribution would be 16 residues plus 90 zeros. In the Monte Carlo sampling, a zero would be selected approximately 85 percent of the time; and a residue from the 16 residue values would be selected at random the other 15 percent of the time.

The Monte Carlo analysis in Table 6 uses residue samples from actual field trial data on apples, oranges, and tomatoes; and because of the complexity of the acute distribution, only selected population groups are displayed.

Table 6. Monte Carlo Acute Dietary Exposure Estimates (mg/kg/day) for the Upper 95, 99, and 99.9th Percentiles for Selected Subgroups

	95%	99%	99.9%
U.S. Population (all seasons)	0.002682	0.005916	0.012706
Non-nursing infants (<1 year)	0.001727	0.004583	0.011140
Children (1-6 years)	0.006711	0.012376	0.023540
Children (7-12 years)	0.003913	0.006959	0.010900

The acute exposure estimates in Table 6 (p. 31) are much lower than those in Table 5 (p. 30) because tolerance level residues are assumed to be present in all crops that could be treated with Insecticide X. The refined analysis shown in Table 6, however, does not make that assumption; it uses actual residue values. More importantly, the refined analysis accounts for the fact that less than the entire crop was treated and that people do not always eat food that has been treated with pesticides.

Drinking Water Exposure Estimates

At this time there are no comprehensive, reliable databases on pesticide residues in drinking water, nor models to predict residue levels. Therefore, EPA relies on models developed for predicting pesticide residues in surface or ground water. These models produce highly conservative estimates of potential pesticide residues that may occur in shallow farm ponds or in shallow, vulnerable ground water sources.

For screening purposes, these values represent worst-case estimates of potential residues in raw, untreated drinking water. Because of their highly conservative nature, EPA uses the models primarily as screening tools to identify possible concerns rather than to develop quantitative estimates of potential exposure. More accurate and reliable models for predicting potential pesticide residues in drinking water are under development.

OCCUPATIONAL EXPOSURE ASSESSMENT

Workers who formulate or package pesticide products in factories, those who apply pesticides for commercial businesses, and those who farm come into contact with pesticides in their course of work. In addition, workers who enter treated fields or greenhouse facilities also may be exposed to pesticide residues. Although pesticide exposure in the work environment cannot be totally eliminated, worker contact with pesticides can be minimized by following product label directions, using appropriate protective clothing and equipment, and practicing good industrial hygiene.

Worker Exposure Related to Work Practices

Exposure assessments are most precise when worker exposure is described clearly and accurately. Variables that influence exposure are

- duration and frequency of exposure,
- protective gear used,

- product formulation,
- route of exposure,
- quantity of pesticide handled,
- type of mixing/loading operations,
- type of application equipment,
- environmental conditions, and
- nature of work tasks following entry into a treated field.

The worker exposure scenario and individual work practices determine estimated worker exposure. For example, a pesticide applicator with one company may take 30 minutes each day to dilute and mix the pesticides that he will use that day, while the rest of the day is spent driving to and from job sites and making applications. Another company may assign one worker the responsibility of handling, mixing, and loading all pesticides for applicators whose sole job is to operate application equipment from within as the products are applied. Workers may be exposed at the job site as they walk through treated areas (turf applications) or as they work in crawl spaces beneath homes (termite treatments). Reentry exposure may involve a field worker who may be exposed to pesticide residues on treated crops when picking cantaloupes by hand.

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Job activities have a direct bearing on how much and when a worker is exposed to pesticides. A person who mixes and loads concentrated pesticides throughout the work day is exposed differently than a person who applies dilute solutions all day but does no mixing, and differently than workers in a field or greenhouse where pesticides were applied several days earlier.

Work-related activities that bring a worker into contact with a pesticide—storing, mixing, loading, rinsing containers, application, and harvesting—should be identified. The use pattern and label information for the pesticide can be used to predict situations in which a worker could potentially be exposed to pesticides. Work regimens can be determined by considering use rates, how long the worker is exposed during each use, how often applications are made, the method of application, the crop/target being treated, the time of day the application takes place, and protective clothing and equipment needed.

Techniques for Measuring Worker Exposure

A work activity pattern describes the tasks that bring a worker into contact with pesticides. The next step in quantifying exposure is to estimate the amount of pesticide to which the worker is potentially exposed during each specific work task.

Accurate estimations of total daily exposure require quantification of the amount of exposure from each activity, such as

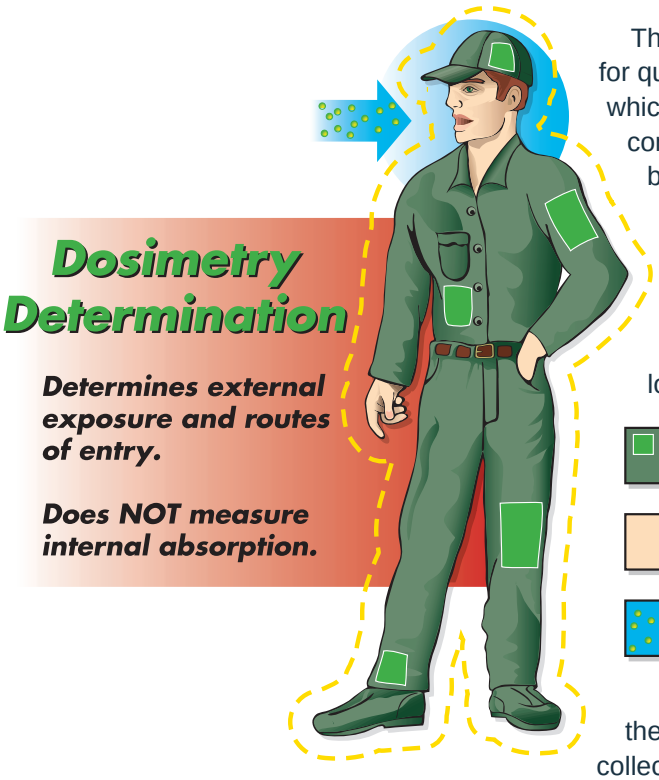
- handling the container,
- opening the container,
- removing the product from the container,
- loading the product into water and mixing,
- rinsing the container,
- handling safety clothing, and
- application.

Exposure monitoring studies have been conducted for a variety of pesticides, using commercial applicators, farmers, and field workers. These studies usually are conducted by the registrant to fulfill federal and state data requirements for the registration or reregistration of pesticide products. Workers are informed about personal protective equipment and its importance during mixing and application. Then they are monitored for exposure as they carry out the various aspects of their job: mixing/loading; application; reentry for harvest, etc. The amount of pesticide found on and under clothing and the amount found in the breathing zone are monitored and quantified during work activity.

California Environmental Protection Agency

Approaches to Quantifying Exposure

Dosimetry



The more common of the two methods for quantifying exposure is *dosimetry,* which estimates the amount of pesticide in contact with clothing, skin, and/or the breathing zone of the worker. There are several passive dosimetry methods, but patches typically are placed under or attached to the outside of clothing on the chest, back, upper arm, forearm, thigh, and lower leg. Patches also can be attached to the front and sides of caps when estimations of exposure to the face and neck are needed. The patches trap residues that would otherwise come into contact with the clothing or skin. At the end of the exposure period, the patches are collected and the trapped residues are removed with solvent and analyzed to determine quantity.

The amount of pesticide recovered from a patch generally is reported as micrograms of pesticide per square centimeter ($\mu g/cm^2$). It can then be standardized *per pound of active ingredient handled* or *per unit of time.* The assumption is that the concentration of pesticide on the patch is indicative of the amount deposited over the entire corresponding body region. The amount of residue (µg) per square centimeter (cm^2) indicated by the patch is multiplied by the total surface area of the body region.

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As an example, a researcher placed patches on the outer clothing on the chest/stomach region of workers picking apples in an orchard. The amount of pesticide retrieved from the patches averaged 0.10 μg/cm^2. The chest/stomach area for an average adult male is 3454 cm^2, so the calculation for exposure of the chest/stomach region was as follows:

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0.10 μg/cm^2 x 3454 cm^2 = 345 μg

Body region values were then summed to derive a value for total pesticide exposure to the outside of the body.

Whole body dosimetry uses clothing actually worn by workers instead of patches as dosimeters: T-shirts, long sleeved shirts, socks, trousers, long underwear, etc. The type of work clothing varies with geographic region, time of year, and product label. Pesticide applicators perform their jobs as usual: mixing and loading, making applications, etc. Their clothing is collected after the completion of each task or at the end of the work day. A single amount of pesticide representative of exposure to the entire body, or an amount for each body region, can be determined by analyzing the intact garments or specific sections, respectively.

Whole body dosimetry studies occasionally utilize techniques to estimate the penetration of pesticides through outer clothing to underclothing. Clothing penetration is derived by dividing the concentration detected on undergarments (inside measurement) by the sum of concentrations found on outer garments (outside measurement) and the inside measurement.

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In the absence of data, an estimate of possible penetration may be used. EPA assumes that 50 percent of pesticide deposited on outer clothing can penetrate to or be deposited on underclothing. The California Environmental Protection Agency (Cal-EPA) assumes this value to be 10 percent. For example, if 20 $\mu g/cm^2$ of pesticide were collected from the back and front portions of coveralls assumed to have a clothing penetration of 10 percent, it is assumed that 2 $\mu g/cm^2$ would reach the underclothing. And underclothes would provide additional protection by preventing a portion of the chemical that reaches it from penetrating to the skin.

Rinses and wipes can be used to measure pesticide residues on the hands, face, and neck. Historically, pesticide residues on the hands have been measured by analyzing the pesticide content of rinsate after washing the hands, by measuring the amount found on hand wipes used after exposure, or by calculating the amount left on cotton glove dosimeters. For instance, field workers picking strawberries might be asked to wash their hands at specific times, during which their rinsate is collected for analyzation. Pesticide residue from the face and neck can be collected by swabbing the skin. There are two techniques used to measure pesticide residue that reaches the hands despite wearing chemical-resistant gloves: analyzation of rinsate from hand washing after removal of chemical-resistant gloves, and analyzation of cotton glove dosimeters worn under chemical-resistant gloves.

Personal air samplers are used to estimate the amount of pesticide in the breathing zone of workers. A battery powered monitoring pump is clipped to the belt and, typically, a flexible tube is run up the back and over the shoulder where it is clipped to the collar of the worker. Each monitoring pump pulls the air through an absorbent filter such as polyurethane foam or organic resin which removes the pesticide from the air and traps them. The pesticide is then extracted with a solvent for quantification.

These techniques are used to estimate external exposure. In the absence of specific data pertaining to dermal or inhalation absorption, 100 percent of the amount inhaled and 10 percent (Cal-EPA) to 100 percent (EPA) of residues on the skin are assumed to be absorbed.

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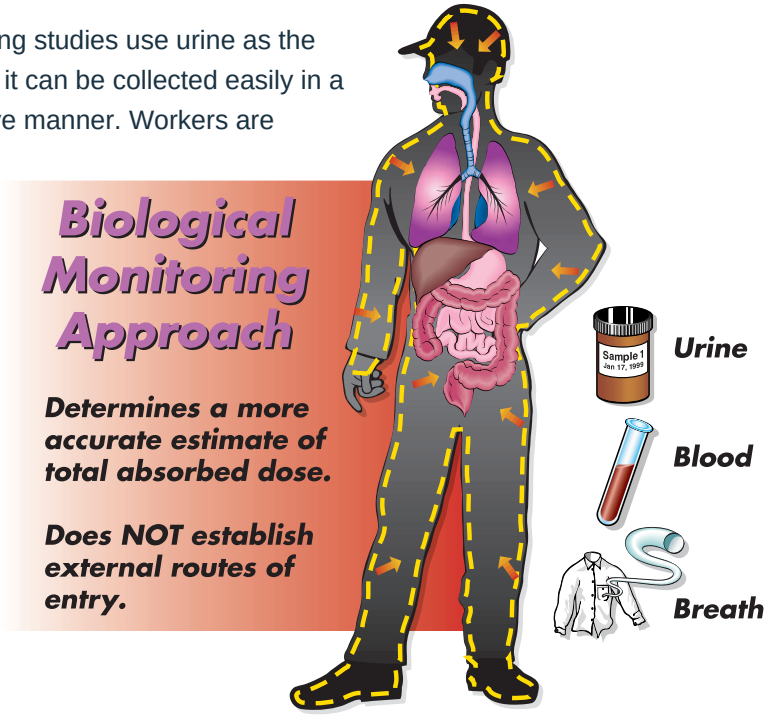
Biological Monitoring

The second approach to quantifying occupational exposure—biological monitoring—provides a measurement of the total amount of pesticide actually absorbed by the worker via all routes (oral, dermal, and inhalation). The technique estimates the actual absorbed dose via analysis of urine, blood, and/or exhalation for the pesticide and/or its metabolites. This technique generally provides a more accurate estimate of the *total* absorbed dose than do external dosimetry techniques, but it does not differentiate between routes of exposure.

