How Protective is the Pesticide Risk Assessment and Registration Process to Humans in the United States?

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Abstract
The need to feed the growing world population is a daunting challenge and improving crop yield using technology (e.g., synthetic pesticides) is a primary solution being utilized by growers globally. However, there is a general perception that the U.S. population is not well protected from the effects of using pesticides. This leads us to a natural question: how protective to humans is the pesticide risk assessment and registration process in the U.S.? In this commentary, we aim to give an overview of the regulatory history of pesticides in the U.S. and systematically discuss the data-driven, comprehensive, and health-protective methods employed by the U.S. Environmental Protection Agency (EPA) in accordance with the stringent mandates of the laws passed by U.S. Congress and the regulations enacted by the EPA to protect the U.S. population. By describing the studies required under the Code of Federal Regulations (CFR), along with the health-protective models and assumptions employed by the EPA to evaluate the potential for human health risks from pesticides, we aim to highlight the *compounding health-protectiveness* of the existing regulatory framework. We emphasize the need to maintain a regulated risk-benefit balance in using modern agricultural technology, similar to what is done with other indispensable modern human innovations and technologies.

Keywords: pesticide risk assessment, pesticide registration, compounding health-protectiveness, human health protection

Acronyms

- AOP - Adverse Outcome Pathway
- BMD - Benchmark Dose
- CFR - Code of Federal Regulations
- DFR - Dislodgeable Foliar Residue
- DFU - Directions for Use
- EPA - US Environmental Protection Agency
- FIFRA - Federal Insecticide, Fungicide, and Rodenticide Act
- fRa - Fold Relative Accuracy
- FQPA - Food Quality Protection Act
- HHRA - Human Health Risk Assessment
- LOAEL - Lowest Observed Adverse Effect Level
- LOC - Level of Concern
- LOQ -Limit of Quantitation

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- MOE - Margin of Exposure
- NOAEL - No Observed Adverse Effect Level
- PDP - Pesticide Data Program
- POD - Point of Departure
- PPE - Personal Protective Equipment
- RfD - Reference Dose
- SOP - Standard Operation Protocol
- TTR - Turf Transferable Residue
- UF - Uncertainty Factor

1. Introduction

The need to feed the growing world population is one of the biggest challenges of the 21st century. It has been predicted that the population will reach close to nine billion individuals by the year 2050 and agricultural outputs will need to increase by as much as 70% between 2009 and 2050 to feed the population (FAO 2009; Popp, J., Hantos, 2011). We are also facing challenges such as climate change, the need to preserve biodiversity, the loss of natural resources such as land and water to urbanization, and the failure of economies. Add to these the loss of crop yield to pests like insects, pathogens, and weeds along with increasing pesticide resistance, and the challenges collectively seem daunting. With the limited availability of arable land and the need to preserve native habitats, technologies such as chemical and biological crop protection products will be imperative to make food available, economical, and nutritious (Popp, J., Hantos, 2011; FAO 2009; Gehen et al., 2019). Multiple studies have demonstrated the economic, social, environmental, and health benefits of using conventional pesticide active ingredient or pesticide-containing products (referred to as 'pesticide' henceforth) (CAST, 2019; Maienfisch & Stevenson, 2015; Popp, 2011). The incorrect use of pesticides, however, can potentially lead to unintended, detrimental social and environmental effects (Cooper & Dobson, 2007; Pimentel, 2009). The main stakeholders involved in agriculture, namely growers, registrants, and regulators, all believe that balancing potential health risks with the social and economic benefits of pesticide use is essential for a sustainable future (Maienfisch & Stevenson, 2015; Popp, 2011). However, there is a public perception that the general U.S. population is not well protected from the effects of using pesticides.

The development, registration, and manufacture of pesticides is highly regulated in the U.S.; all pesticide active ingredients and formulations go through a comprehensive regulatory evaluation process for their intended use and are registered for that use only when the consumer