Most biological monitoring studies use urine as the sampling medium because it can be collected easily in a quantitative and noninvasive manner. Workers are monitored one to two days prior to exposure to the pesticide to confirm that they have not been exposed to it previously. Total urine output generally is collected and assayed for pesticide residues for 48–96 hours after handling of the pesticide or until prescreening levels are regained.



Estimating Occupational Exposure

When direct measurements of worker exposure are not available, occupational exposure is estimated. The absorbed daily dose is the estimated total amount of a pesticide that a person absorbs systemically each day that they are exposed to it; all routes of exposure are considered: oral, dermal, and inhalation.

Absorbed daily dose also may be expressed as route-specific, such as the *dermal* absorbed daily dose, and it can be determined using estimates of external exposure (from passive dosimetry studies) in conjunction with estimated absorption percentages for each route of exposure.

Exposure Calculated by Various Approaches

Exposure estimates are obtained from three general sources: generic data, generic data with chemical-specific attributes, and chemical-specific exposure monitoring.

Generic Data

The magnitude of exposure to pesticides generally is not chemical-specific; it mostly depends on the type of formulation, method of application, use rate, and protective clothing used. Therefore, occupational exposure often can be estimated by using surrogate data developed previously for other chemicals. Pesticide companies have voluntarily pooled a large amount of exposure data into a single generic database called the Pesticide Handlers' Exposure Database (PHED); it is available to the public through EPA.

PHED data may be segregated based on type of formulation (granular, EC, wettable powder), method of application (aerial, ground boom, air blast, backpack), use rates, and protective equipment required. PHED contains data to estimate exposure to a mixer/loader, an applicator, a combined mixer/loader/applicator, and a flagger. Thus, PHED may be used for a surrogate estimate of inhalation and dermal exposure for many exposure scenarios. Exposure calculations in a preliminary assessment typically use the following assumptions to predict the absorbed daily dose:

- Maximum use rates for assessing short-term exposure, and average use rates for assessing intermediate and long-term exposure.
- Pesticide penetration through outer clothing is assumed to be 10–50 percent. However, PHED typically provides actual measurements under a single layer of clothing, which negates the need to estimate clothing penetration.
- Dermal absorption is assumed to be 100 percent when pesticide-specific data are not available, although regulatory agencies other than EPA assume 10 percent.

- Maximum acres treated per day or year when assessing short-term risk, and average acres treated per day or year when assessing intermediate or long-term risk.

Generic Data with Chemical-Specific Attributes

The generic data/pesticide-specific data approach to assessment replaces generic information with product-specific data. For example, a dermal absorption study may indicate that 10 percent of the pesticide that *reaches* the skin may actually *penetrate* the skin; so 10 percent would replace the value of 100 percent dermal absorption. Another study may show only 10 percent penetration through clothing to the skin, in which case 10 percent would replace the value of 50 percent clothing penetration.

Chemical-Specific Exposure Monitoring

Chemical-specific exposure monitoring relies on field studies that provide actual exposure data on the pesticide, relative to specific tasks. It is common for these studies to include measurements of pesticides on skin surfaces as well as actual biological monitoring of the applicator.

Predicting Exposure for a Mixer/Loader/Applicator by External Methods

The following example illustrates the absorbed daily dose calculation when using chemical-specific measurements of external exposure.

Total External Deposition on Clothes and Exposed Skin

Pesticides were extracted from patches, hand washes, and face and neck wipes for quantifying exposure of adult males during mixing/loading and application activities; residue levels were reported for each body region. The total amount of pesticide present on outer clothing was determined to be 6958 µg per person per work day (Table 7, p. 41).

With patches, this was calculated by multiplying the surface area for each region by the amount of pesticide per cm^2. (The surface area and dosimeter residue values per cm^2 are not used for wipes and washes, as these techniques collect the total residue from exposed skin.) The results for all body regions are summed to yield the total external deposition, often referred to as the potential dermal exposure.

Table 7. External Pesticide Deposition on Clothes and Skin

Location On Body	Sample Type	Surface Area of Region (cm^2)	Mean Patch Residue ($\mu g/cm^2$)	Total Residue (μg)
Head (face excluded)	patch	630	0.02	13
Face	wipe	NA	NA	19
Back of neck	wipe	NA	NA	4
Front of neck	wipe	146	NA	6
Chest/Stomach	patch	3454	0.87	3005
Back	patch	3454	0.58	2003
Upper arms	patch	1479	0.20	296
Forearms	patch	1211	0.16	194
Hands	wash	NA	NA	302
Thighs	patch	3663	0.09	330
Lower legs	patch	2455	0.32	786
				6958

Total Dermal Exposure (μg/person/day)

The total estimated amount of pesticide deposited on the clothing and exposed skin (i.e., the potential dermal exposure) in the example is 6958 μg. However, clothing essentially intercepts a portion of the pesticide that reaches it, preventing it from contacting the skin beneath. An evaluation of concurrent exposure values on and under clothing, in studies reported in the Pesticide Handlers' Exposure Database, indicates a 10 percent default for protection afforded by one layer of clothing. In this example, it is assumed that the worker wears a long-sleeved shirt and long pants; 6614 μg are deposited on clothing and 344 μg on uncovered skin (head, face, neck, and hands). Thus, 661 μg (6614 μg x 0.10) of pesticide would be expected to contact the skin after penetration through the clothing of the upper and lower arms, upper and lower legs, and front and back torso. Adding the 661 μg to the 344 μg that directly contacted the skin indicates a total estimated dermal exposure of 1005 μg per person per day.

Penetration Through Skin

Human dermal absorption studies indicate that 1–10 percent of many pesticides actually is absorbed through the skin. *In vivo* and *in vitro* studies with rat skin, which is more permeable than human skin for many pesticides, show that pesticide absorption typically ranges from 1 to 30 percent.

In the previous example, 1005 µg of the pesticide reaches the skin surface. The next step is to estimate the percentage that penetrates through the skin and enters the circulatory system. A study of laboratory animals indicated 5 percent dermal absorption. Exposure for a full work day is calculated as follows:

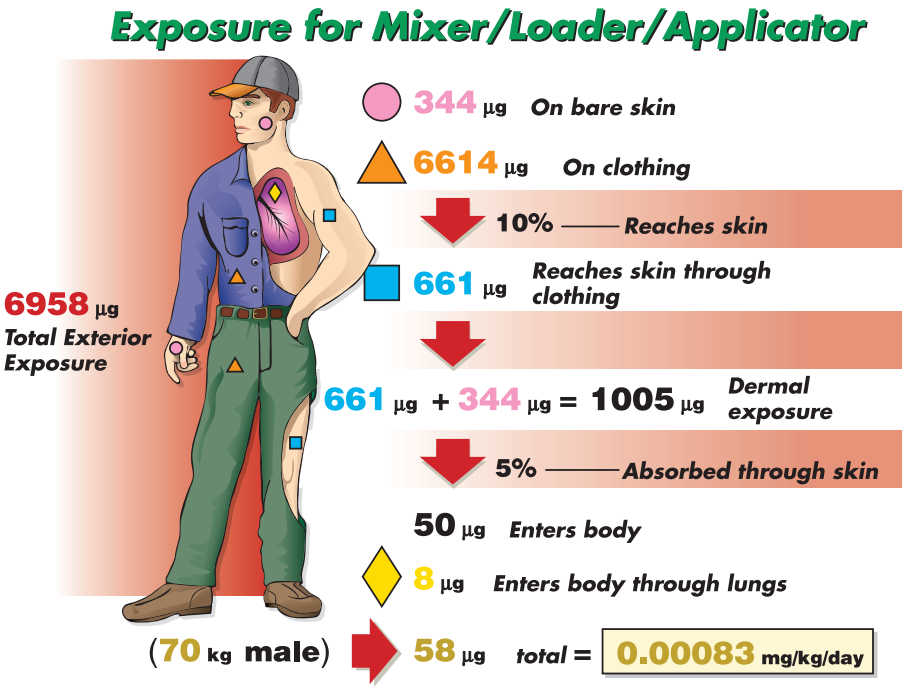
1005	µg deposited on skin per day
x 0.05	(5% dermal absoprtion)
50	µg absorbed per person per day

Penetration to the Lungs

There is very little data on what percent of pesticide inhaled is actually absorbed. But it is generally assumed that air monitoring pumps equate inhalation, that is, that 100 percent of pesticides collected in air monitoring pumps would reach the lungs and penetrate the lung membranes if inhaled. Thus, if studies using monitoring pumps show that workers inhale 1 µg per hour, the resulting daily absorption (dose) through inhalation is calculated as follows:

1 µg/hour	
x 8-hour work day	
8 µg inhaled daily	

The calculation assumes continuous exposure and a constant breathing rate over the period of time specified; but exposure assessments typically have shown that less than 5 percent of total exposure is through inhalation.



Absorbed Daily Dose (ADD)

In the preceding example, the ADD of 58 µg per day includes contributions from the skin (dermal absorbed daily dose of 50 µg/day) and the lungs (inhaled absorbed daily dose of 8 µg per day). The ADD of 58 µg/day typically is then converted to milligrams per kilogram per day (mg/kg/day).

The following example shows how the absorbed daily dose values (µg/day) are converted to absorbed dose expressed as mg/kg/day for a 70 kg male. The 70 kg male is representative of an average adult male; a 60 kilogram adult female also could be used. Body weight values actually used vary with the regulatory body (EPA, Cal-EPA, Canada, Japan, Europe).

$$\frac{58\ \mu g/day}{1000\ \mu g/mg} \times \frac{1}{70\ kg} = 0.00083\ mg/kg/day$$

Predicting External Exposure for a Reentry Worker

Workers may reenter treated fields to perform tasks such as weeding, thinning, and harvesting. Estimates of reentry worker exposure typically are based on the amount of pesticide residue on crop foliage and the amount that transfers from the foliage onto the skin or clothing of the workers. The type of crop and the particular work activity are influencing factors. The remaining steps used to calculate the absorbed daily dose are similar to those previously discussed for mixers, loaders, and applicators.

Dislodgeable Foliar Residue

Dislodgeable foliar residue (DFR) is the amount of residue that can be removed from plant foliage, and that could serve as a source of exposure for workers who weed, harvest, or perform other work activities in treated fields. DFR measurements are repeated over an extended period of time following application so that the rate of residue dissipation can be measured. They are pesticide-specific and depend on the physical, chemical, and environmental fate properties of the pesticide in its formulation.

DFR studies are conducted by applying the end use product to various crops at the highest concentration and the shortest reapplication interval allowed by the pesticide label. The design of the study indicates when leaf samples are to be collected; for example, samples could be taken within 4–12 hours and at 1, 2, 5, 7, 14, 21, 28, and 35 days after application. A leaf punch is used to sample foliage from the top, medium, and lower part of the plant. The collected leaf tissue is placed into a container with aqueous surfactants (e.g., mild detergents), then shaken or agitated. The amount of pesticide measured in the aqueous solution is

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considered potentially dislodgeable. The relevant DFR is taken from the part of the foliage with which a worker typically comes into contact.

The amount of residue that workers collect on their clothing or exposed skin obviously depends on the amount of foliage they contact. For example, a person harvesting strawberries is expected to come into contact with less foliage than a worker harvesting peaches or apples.

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As a default, EPA assumes that 20 percent of pesticides applied to agricultural crops are initially available as DFRs. This assumption is borne of multiple DFR studies submitted to EPA. Day 0 (day of application) DFR values for agricultural crops commonly range from 0.5 $\mu g/cm^2$ to 10 $\mu g/cm^2$, depending on application rates. Dissipation of DFRs after Day 0 is chemical-specific.

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Transfer Coefficient

A *transfer coefficient (TC),* referenced in earlier literature as the transfer *factor,* is used to estimate the amount of pesticide transferred onto workers from a previously treated surface.

The transfer coefficient is different from a dislodgeable residue in that it is not pesticide-specific and is more dependent on the crop treated, the nature of the application, and the extent of foliar contact.

Transfer coefficients are calculated as follows:

$$\text{TC } (cm^2/\text{hour}) = \frac{\text{Measured Exposure } (\mu g/\text{hour})}{\text{Dislodgeable Foliar Residue } (\mu g/cm^2)}$$

For example, a DFR of 1.9 $\mu g/cm^2$ was determined for cantaloupe vines for a fungicide where harvest exposure was 324 μg/hour. Thus, using the above formula, the TC for harvesting cantaloupes is 170 cm^2/hour (324 $\mu g/hr \div 1.9 \mu g/cm^2$).

Table 8 presents generic transfer coefficients for five work tasks classified by type of crop, method of harvest, and body regions that come into contact with pesticide residues during harvest.

Table 8. Generic Transfer Coefficients

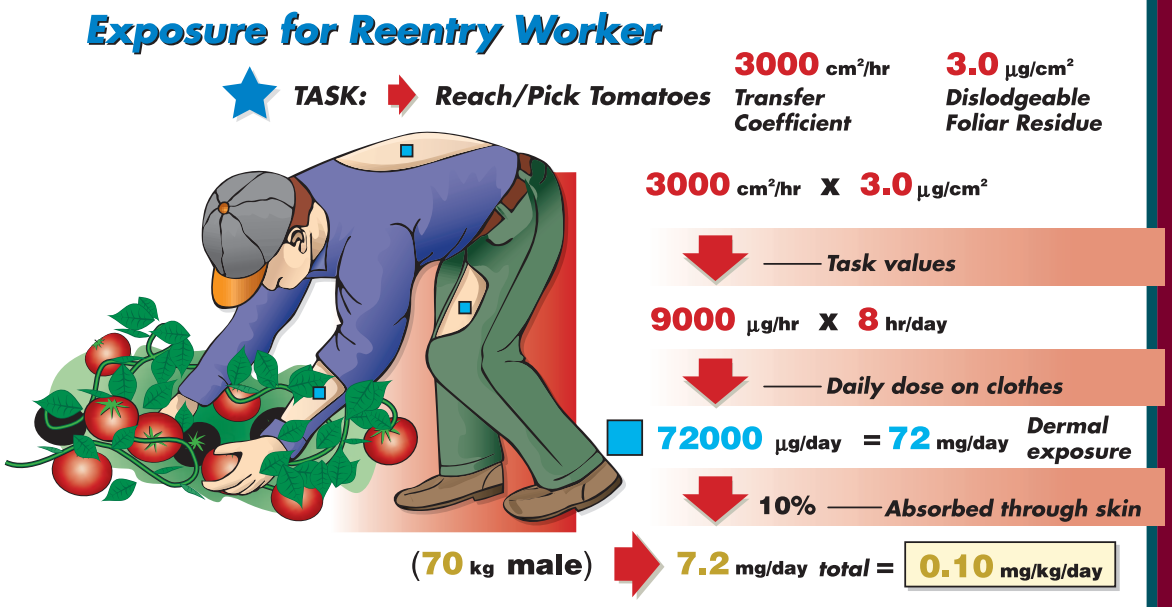
Work Task	Body Contact Areas	Crop Type	TC (cm^2/hr)
Sort/Select	Hand	Tomatoes (mechanical)	100
Reach/Pick	Hand + Arm	Lettuce	200-700
Reach/Pick	Hand + Arm + Leg	Tomatoes (pole)	1000-3000
Search/Reach/Pick	Upper Body	Tree Fruit	3000-6000
Expose/Search/ Reach/Pick	Whole Body	Grapes	8000-25000

Dermal exposure can be estimated by using generic default transfer coefficients in conjunction with chemical-specific, dislodgeable foliar residues as illustrated in the following examples. In the tomato reach-and-pick work task, the initial dislodgeable foliar residue for one pesticide was found to be 3.0 $\mu g/cm^2$, and a generic transfer coefficient of 3000 cm^2 /hr was assumed. Thus,

Total Dermal Exposure = 3.0 $\mu g/cm^2$ x 3000 cm^2/hr = 9000 μg/hour
= 8-hr work day x 9000 μg/hr = 72,000 μg/day
= 72,000 μg/day/1000 μg/mg = 72 mg/day

Residue Penetrating the Skin = 72 mg/day x 0.1 (dermal penetration) = 7.2 mg/day

Dermal Absorbed Daily Dose for a 70 kg male = 7.2 mg/day x 1/70 kg = 0.10 mg/kg/day



Case Study Exposure Assessment Using PHED

An assessment of potential exposure and risk to workers associated with occupational use of Insecticide X, an insecticide applied to corn, was performed using the following information. This example is typical of actual assessment and combines default assumptions with reliable data extracted from initial exposure assessment of the insecticide.

- Pesticide type: foliar-applied corn insecticide
- Pesticide formulation: water dispersible granules
- Pesticide use rate: maximum label rate of 0.0312 pounds active ingredient (AI) per acre
- Application timing allowed by the label: once every 14 days
- Application method: ground boom sprayer attached to a truck or tractor equipped with spray tank
- Water volume: 10–30 gallons per acre
- Based on agricultural census data, it is assumed that a 400-acre corn field is treated by a commercial applicator at the rate of 200 acres per day. The commercial applicator is assumed to handle the product 30–60 days during a 90-day period during May/June/July.
- Exposure input values:
  a. Exposures are estimated for a mixer/loader and an applicator.
  b. One hundred percent of the estimated inhaled dose is absorbed.
  c. Ten percent of the chemical that contacts the worker's skin is absorbed by the body.
  d. The insecticide is applied to 200 acres of corn per day.
  e. The individual will handle a maximum of 6.25 pounds of the active ingredient in one working day:

     (0.0312 lb active ingredient/acre x 200 acres)

- Mixer/loader exposure values:
  a. Wears clothing required by the label: long pants, long-sleeved shirt, and gloves
  b. PHED default inhalation rate is 25 liters per minute for light work activity.
  c. Exposure rates were determined from PHED, as follows:
     Inhalation Exposure = 0.68 µg/lb active ingredient
     Dermal Exposure = 93.2 µg/lb active ingredient
- Applicator exposure input values:
  a. Wears clothing required by the label: long pants and long-sleeved shirt
  b. Default inhalation rate of 25 liters per minute for light work activity
  c. Applicator exposure was estimated from PHED, as follows:
     Inhalation Exposure Rate = 1.8 µg/lb active ingredient
     Dermal Exposure Rate = 16.6 µg/lb active ingredient

Table 9. Example of Occupational Exposure Assessment Using Pesticide Handler Exposure Database

Work Scenario	Exposure Type	Exposure Per Pound Handled (µg per pound active ingredient)	Active Ingredient Handled (pounds/day)	Exposure (µg/day)	Absorbed Dose (µg/day)
Mixer/Loader	Inhalation	0.68	6.25	4	4
	Dermal	93.20	6.25	583	58
Applicator	Inhalation	1.80	6.25	11	11
	Dermal	16.60	6.25	104	10
			Total	702	83

Daily Dermal Exposure (mixer/loader) = $\frac{583\ \mu g/day}{1000\ \mu g/mg \times 70\ kg}$ = 0.0083 mg/kg/day

Daily Dermal Exposure (applicator) = $\frac{104\ \mu g/day}{1000\ \mu g/mg \times 70\ kg}$ = 0.0015 mg/kg/day

Total Daily Dermal Exposure (mixer/loader/applicator) = 0.0083 + 0.0015 = 0.0098 mg/kg/day

Absorbed Daily Dose (mixer/loader) = $\frac{62\ \mu g/day}{1000\ \mu g/mg \times 70\ kg}$ = 0.00089 mg/kg/day

Absorbed Daily Dose (applicator) = $\frac{21\ \mu g/day}{1000\ \mu g/mg \times 70\ kg}$ = 0.0003 mg/kg/day

Absorbed Daily Dose (mixer/loader/applicator) = 0.0012 mg/kg/day

RESIDENTIAL EXPOSURE ASSESSMENT

Increasingly, government and industry scientists are asked about human risk stemming from pesticide use in and around the home; e.g., indoor applications to carpet and pets and outdoor applications to turf, vegetable gardens, and ornamental plantings. A key aspect in evaluating residential exposure is recognition of the unique "properties" of the residential environment, itself, and recognition that routine home activities bring people into contact with treated areas. Residential exposure assessment involves consideration of multiple routes (oral, dermal, and inhalation) and pathways (e.g., contact with treated turf, contact with treated pets) and the source of exposure (indoors or out).

Outdoor Exposure Studies

Turf applications rate first in human exposure among outdoor pesticide uses, although applications to ornamental and landscape plantings also can pose a risk. Residues on treated surfaces such as turf can be determined by measuring dislodgeable and transferable residues. Dislodgeable residues are those that *potentially* can be transferred from a given surface. Transferable residues are those that are *actually* transferred during normal human contact with the treated surface. In pesticide use studies on turf, the highest labeled rate is applied during the time of year correlating to local use. Dislodgeable residues from samples taken just prior to application, immediately after (once residues have dried), and at various intervals for several days thereafter are measured to determine how fast the pesticide residue dissipates after application and how much of it potentially could be transferred by human contact.

Indoor Exposure Studies

Indoor assessments are complicated by the diversity of pesticide application methods. Treatments may entail crack and crevice, carpet, moth repellent, termiticide, disinfectant, and pet product applications; room foggers also may be used. Human contact with indoor pesticide residues may vary significantly: from highly unlikely with pesticides applied behind cabinets, for example, to highly probable in the case of broadcast applications to carpets for flea control. Humans may witness dermal exposure to pesticide residues on carpets, vinyl tile, upholstery, counter tops, and pets, while airborne residue and dust may cause inhalation exposure. Potential human residential exposure is influenced by the type of product used, the physical/chemical characteristics of the product, and the indoor environment: room size, air exchange rates, temperature, types of surfaces (such as carpet, upholstery, vinyl), and the nature of human activities that take place in the home.

Important Factors that Influence Residential Exposure

Key factors to consider in evaluating potential residential exposure to pesticides include the following.

Residential Building Factors

Room configuration, construction materials, and ventilation determine the probability of human exposure following indoor pesticide applications. The number of windows and doors open, the rate of mechanical ventilation and air mixing, and the rate of outside air infiltration influence the dilution of pesticide-contaminated indoor air. Climatic influences such as season and temperature also have an effect.

Demographic Factors

Infants, toddlers, and the elderly are considered more sensitive to pesticide exposure than other age groups. Other important factors include body weight, which varies among and within age and gender categories; inhalation rates, which vary primarily by age, gender, and activity level; activity patterns; and the relationship of these physiological and behavioral factors to demographics, geographic location, and time of application.

Human Activity Patterns

The ways that people are exposed to pesticides in residential settings are remarkably different from those of workers exposed on the job. Most work-related tasks are routine and repetitive; therefore, work habits that lead to worker exposure are predictable. Home activities are less routine, less repetitive, less predictable.

Infants and toddlers spend considerable time crawling and playing on floors and carpets and therefore breathe air that is nearer the floor; they wear relatively little clothing and spend more time indoors than adult members of the same family. A person exercising on a treated carpet and teenagers playing on a treated lawn are but two behaviors that can bring older family members into contact with pesticide residues.

Exposure Frequency and Duration Characteristics

Frequency (days per year, years per lifetime) and duration (minutes or hours per day) are critical in estimating residential exposure. Both factors depend on how the product is used and the kinds activities that bring individuals into contact with treated areas.

Product Characteristics

Perhaps the most important contributing factors to dermal and inhalation exposure are the nature of the pesticide product, the form in which it is released (e.g., fine respirable aerosol, nonrespirable coarse aerosol, vapor), the concentration of the active ingredient, the formulation, and the method of application.

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Outdoor Residential Exposure Task Force

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Physical and Chemical Properties

Several factors are important with respect to the physical and chemical properties of the pesticide: molecular weight; vapor pressure (Does it release as a vapor, and how quickly?); solubility in fat and water; and breakdown to other chemicals. These factors determine the chemical rate of evaporation into the air, after application, and how much of the pesticide actually will transfer from carpet to hands—and from hands to mouth, in the case of young children.

Exposure Pathways and Routes

Key exposure routes and pathways routinely considered for adults, children, and infants following either indoor or outdoor residential pesticide use:

- potential consumer exposure (dermal and inhalation) during application
- potential post-application dermal exposure
- potential post-application inhalation exposure
- potential post-application, nondietary, incidental oral exposure (e.g., from toys or hand-to-mouth transfer)

Incidental ingestion of soil, grass, and other environmental media also may be considered. Incidental ingestion of surface residues via the hands is based on the assumed transfer of residue from surface to hands to mouth. Inherent to this assumption is that children, through mouthing the hands (or contaminated objects), can remove and ingest pesticide

residues. The uncertainty associated with the frequency of hand- or object-to-mouth behavior must be acknowledged explicitly. Studies generally show that the conservative, screening-level exposure estimates of potential incidental ingestion are exaggerated as compared to estimates derived via hand rinse and wipe monitoring data.

It is important to acknowledge that current direct and indirect monitoring data do not suggest that hand- or object-to-mouth transfer and incidental ingestion are significant routes of exposure. Additional data are needed to better define the variability and uncertainty of residue transfer from treated surfaces to hands (wet or dry) to mouth.

Product Use Patterns

Monitoring data must be considered with label and use information such as application rate, method of application, site of application, timing, and frequency of application to gain an understanding of residential exposure. Oral, dermal, and inhalation exposure may be calculated separately or combined as a single estimate of systemic exposure or absorbed dose.

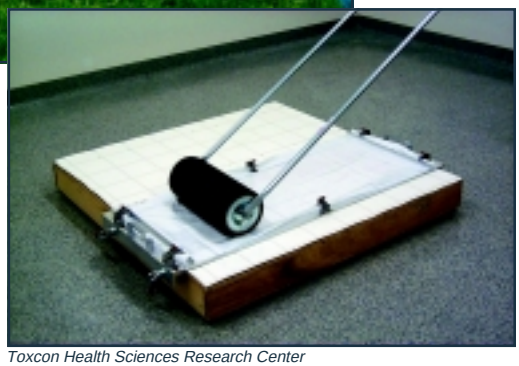
Techniques Used in Monitoring Residential Exposure

There are several methods for measuring residential exposure using external dosimetry and/or biological monitoring.

Compliance Assessment and Training Services

Indoor and Outdoor Rollers

The roller technique typically constitutes use of a polyurethane foam (PUF) pad placed over a metal roller which holds the PUF in place. Transferable residues are measured by pushing the roller in two directions over a portion of the treated area. Inside the roller is a premeasured weight that provides consistency in pressure as it rolls across a treated carpet or lawn. When sampling is complete, the foam is removed from the roller and the pesticide residue quantified.



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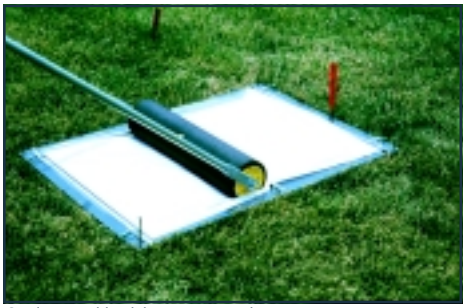

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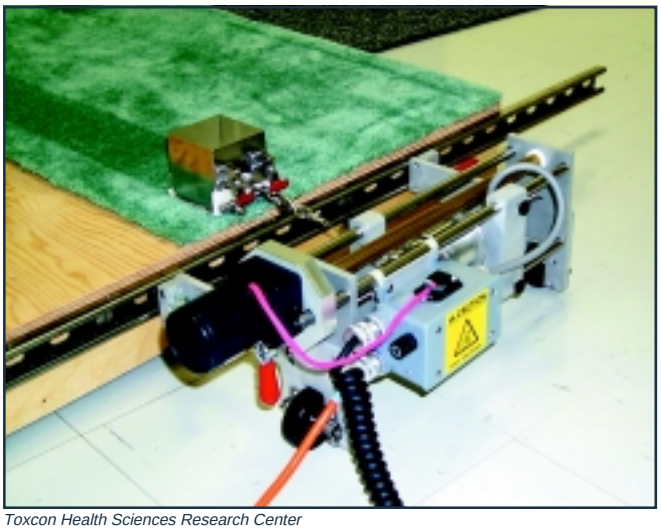
An alternate method is to place a sheet of cloth over the carpet or lawn and push the metal roller across it; the cloth is then analyzed for pesticide residue.



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Drag Sleds

A drag sled is a weighted block with a removable cotton (denim) dosimeter attached to the bottom surface. The sled is dragged across a predefined treated area and the denim analyzed for pesticide residue.

Hand Presses

Adult subjects press their hands with predetermined force against a treated surface. The hands are immediately wiped or washed in a solvent such as isopropanol and the solvent analyzed for pesticide residue.

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Coupons

Coupons made of cotton, aluminum foil, or glass are placed throughout the area to be treated, then collected for quantification periodically during the pesticide application. Those collected immediately following application can be used to estimate the amount of pesticide deposited per unit of surface area treated; and those collected and analyzed, later, can provide information on the rate of degradation of the pesticide. Fresh coupons placed *following* application can be used to measure movement and repositioning of residues.

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Area and Personal Air Monitoring

Stationary air sampling devices measure airborne contamination throughout a treated house. They are strategically placed in kitchens, basements, bedrooms, and family rooms to measure pesticide movement throughout the home. Each device has a pump that draws air through a pesticide-extracting charcoal or resin filter. Samples are taken near the floor; at heights representative of a child's breathing area; and at heights representing adults' breathing space, seated and standing. Indoor air concentrations of the pesticide are measured during application and repeated several times during the first 24 hours, then less frequently. Personal air samples measure contamination levels in the breathing zone of individual household members. Personal sampling pumps generally are clipped to the shirt collar to measure the amount of pesticide residue in air reaching the mouth and nose.

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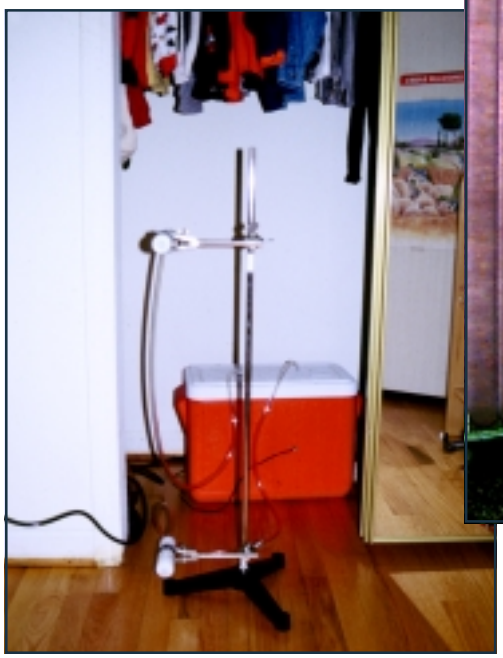

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Human Volunteer Monitoring Studies

Human volunteer monitoring studies often involve the use of whole body dosimeters, air sampling, or biological monitoring methods. Although study designs vary, volunteers' activities are documented. Choreographed activities such as crawling across a treated carpet facilitate researchers' ability to relate environmental measurements to actual human exposure.

Jazzercise™ routines have been used to measure inhalation and dermal exposure following pesticide treatment.

California Environmental Protection Agency

California Environmental Protection Agency

Jazzercise™ is an exercise program consisting of a set number of 3-minute routines led by certified instructors. The exercises selected are those that bring volunteers into repeated intensive contact with a pesticide-treated surface such as carpeting. Adult volunteers are provided a complete set of cotton underclothing and outerwear. They are assigned to specific areas within the treated room where they perform the exercise routines. At the conclusion of the program, volunteers place their clothing into separately marked plastic bags for chemical analysis.

Case Study of Residential Exposure Assessment

The following sample calculations are representative of methods used to assess same-day, post-application exposure of children 1–6 years old. Similar methods are used for assessing exposure of other population subgroups.

Label Directions and Product Use Information

The product used in this example is Insecticide X, formulated as a 6-ounce fogger. Instructions for this product indicate the following:

- The fogger will treat up to 6000 cubic feet of unobstructed space (i.e., a room with approximate dimensions of 26′ x 30′ x 8′).
- Only one container should be used in rooms 12′ x 12′ x 8′ or smaller.
- The fogger should not be used in areas less than 100 cubic feet.
- Insecticide X should not be used in serving areas where food could be exposed.
- The user is instructed to open cabinets and doors in the treatment area; remove or cover exposed food, dishes, and food-handling equipment and surfaces; remove pets and plants; shut off fans and air conditioners; and close doors and windows.
- The user is instructed to keep the treated home closed for 2–3 hours before reentering.
- Prior to reoccupying the treated area, the user should ventilate the area by opening all doors and windows for 30 minutes.

Potential Post-Application Exposure of Children 1–6 Years Old by Inhalation of Airborne Aerosols

For the purpose of estimating potential "day of application" inhalation exposure to the insecticide, the airborne concentration estimate is based on the results of a total release fogger exposure monitoring study. In the current example, when the consumer is instructed to reenter the home 2–3 hours after application, the mean indoor air concentration equals the analytical detection limit of 0.000175 mg/m^3. Based on the fact that samples corresponding to the time of reentry were at or below the detection limit, the average aerosol air concentration value of 0.000175 mg/m^3 is used to represent the highest potential airborne exposure.

The equation for estimating potential inhalation exposure and absorbed dose is developed as follows.

CP: Concentration of Product (active ingredient in mg/m^3)

As noted previously, a conservative estimate of post-application air concentration is 0.000175 mg/m^3.

IR: Inhalation Rates (m^3/hr)

Inhalation rates are affected by numerous individual characteristics including age, gender, weight, health status, and level of activity (e.g.,

sleeping, walking, running, jogging). EPA'S *Exposure Factors Handbook* (www.epa.gov/ncea/expofac.htm) reviews studies that provided inhalation rates at various activity levels. The handbook summarizes the average number of hours per day spent resting and performing various levels of activity (light, moderate, and heavy). For this sample assessment, the inhalation rate for children is estimated at 0.47 m^3/hr.

CCF: Concentration Correction Factor (unitless)

This factor adjusts air concentration based on a comparison of the amount of active ingredient released from the product being evaluated to the amount released in previous studies. This assumes that all other factors that affect air concentrations (temperature, air exchange, etc.) remain the same as those recorded during the monitoring study. For this example, the 6-ounce fogger releases 1.87 times the amount used in a surrogate fogger study.

PAF: Pulmonary Absorption Factor (percentage)

A default value of 100 percent absorption generally is used; that is, 100 percent of the chemical entering the lungs is assumed to be absorbed by the respiratory system.

ED: Exposure Duration (hours/day)

Air monitoring data suggest that aerosols are airborne for approximately 2 hours following use of a fogger. This assessment assumes that 2 hours is a reasonable estimate of exposure.

BW: Body Weight (kg)

The mean body weight of male and female children 2–7 years old (EPA's *Exposure Factors Handbook)* is 18.9 kg. The post-application inhalation daily exposure and absorbed daily dose for children is calculated as follows.

$$\text{Inhalation Daily Exposure} = \frac{(CP) \times (IR) \times (CCF) \times (ED)}{BW}$$

$$\text{Inhalation Daily Exposure} = \frac{(0.000175\ mg/m^3) \times (0.47\ m^3/hr) \times (1.87) \times (2\ hr/day)}{18.9\ kg}$$

$$\text{Inhalation Daily Exposure} = 0.000016\ mg/kg/day$$

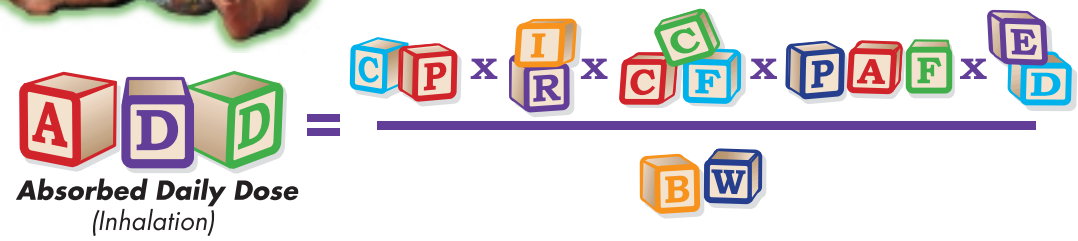
$$\text{Inhalation Absorbed Daily Dose} = \text{Inhalation Daily Exposure} \times PAF$$

$$\text{Inhalation Absorbed Daily Dose} = (0.000016\ mg/kg/day) \times (1.0)$$

$$\text{Inhalation Absorbed Daily Dose} = 0.000016\ mg/kg/day$$

Post Application Exposure From Inhalation

CP: How much product is in the air?
IR: How much air does the child breathe?
CCF: How does the product compare with others?
PAF: How much is absorbed by the lungs?
ED: How long was the child exposed?
BW: How much does the child weigh?



Potential Post Application Exposure of Children 1–6 Years Old from Dermal Contact with Treated Surfaces

The Jazzercise™ study method was used for estimating potential day-of-application dermal contact with floor surfaces. The procedure for estimating potential dermal exposure is based on the use of transfer factors from indoor rollers.

The general equation for estimating potential dermal exposure and absorbed dose is as follows.

Sum: Total Dermal Exposure

This exposure summation represents the combination of body-specific transfer factors (TF), transferable residues (TR), and surface area (SA). A dislodgeable chemical residue is the portion deposited on a solid surface, which may be dislodged by direct contact to human skin or clothing: the maximum amount potentially available on a given day.

A transferable pesticide residue is the amount that can be removed from a treated surface onto other objects, including humans. The scenario for infants and children assumes nakedness; thus, the TFs and SAs used in these calculations are for uncovered body areas. The clothing scenario used for dermal exposure calculations resulted in the following estimations of body surfaces.

Surface Areas for Clothing Scenarios Used in Dermal Exposure Calculations for Children

Body Part	Children 1-6 Years Old cm^2
Arms (uncovered)	1085
Upper Body (uncovered)	1615
Legs (uncovered)	1650
Lower Body (uncovered)	1220
Hands (uncovered)	452
Feet (uncovered)	553

As an example, the total dermal exposure (mg) *summation* calculation (summed across TF x TR x SA for each body part) for children is as follows.

Table 10. Dermal Exposure Calculation for Children

Body Area	TF Unitless	TR mg/cm^2	SA cm^2	Dermal Exposure mg
Arms + Upper Body	2.4	0.0000064	2,700	0.0415
Legs + Lower Body	2.4	0.0000064	2,870	0.0440
Hands	12.6	0.0000064	452	0.0364
Feet	13.6	0.0000064	553	0.0481
			Total	0.1700

The TF for each body part and the mean TR estimates used in this example were obtained from a study published by the California Department of Pesticide Regulation.

CF: Dermal Experimental Correction Factor

The dermal experimental correction factor adjusts the milligrams of dermal exposure (derived from summation calculations previously described) based on the amount of active ingredient released from the product used in the surrogate dermal monitoring study versus the amount of active ingredient released from the product being evaluated.

The product assessed in this example released 1.87 times the active ingredient released in the California reference study.

DAF: Dermal Absorption Fraction for Active Ingredient (unitless)

It is assumed for this example that 10 percent of the pesticide on the skin is absorbed into the body.

BW: Body Weights for Children (kg)

The mean body weight for male and female children (2–7 years old) is 18.9 kg (EPA *Exposure Factors Handbook).*

Post Application Exposure from Dermal Contact

SUM: How much residue is transferred to the skin?
CF: How does the product compare with others?
DAF: How much product absorbs into the body?
BW: How much does the child weigh?

Absorbed Daily Dose (Dermal) = (SUM x CF x DAF) / BW

Post-Application Dermal Daily Exposure and Absorbed Daily Dosage is calculated as follows:

$$\text{Dermal Daily Exposure} = \frac{(\text{Sum}) \times (\text{CF})}{\text{BW}}$$

$$\text{Dermal Daily Exposure} = \frac{0.17 \text{ mg} \times 1.87}{18.9 \text{ kg}} = 0.017 \text{ mg/kg/day}$$

Dermal Absorbed Daily Dose = Dermal Daily Exposure x DAF

Dermal Absorbed Daily Dose = (0.017 mg/kg/day) x (0.1)

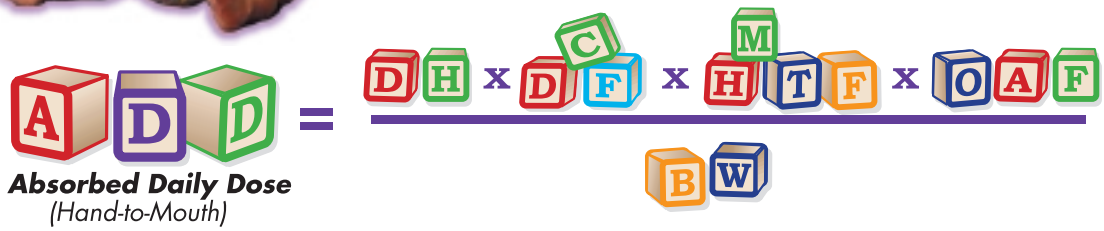
= 0.0017 mg/kg/day

Potential Post-Application Exposure of Children Aged 1–6 by Hand-to-Mouth Transfer from Treated Surfaces

Hand-to-mouth transfer residue data from 20 minutes of Jazzercise™ is used as a surrogate. It is substantiated by a study involving broadcast

Post Application Exposure from Hand-to-Mouth Contact

- **DH:** How much exposure was estimated for the hands?
- **DCF:** How does the exposure compare with others?
- **HMTF:** How much was transfered from hands to mouth?
- **OAF:** How much is absorbed orally?
- **BW:** How much does the child weigh?



application to carpets, with attention to post-application inhalation as well as dermal exposure monitoring and biomonitoring. Usual child activities (playing with blocks, crawling, walking, etc.) were performed by adult volunteers over a four-hour period. Comparison of hand-rinse data to residues transferred onto glove dosimeters revealed remarkably similar totals.

The general equation for estimating potential dermal exposure to hands and subsequent incidental oral exposure or absorbed dose is as follows.

DH: Daily Dermal Exposure to Hands (mg/day)

Hand exposure estimates represent a combination of the hand transfer factor (TF), transferable residue (TR), and hand surface area (HSA):

$$DH = TF \times TR \times HSA$$

Daily dermal exposure to hands is calculated as 0.0364 mg.

DCF: Dermal Experimental Correction Factor (unitless)

The DCF adjusts milligrams of dermal exposure (derived from summation calculations as previously described) based on the amount of

active ingredient released from the surrogate dermal monitoring study versus the amount of active ingredient released from the product being evaluated. The product assessed in this example released 1.87 times the active ingredient released in the California reference study.

HMTF: Hand-to-Mouth Transfer Factor (unitless)

Hand-to-mouth transfer estimation for children and infants is based on data from hand-wash removal efficiency studies. The data for lipophilic compounds suggest that water-only rinsing of hands results in less than 5 percent removal. In contrast, more rigorous solvent-based rinsing removes 20–40 percent of the pesticide. So incidental oral exposures are based on the assumption that approximately 10 percent of residues on hands are transferred to the mouth and subsequently ingested as a result of hand-to-mouth behavior among children.

OAF: Oral Absorption Fraction for Active Ingredient (unitless)

An oral (gastrointestinal) absorption factor of 100 percent is used as a default assumption.

BW: Body Weight (kg)

The mean body weight across male and female children aged 2–7 is 18.9 kg (from EPA's *Exposure Factors Handbook).*

Post-application Oral Daily Exposure and Absorbed Daily Dose is calculated as follows:

$$\text{Oral Daily Exposure} = \frac{(DH) \times (DCF) \times (HMTF)}{BW}$$

$$\text{Oral Daily Exposure} = \frac{(0.0364 \text{ mg/day}) \times (1.87) \times (0.1)}{18.9 \text{ kg}}$$

$$= 0.00036 \text{ mg/kg/day}$$

$$\text{Oral Absorbed Daily Dose} = \text{Oral Daily Exposure} \times OAF$$

$$\text{Oral Absorbed Daily Dose} = 0.00036 \text{ mg/kg/day} \times 1 = 0.00036 \text{ mg/kg/day}$$

RISK CHARACTERIZATION

The final step in risk *assessment* is risk *characterization,* which involves integration of toxicological data with exposure data to estimate the level of human risk. Risk characterization also includes a description of assumptions and uncertainties that go into the evaluation of risk.

Approaches to risk characterization differ, depending on whether the toxicity end point of concern has a threshold. It is generally assumed that most types of toxic effects have thresholds below which adverse effects will not occur. Other types, such as genotoxic carcinogens, often are assumed to have no threshold; i.e., there is some probability of harm at any level of exposure.

Risk Assessment for Threshold Effects

For threshold effects, risk assessments normally are conducted by utilizing a Margin of Exposure (MOE) or a Reference Dose (RfD) approach. In the MOE approach (known outside the U.S. as the Margin of Safety), the anticipated human exposure level is compared to the lowest NOAEL from an appropriate toxicology study.

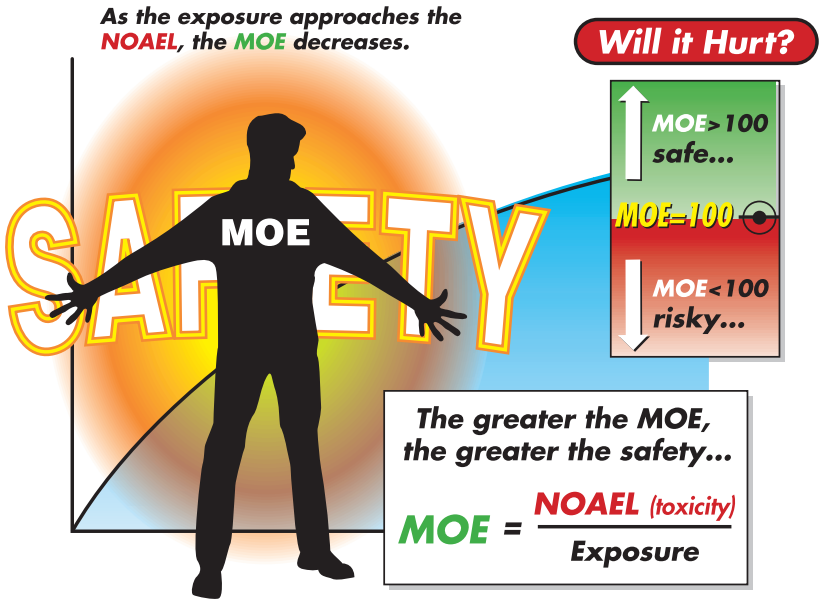
$$\text{Margin of Exposure} = \frac{\text{No Observed Adverse Effect Level}}{\text{Estimated Human Exposure}}$$

Example: If the NOAEL is 30 mg/kg/day and the estimated human exposure is 0.5 mg/kg/day, the MOE is 60:

$$\text{Margin of Exposure} = \frac{30 \text{ mg/kg/day}}{0.5 \text{ mg/kg/day}} = 60$$

Important considerations in selecting a study from which the NOAEL is derived are as follows:

- Animal model used
- Type of study



- Study design
- Route of administration
- Study duration

Ideally, the route of administration and study duration should be comparable to those of the human exposure scenario being evaluated. Depending on the pesticide's uses, NOAELs from several different studies may be utilized in a comprehensive risk assessment.

After a thorough review of toxicology data, critical toxicological end points were identified for use in assessing potential risks of Insecticide X with both agricultural and residential uses (see Table 11, p. 65).

The greater the MOE, the greater the degree of safety. In general, an MOE should be at least 100 if the NOAEL is derived from an animal study; it should be at least 10 if the NOAEL is derived from human data. An MOE of 100 means that the estimated level of human exposure is 100 times lower than the highest dose that produced no adverse effects in the toxicology study. Larger MOEs may be required under certain conditions: for example, if there are concerns about the quality or completeness of the database or about possible increased sensitivity of infants or children.

The Reference Dose (RfD) approach is similar to the MOE approach except that the anticipated human exposure level is compared to the appropriate RfD instead of the NOAEL. RfD is defined as the estimated human exposure level believed to have no adverse impact on human health. A chronic RfD (also called the Acceptable Daily Intake) is defined as the level to which a human can be exposed every day for a lifetime without experiencing adverse effects. More recently, acute RfD's—that is, estimates of the amount of pesticide to which an individual can be exposed in one day without experiencing adverse health effects—also have been established.

Table 11. Critical Toxicological End Points (NOAELs) Identified for Use in Risk Assessment for Insecticide X

Exposure Scenario	Appropriate Toxicological Study	NOAEL
Acute dietary	acute rat neurotoxicity	25 mg/kg/day
Chronic dietary	2-year rat feeding	1 mg/kg/day
Short-term (1–7 days) and intermediate (1 week to several months) inhalation	28-day rat inhalation	3 mg/cubic meter (0.003 mg/liter, or ca. 0.235 mg/kg/day)
Short-term and intermediate dermal	21-day rat dermal	250 mg/kg/day
Chronic dermal and inhalation	2-year rat feeding (assuming 100% inhalation and 10% dermal absorption)	1 mg/kg/day
Short-term and intermediate (multi-route, systemic)	90-day dog feeding study (assuming 100% oral absorption)	15 mg/kg/day

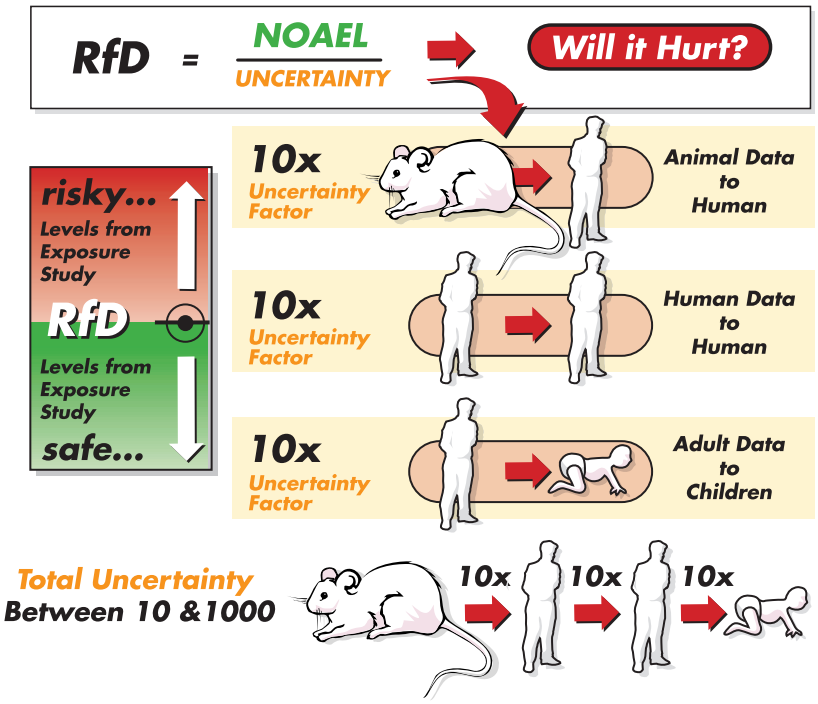
RfD's are calculated by dividing the lowest NOAEL from an appropriate toxicology study on the most sensitive animal species (or humans) by the appropriate *uncertainty factors* (also referred to as *safety factors*).

$$\text{RfD} = \frac{\text{No Observed Adverse Effect Level}}{\text{Uncertainty Factors}}$$

Uncertainty factors are established by EPA policies. Most commonly, uncertainty factors of 10x each are applied to account for *inter*species extrapolation (animals to humans) and intraspecies variation (differences among humans), for a total uncertainty factor of 100. Additional uncertainty factors of 3–10x each also may be applied to account for lack of an appropriate NOAEL or an incomplete toxicity database, or, as a result of FQPA, to provide additional protection for infants and children. The total uncertainty factor can range from 10x (if the NOAEL is derived from a human study) to 10,000x, although it rarely exceeds 1000x. The division of the NOAEL by these uncertainty factors provides reasonable assurance that exposure to the chemical at a dose less than or equal to the RfD will not pose significant human risk.

Consider the following factors in calculating an RfD:

- NOAEL of 200 mg/kg/day from a rat development toxicity study
- NOAEL of 50 mg/kg/day from a rabbit developmental toxicity study



- NOAEL of 100 mg/kg/day from two-generation rat reproduction study
- NOAEL of 75 mg/kg/day from a one-year dog feeding study
- NOAEL of 25 mg/kg/day from an 18-month mouse feeding study
- NOAEL of 10 mg/kg/day from a two-year rat feeding study

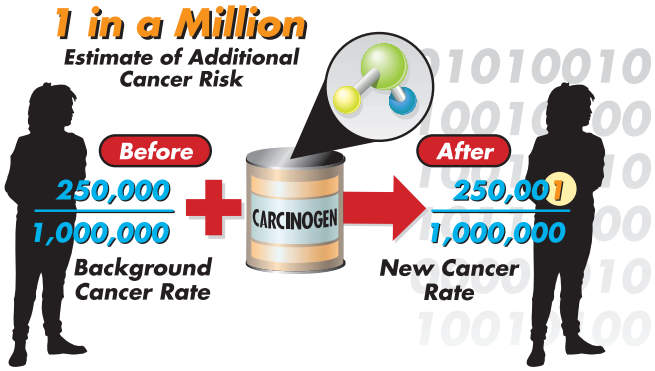
In this case the RfD generally would be calculated as 0.1 mg/kg/day, utilizing the lowest NOAEL (10 mg/kg/day from the 2-year rat feeding study) and a 100-fold safety factor.

Unacceptable MOEs or estimated exposures greater than the RfD indicate that

- a more refined exposure assessment needs to be completed;
- mitigation measures need to be used (e.g., use of a different formulation, protective clothing, enclosed tractor cabs, and longer reentry intervals);
- the product should not be registered;
- the product should be taken off the market (if previously registered).

Risk Assessment for Non-Threshold Effects

EPA regulates carcinogens and considers cancer to be a non-threshold effect. Therefore, cancer risk assessment in the United States usually does not compare anticipated human exposure levels to an RfD, nor is an MOE determined. Instead, assessment provides an estimate (expressed as a probability) of the excess risk of cancer resulting from exposure to the pesticide. For instance, a calculated risk of 1×10^{-6} (1 in 1,000,000) means that a person would have no more than a one-in-



a-million chance of developing cancer in excess of the background incidence in the general population. This level of excess cancer risk generally is considered acceptable for the general public, while higher estimated levels such as 1 x 10^{-5} (1 in 100,000) or even 1 x 10^{-4} (1 in 10,000) may be considered acceptable for some occupational exposures.

Using Mathematical Models to Predict Cancer Risks

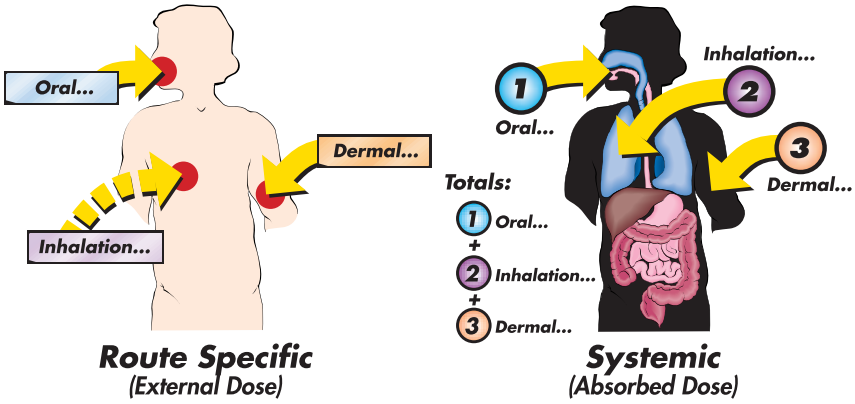
In the United States, the potential carcinogenic risk to humans from exposure to carcinogens is most often estimated using mathematical models. All mathematical models used for cancer risk assessment extrapolate from high dose levels used in animal studies to much lower human exposure levels. But results of extrapolation can differ substantially, depending on the model used. The slope of the dose-response curve calculated by models that assume linearity at low dose often is used to describe cancer potency: the steeper the response curve, the more potent the carcinogen. Since there is always some uncertainty associated with the calculated dose-response curve, there is always a chance that the slope of the true dose-response curve could be higher or lower than calculated. Statisticians have developed methods that allow estimation of both the upper and lower limits of the calculated dose-response curve. Thus, statisticians say that the true dose-response curve will fall somewhere between the lower and upper estimates 95 percent of the time.

The upper estimate of tumor potency (often referred to as q*, pronounced “q-star”) developed by mathematical models is most frequently reported as the most conservative and produces the highest estimation of potential risk. However, the lower estimation of risk, which can be zero, has the same chance as the upper estimate of being the *true* estimate of risk. So in order to provide an unbiased assessment and an indication of uncertainty of the derived estimate, risk assessment must yield the most likely estimate of risk as well as the upper and lower estimates.

For example, the best estimate of cancer risk from lifetime exposure to a 1 mg/kg/day dose of an animal carcinogen might be 1 x 10^{-8}, (1 in 100,000,000) with upper and lower estimates of 1 x 10^{-6} and zero, respectively. In other words, 95 times out of 100 the true risk of cancer from such exposure will fall somewhere between zero and 1 x 10^{-6}. EPA focuses and regulates conservatively on the upper estimate. In this example, risk is calculated as one in a million instead of one in 100 million.

Route-Specific and Systemic Risk Assessment

Dietary risk assessment is more straightforward than occupational or residential risk assessment. It involves evaluating potential risk from single-route exposure similar to that used to generate most toxicology data. Dietary risk assessment generally is conducted by comparing



estimated dietary exposure to results from toxicology studies in which the pesticide was administered orally (diet, stomach tube, or capsule). On the other hand, occupational and residential risk assessment usually involves evaluating multiple routes of exposure: dermal; inhalation; and, particularly for residential exposure to children, incidental oral ingestion.

Two different approaches can be used to assess potential risk from multiple sources of exposure: a route-specific approach, as in dietary risk assessment; and a systemic (oral equivalent) dose approach. Each has its advantages and disadvantages.

In a route-specific risk assessment, the estimated dermal or inhalation exposure is compared to the appropriate end point from a toxicology study in which a comparable route and duration of exposure were used. For example: A farm worker who uses pesticides for a few weeks each year is at risk of exposure. The potential for dermal exposure during application or reentry can be evaluated by comparing his estimated exposure level to the NOAEL from a 21- or 90-day dermal toxicity study.

Similarly, potential risk from repeated inhalation exposure can be compared to the NOAEL from a 28- or 90-day inhalation study. If the toxic effect is the same regardless of the route of exposure, potential risk from occupational and residential exposure also can be assessed on a systemic basis.

In systemic risk assessment, the total amount of pesticide absorbed into the body via combined dermal, inhalation, and/or oral exposure is calculated as (and compared to) a systemic (or oral equivalent) NOAEL probably derived from a subchronic feeding study.

The advantages of route-specific risk assessment are that

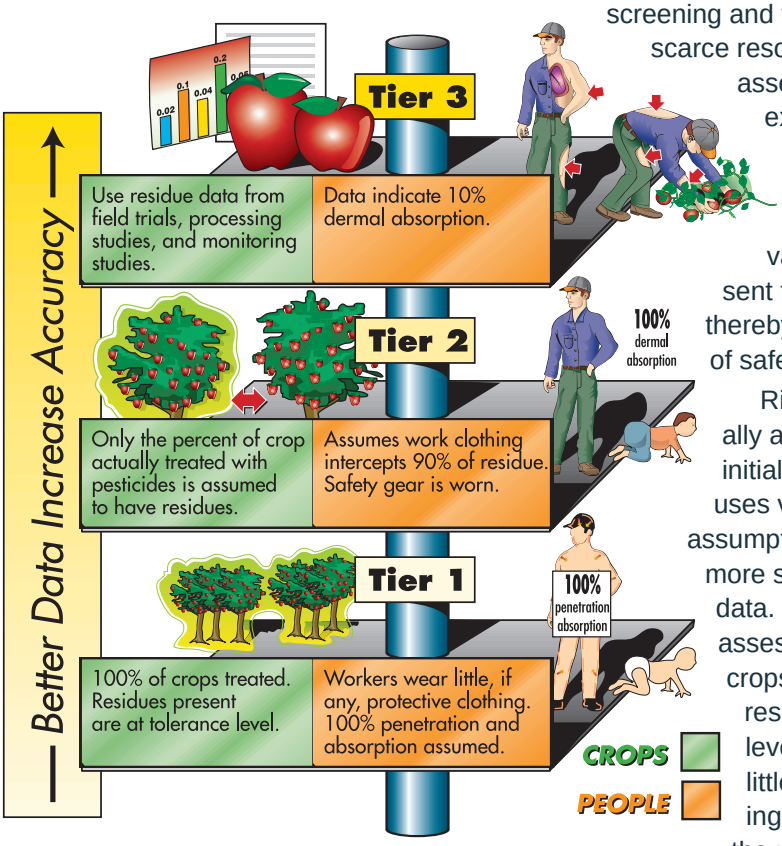
- it accounts for possible differences in the way chemicals behave among various routes of exposure, and

- it can be used even if the most sensitive toxic end point differs, depending on the route of exposure.

Most toxicity studies are based on oral exposure; few are based on dermal or inhalation exposure. Thus, route-specific toxicity data of appropriate duration may not always be available for the occupational or residential exposure scenario in question. Conversion of all exposures to systemically absorbed or oral equivalents offers two advantages: considering all exposures simultaneously, and comparing them to a more comprehensive toxicity database. Ideally, the systemic method requires knowing the rate or percentage of dermal pesticide absorption or inhalation. As a default, dermal and inhalation absorption often are assumed to be 100 percent and to occur at the same rate as oral absorption. The decision whether to use route-specific or systemic risk assessment methodology generally depends on the proposed exposure scenario and the toxicity data available.

Review of Risk by Tiers or Step-Wise Analysis

It is common for regulatory authorities to screen for pesticides by using conservative, worst-case estimates of exposure. This expedites screening and facilitates the budgeting of scarce resources. Worst-case assessments exaggerate exposure, yielding higher estimates than would actual exposure. They are considered "conservative" in that they represent the worst case scenario, thereby affording a wide margin of safety.



Tiered Approach to Risk Assessment

Risk assessment is generally a multi-tiered process. The initial or Tier 1 risk assessment uses very conservative "default" assumptions in the absence of more specific, reliable exposure data. For example, Tier 1 assessments assume that all crops are treated; that all residues reach tolerance levels; that workers wear little, if any, protective clothing; and that 100 percent of the pesticide that contacts the skin is absorbed. Dietary, residential, and/or occupational exposure

estimates calculated under these conditions may be hundreds or thousands of times higher than actual exposure. However, if the risk estimates from these conservative assumptions are considered acceptable, no further evaluation is necessary.

Initial risk calculations that do not yield acceptable risk estimates using default assumptions do not necessarily indicate excessive risk. Rather, they indicate the need to incorporate more detailed and reliable data for key parameters: frequency, duration, and magnitude of exposure. It is important to remember that adjustments made by exposure analysis do not change actual exposure; they simply modify *estimates* of exposure. And the resulting, more realistic exposure estimates form the basis for higher tier analysis.

The greater the concern for risk posed by a pesticide, the greater the need to replace default assumptions with more reliable data. Only when refined, upper tier risk assessments yield unacceptable risk is there true cause for concern.

The Tiered Approach to Risk Assessment

Following is an example of a multi-tiered approach to dietary risk assessment; a similar approach can be used in occupational and residential assessment.

Tier 1

In an initial risk assessment using conservative default assumptions of 100 percent crop treated and all residues present at the tolerance level, the TMRC's for five pesticides are calculated to be

- 0.001 mg/kg/day for pesticide A,
- 0.01 mg/kg/day for pesticide B,
- 0.1 mg/kg/day for pesticide C,
- 1.0 mg/kg/day for pesticide D, and
- 3.0 mg/kg/day for pesticide E

Although most pesticides have different chronic RfD's, for simplicity it is assumed that the RfD for each of the five chemicals is the same: 1.0 mg/kg/day. The 1.0 mg/kg/day chronic reference dose is compared to the total amount of each pesticide consumed. Individual dietary consumption of pesticides A, B, and C is substantially below the chronic RfD; thus, it is assumed that dietary consumption of these pesticide residues will not cause adverse human health effects.

Pesticide D results are borderline, so it does not pass Tier 1 risk assessment. And the possibility that Pesticide E may pose dietary risk to humans cannot be excluded since the Tier 1 estimated consumption exceeds the chronic RfD. Therefore, both pesticides D and E are candidates for Tier 2 risk assessment.

Tier 2

In Tier 2, only the percentage of crops actually treated are assumed to contain residues. In this example, TMRCs for pesticides D and E are 1.0 and 3.0 mg/kg/day, respectively. However, if data were available to indicate that not more than 50 percent of labeled crops are in fact treated, the assumed ARCs would be 0.5 and 1.5 mg/kg/day, respectively. Thus, the anticipated dietary exposure to Pesticide D (0.5 mg/kg/day) is clearly below the chronic RfD of 1.0 mg/kg/day, and no further refinement of the risk assessment process is needed. Pesticide E is a candidate for a Tier 3 assessment, however, since its potential exposure (1.5 mg/kg/day) exceeds the RfD.

Tier 3

In Tier 3 risk assessment, anticipated residues are even further refined by using residue data from field trials, processing studies, and/or monitoring studies.

In this example, data indicates that Pesticide E readily degrades during storage, and that much of the residue is removed during handling or washing of fruits and vegetables prior to distribution to grocery stores. Based on these data, the ARCs from pesticide E are further reduced to 0.14 mg/kg/day, which is well below the RfD. Thus, the use of ARCs that incorporate better data allows risk assessors to conclude that there is no unreasonable risk from consuming foods from crops treated with this pesticide.

Dietary Risk Assessment

Organization of food consumption data may vary, depending on the purpose of the dietary exposure analysis. And the purpose of analysis may vary according to whether the toxicological effect under consideration is chronic (long-term) or acute (short-term).

In assessing dietary exposure to the chronic toxicological effects of pesticides, most regulatory authorities consider some measure of typical food intake, such as mean or median food consumption values. But for compounds that might be acutely toxic, it is important to know if the dietary intake over a relatively short period of time (such as a day) is safe. By examining exposure at such an extreme, acute assessment protects the safety of people who ingest more pesticide residues than virtually anyone else in the population.

Acute Dietary Risk

Acute dietary risk is evaluated with the MOE or the acute RfD (aRfD) approach. The toxicity end point for acute dietary risk assessment must yield the toxic effect after only one or two exposures. In most cases, end points are derived from either acute neurotoxicity or developmental toxicity studies.

The exposure estimate in acute risk assessment is intended to represent the highest amount of residue that an individual is likely to consume in a single day. In a Tier 1 acute risk assessment, it is assumed that all commodities for which a pesticide tolerance is established contain residues at the tolerance level. In subsequent tiers, the highest residue level observed in field trials, monitoring data (only if the samples aren't pooled or composited), or market basket surveys is used to estimate residues for commodities consumed as a single item (e.g., apple,orange, banana, potato). Adjustments for percentage of crop treated and the use of average rather than maximum residue levels help in estimating residues in blended commodities such as corn oil, flour, juice, and milk; since these items are derived from multiple crops, it is unlikely that all were treated with the pesticide.

A distribution of single-day exposures is calculated for acute dietary assessment, based on the distribution of individual consumption values within the population. The MOE is then calculated for each of those exposure values, yielding a distribution of MOEs for the population. The results of acute dietary risk assessment are presented as the MOE for a specified percentiles (such as the 95th, 99th, or 99.9th) of the population subgroup of interest. Alternatively, the results can be expressed as a percentage of the acute RfD.

Table 12 shows the output from a Tier 1 acute dietary risk assessment for the U.S. population for Insecticide X. The estimated exposures indicate complete distribution as summarized in Table 5 (p. 30). The acute oral toxicity end point for Insecticide X is a NOAEL of

Table 12. Tier 1 Acute Dietary Risk Assessment for Insecticide X

U.S. Population Percentile	Exposure (TMRC; mg/kg/day)	Percent Acute RfD (aRfD = 0.25)	Margin of Exposure (NOAEL = 25 mg/kg/day)
10th	0.000186	0.1	134,409
20th	0.000381	0.2	65,617
30th	0.000629	0.3	39,746
40th	0.000992	0.4	25,202
50th	0.001583	0.6	15,793
60th	0.002644	1.1	9455
70th	0.004591	1.8	5445
80th	0.008122	3.2	3078
90th	0.014371	6.7	1740
95th	0.022468	9.0	1113
97.5th	0.032846	13.1	761
99th	0.049183	19.7	508
99.5th	0.064399	25.8	388
99.75th	0.079281	31.7	315
99.9th	0.103411	41.4	242

25 mg/kg/day (Table 11, p. 65) from an acute rat neurotoxicity study utilizing a 100-fold uncertainty factor, and an acute reference dose (aRfD) calculated as 0.25 mg/kg.

Exposure at the 90th percentile of the population is 0.014371 mg/kg/day, or less, and accounts for 6.7 percent of the acute reference dose. Exposure of the remaining 10 percent of the population, then, is at least 0.014371 mg/kg/day. If an MOE had been less than 100 or the exposure greater than the RfD, further refinements would be necessary, i.e., more precise and/or reliable estimates of exposure would be needed to demonstrate adequate margins of safety. If the MOE or the RfD percentage remained unacceptable after refinement, various mitigation steps would have to be taken to reduce exposure.

Chronic Dietary Risks

Potential risk from chronic dietary exposure to pesticide residues is estimated by comparing average residue consumption and the chronic RfD. Risk is considered acceptable as long as the estimated exposure level is less than (or equal to) the RfD. If the pesticide is a non-threshold carcinogen, an estimated cancer risk potential would be calculated using mathematical models.

Table 13 (p. 74) presents an example of chronic dietary risk assessment for Insecticide X. Exposure estimates are based on mean residues from field trials, and a chronic RfD is assumed: 0.01 mg/kg/day, based on a NOAEL of 1 mg/kg/day in the chronic rat study and a total uncertainty factor of 100. It also is assumed that the database for Insecticide X is complete and that no evidence of increased sensitivity in infants or children is noted. Thus, in this case, no additional uncertainty factor is needed to protect children.

In this example, the average dietary intake of Insecticide X for the total U.S. population (0.000152 mg/kg/day) represents 1.5 percent (0.000152/0.01) of the chronic reference dose. Exposures are relatively constant throughout the year and do not appear to be affected by geography or race. Children aged 1–6 years comprise the group with the highest potential exposure, ingesting an average of 0.000418 mg/kg/day of Insecticide X, or 4.2 percent (0.000418/0.01) of the chronic RfD. Thus, in all cases—even with conservative assumptions regarding anticipated exposure—the total consumption of Insecticide X is estimated well below the chronic RfD level assumed to cause no adverse human health effects. Chronic dietary exposure to Insecticide X is judged acceptable.

Dietary Cancer Risks

Potential cancer risk from dietary exposure to non-threshold carcinogens generally is estimated by multiplying the average consumption of pesticide residue by the q*, that is, by the upper potency estimate associated with that chemical. This calculation provides a 95th percentile upper estimate of excess risk of cancer resulting from ingestion. In other

Table 13. Chronic Dietary Risk Assessment for Insecticide X

Population Subgroup	Total Exposure (ARC, mg/kg/day)	Percent of Reference Dose
General Population		
U.S. population, 48 States-All Seasons	0.000152	1.5
U.S. Population By Season		
Spring	0.000150	1.5
Summer	0.000146	1.5
Autumn	0.000157	1.6
Winter	0.000156	1.6
U.S. Population by Region		
Northeast	0.000185	1.9
North Central	0.000152	1.5
Southern	0.000135	1.4
Western	0.000151	1.5
U.S. Population by Race		
Hispanics	0.000180	1.8
Non-Hispanic Whites	0.000145	1.5
Non-Hispanic Blacks	0.000162	1.6
Non-Hispanic other than Black or White	0.000185	1.9
U. S. Population by Pregnancy Status		
Females (13+, pregnant/not nursing)	0.000144	1.4
Females (13+, nursing)	0.000143	1.4
U.S. Population by Age and Gender		
Nursing infants (<1 year old)	0.000041	0.4
Non-nursing infants (<1 year old)	0.000122	1.2
Children (1-6 years)	0.000418	4.2
Children (7-12 years)	0.000239	2.4
Males (13-19 years)	0.000165	1.7
Females (13-19 years,	0.000104	1.0
not pregnant or nursing)	0.000147	1.5
Males (20+ years)	0.000098	1.0
Females (20+ years,	0.000115	1.2
not pregnant or nursing)	0.000115	1.2

words, the true excess risk of cancer is equal to or less than the calculated value 95 percent of the time.

In this example, it is assumed that Insecticide X is a non-threshold carcinogen, and that the q* is 3×10^{-3} $(mg/kg/day)^{-1}$. Estimates of dietary consumption used to evaluate chronic dietary risk are used to estimate potential dietary cancer risk. In this case, the average dietary consumption by the overall U.S. population is 0.000152 mg/kg/day. Based on these exposure estimates, the 95th percentile upper estimate of excess cancer risk for the overall population is calculated as 4.0×10^{-7} (0.000152 mg/kg/day x 0.003 $(mg/kg/day)^{-1}$. The upper estimate of potential cancer risk for the overall U.S. population is less than 1×10^{-6} (one in a million), which is considered acceptable.

Occupational Risk Assessment

Example of a Route-Specific Dermal Risk Assessment for Mixer/Loader/Applicator

The total dermal exposure to Insecticide X during mixing, loading, and application to corn was previously estimated to be 687 µg/day (p. 47). In this example, it is assumed that a 70 kg worker mixes, loads, and applies Insecticide X ten to fifteen days over a 3-month period. If the NOAEL for Insecticide X in a 21-day dermal toxicity study is 250 mg/kg/day, the short-term or intermediate route-specific dermal MOE for this worker is calculated as follows:

$$MOE_{dermal} = \frac{NOAEL}{Daily\ Dermal\ Exposure}$$

$$Daily\ Dermal\ Exposure = \frac{687\ \mu g/day}{1000\ \mu g/mg \times 70\ kg}$$

$$Daily\ Dermal\ Exposure = 0.0098\ mg/kg/day$$

$$MOE_{dermal} = \frac{250\ mg/kg/day}{0.0098\ mg/kg/day} = 25{,}510$$

Example of a Systemic Risk Assessment for a Mixer/Loader/Applicator

Using the same example, the total absorbed daily dose for a worker mixing, loading, and applying Insecticide X to corn was previously estimated to be 0.0012 mg/kg/day (p. 47). If the lowest NOAEL for Insecticide X in a 90-day feeding study is 15 mg/kg/day, the MOE for intermediate exposure for this worker is calculated as follows.

$$\text{MOE} = \frac{\text{NOAEL}}{\text{Absorbed Daily Dose}}$$

$$\text{Absorbed Daily Dose} = \frac{0.0012 \text{ mg/kg/day applied} \times 15 \text{ days applied}}{90 \text{ days}}$$

$$\text{Absorbed Daily Dose} = 0.0002 \text{ mg/kg/day}$$

$$\text{MOE} = \frac{15 \text{ mg/kg/day}}{0.0002 \text{ mg/kg/day}} = 75{,}000$$

To assess the potential risk posed by chronic exposure or the risk for cancer produced by a threshold carcinogen, the MOE is calculated by comparing the average absorbed daily dose over one year (for chronic effects) or a lifetime (for threshold carcinogens) to the appropriate chronic NOAEL. Further refinement by replacing the maximum application rate with average or typical rates could be calculated in this example.

However, the large MOE yields refinement unnecessary. The potential risk for any acute toxic effect generally is evaluated by comparing the highest absorbed daily dose (ADD), i.e., without averaging, to the appropriate acute oral toxicity end point. Thus, for Insecticide X the MOE for acute exposure is calculated by comparing the total ADD derived from dermal plus inhalation exposure to the NOAEL from the acute neurotoxicity study.

$$\text{MOE} = \frac{\text{NOAEL}}{\text{Total ADD}} = \frac{5 \text{ mg/kg/day}}{0.0012 \text{ mg/kg/day}} = 4{,}167$$

These MOEs are well above the value of 100 usually deemed acceptable for agricultural workers, even when conservative assumptions are used in the estimation of exposure potential. Therefore, the application of Insecticide X to corn poses no significant risk to agricultural workers.

Residential Risk Assessment

As in the case of occupational exposure, residential risk assessment is conducted using either the route-specific or the systemic approach. In this example, an acute potential toxicity is assumed; thus the focus is on day-of-application exposure and absorbed dose. It is assumed that Insecticide X is not used outdoors, so the residential risk assessment is conducted as follows.

Inhalation Daily Exposure = 0.000016 mg/kg/day (page 57)

Inhalation Absorbed Daily Dose =

0.000016 mg/kg/day (assuming 100% inhalation absorption)

Dermal Daily Exposure = 0.017 mg/kg/day (p. 60)
Dermal Absorbed Daily Dose = 0.0017 mg/kg/day
(assuming 10% dermal absorption;
Incidental Oral Exposure = 0.00036 mg/kg/day (p. 62)
Incidental Oral Absorbed Daily Dose = 0.00036 mg/kg/day
(assuming 100% oral absorption)
Short-term to intermediate dermal NOAEL = 250 mg/kg/day
Short-term to intermediate inhalation NOAEL = 0.235 mg/kg/day
Short-term to intermediate (multi-route, systemic) NOAEL = 15 mg/kg/day

Route-Specific Residential Risk Assessment

$$MOE_{inhalation} = \frac{NOAEL}{Inhalation\ Daily\ Exposure} = \frac{0.235\ mg/kg/day}{0.000016\ mg/kg/day} \approx 15{,}000$$

$$MOE_{dermal} = \frac{NOAEL}{Dermal\ Daily\ Exposure} = \frac{250\ mg/kg/day}{0.017\ mg/kg/day} \approx 15{,}000$$

$$MOE_{incidental\ oral} = \frac{NOAEL}{Incidental\ Oral\ Absorbed\ Daily\ Dose} = \frac{15\ mg/kg/day}{0.00036\ mg/kg/day} \approx 42{,}000$$

Systemic Residential Risk Assessment

$$MOE = \frac{NOAEL}{Average\ Absorbed\ Daily\ Dose} = \frac{15\ mg/kg/day}{0.000016 + 0.0017 + 0.00036} = 7{,}225$$

These MOEs are well above the value of 100, which is usually deemed acceptable for potential indoor exposure. Therefore, indoor application of Insecticide X as a fogger (according to label directions and following reentry restrictions) should pose no significant risk to children.

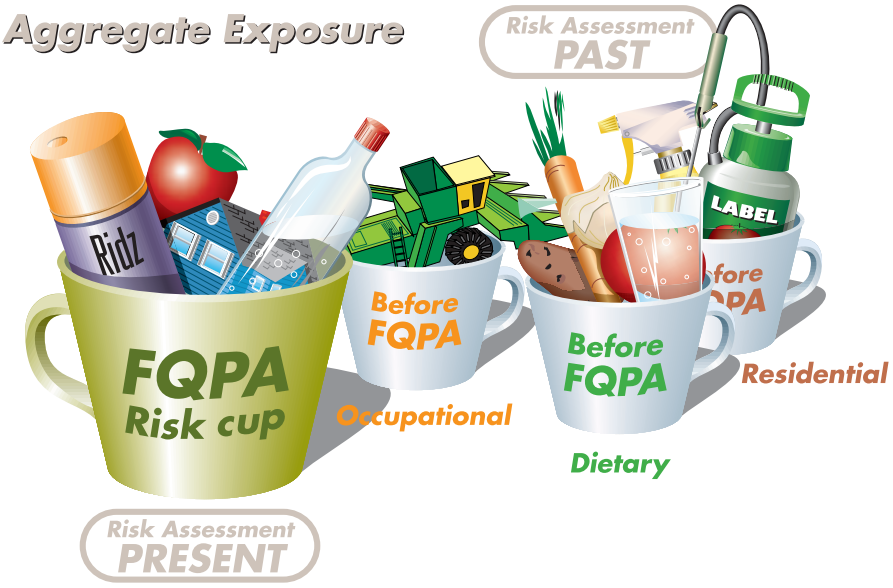
AGGREGATE RISK ASSESSMENT UNDER THE FOOD QUALITY PROTECTION ACT

The general public may be exposed to pesticides via multiple routes (inhalation, oral, dermal) and sources (air, water, food, soil, and various surfaces in and outside the home). The FQPA now requires EPA to evaluate potential aggregate risk to an individual who may be exposed to pesticides from one or more sources simultaneously.

The “Risk Cup” Analogy

The “risk cup” symbolizes how the new safety standard—reasonable certainty that no harm will result from aggregate exposure to pesticide residues—will be evaluated and implemented by EPA. It represents the total amount of pesticide residue to which a person might be exposed from all sources (diet, water, residential uses) without significant risk. The total allowable exposure, i.e., the size of the risk cup, is based on findings from toxicological studies including appropriate uncertainty and safety factors. For example, in assessing chronic toxicity to the general population, the risk cup is based on the pesticide’s chronic reference dose. A different size risk cup generally is used to assess potential risk from acute exposure and, depending on whether or not additional safety factors are imposed, to assess potential risk to infants and children.

The assumption is that when the predicted exposure from pesticides or groups of pesticides exceeds risk cup capacity, the pesticide or group



of pesticides fails to meet the “reasonable certainty of no harm” standard written into FQPA. Conversely, exposure levels not exceeding total risk cup capacity are deemed to meet the standard.

The risk cup analogy can be applied to aggregate risk assessment conducted on a single chemical, or to a combined or cumulative risk assessment conducted on multiple chemicals with a common mechanism of toxicity. Determining the best way to assess risk from multiple routes of exposure and/or from multiple chemicals will be a major risk assessment challenge over the next few years.

The development of a risk cup including aggregate and cumulative exposures—multiple sources and common mechanisms of toxicity—will require new methodologies; and more sophisticated risk assessments than those used previously will be needed. Although highly conservative assumptions often have been used to demonstrate negligible risk for

single compounds, the inclusion of multiple routes of exposure and multiple chemicals in the same risk cup will require more comprehensive and accurate data to demonstrate reasonable certainty of no harm, thereby avoiding use cancellations.

CONCLUSION

The risk of pesticide exposure to human health is a function of both exposure and toxicity. Since both measurements involve a degree of uncertainty, risk assessments generally use very conservative assumptions to assure adequate margins of safety. The risk assessment process generally proceeds in a tiered manner from assessments based on very limited data with very conservative assumptions through assessments

with extensive data and a solid understanding of the pesticide and its human exposure effects. The tiered approach allows for low risk pesticides with large margins of exposure to be screened out of the risk assessment process at a very early stage; this facilitates the direction of resources to assessment of risk posed by those pesticides of greatest concern to human health.

State-of-the-art risk assessment methodologies are used to assess exposure and risk to special subpopulations. Therefore, risks to infants and children and to workers are evaluated separately from those posed to human populations in general. Risk assessments are increasingly concerned with the aggregate risk of pesticide exposure to humans where the combination of risk from multiple sources (air, food, water, playground, home, etc.) are considered.

Despite the public desire for zero risk, the world is not risk free. Recognition of the risks associated with pesticide use leads to informed decision-making in identifying those levels of risk acceptable to society. Risk assessment, product labeling, governmental enforcement, and applicator and consumer education form the foundation of a comprehensive framework to regulate the manufacture, use, and disposal of pesticides, and to ensure that adverse effects on human health and the environment are minimized. Responsible management of pesticide risks and benefits allows optimal benefits in terms of public health, safety, and prosperity.

ACKNOWLEDGMENTS

All illustrations are by artists Steven and Paula Adduci, i2i Interactive, Campbell, California. Their artistic interpretations enhance this publication, and we thank them. Financial support was provided by the United States Environmental Protection Agency, Region 5; United States Department of Agriculture Cooperative State Research, Education, and Extension Service; United States Department of Agriculture Office of Pest Management Policy; Outdoor Residential Exposure Task Force; American Crop Protection Association; and Educational Endowment Fund of the American Chemical Society.

The following individuals also contributed to the development of *Pesticides and Human Health Risk Assessment.*

- Christopher Burger, Applied Pharmacology and Toxicology
- Kathleen Brown, Harvard School of Public Health
- Cathy Campbell, Health Canada
- Beth Carroll, Novartis Crop Protection
- Janice Chambers, Mississippi State University
- Sunmao Chen, Novartis Crop Protection
- John Cowell, Monsanto
- Sue Crescenzi, Steptoe & Johnson
- Ray de Castro, Harvard School of Public Health
- Dennis Gibbons, California Department of Pesticide Regulation
- Edward Gray, Jellinek, Schwartz & Connolly
- Bert Hakkinen, The Procter and Gamble Company
- Paul Hamey, Pesticides Safety Directorate
- Dinah Koehler, Harvard School of Public Health
- Bob Krieger, University of California, Riverside

- Raymond Layton, DuPont Agricultural Products
- Robert Lewis, United States Environmental Protection Agency
- Steven Lewis, Exxon Biomedical Sciences
- Yoshihide Matoba, Sumitomo Chemical Company
- David McCallum, Focus Group
- Michael McClean, Harvard School of Public Health
- Ronald Mull, DuPont Agricultural Products
- Robert Pauline, Chemical Specialties Manufacturers Association
- Swati Prakash, Harvard School of Public Health
- Peter Robinson, The Procter and Gamble Company
- John Ross, California Department of Pesticide Regulation
- Ruby Reed, California Department of Pesticide Regulation
- Jess Rowland, United States Environmental Protection Agency
- Charles Santerre, Purdue University
- Allen Scarborough, Rhone-Poulenc
- Larry Smith, LS Consulting Service
- Jack Spengler, Harvard School of Public Health
- Edwin Tinsworth, Jellinek, Schwartz & Connolly
- Pamela Williams, Harvard Center For Risk Analysis
- John Worgan, Health Canada
- Joop van Hemmen, TNO Nutrition and Food Research Institute

ACRONYMS USED IN THIS PUBLICATION

ADD	Absorbed Daily Dose
AI	Active Ingredient
ARC	Anticipated Residue Contribution
aRfD	Acute Reference Dose
BW	Body Weight
Cal-EPA	California Environmental Protection Agency
CCF	Concentration Correction Factor
CF	Correction Factor
CP	Concentration of Product
CSFII	Continuing Survey of Food Intake by Individuals
DAF	Dermal Absorption Fraction
DCF	Dermal Experimental Correction Factor
DFR	Dislodgeable Foliar Residue
DH	Daily Dermal Exposure to Hands
EC	Emulsifiable Concentrate
ED	Exposure Duration
EPA	United States Environmental Protection Agency
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
GLP	Good Laboratory Practices
HMTF	Hand-to-Mouth Transfer Factor
HSA	Hand Surface Area
IR	Inhalation Rate
LOAEL	Lowest Observed Adverse Effect Level
MOE	Margin of Exposure
NOAEL	No Observed Adverse Effect Level
OAF	Oral Absorption Fraction for Active Ingredient
PHED	Pesticide Handler's Exposure Database
PAF	Pulmonary Absorption Factor
PDP	USDA's Pesticide Data Program
PHED	Pesticide Handlers' Exposure Database
ppm	Parts Per Million
PUF	Polyurethane Foam
RAC	Raw Agricultural Commodity
RfD	Reference Dose
SA	Surface Area
TC	Transfer Coefficient
TF	Transfer Factors
TMRC	Theoretical Maximum Residue Contribution
TR	Transferable (or Transfer) Residue
USDA	United States Department of Agriculture
$\mu g/cm^2$	Micrograms Per Square Centimeter
µg/kg/day	Micrograms Per Kilogram Per Day

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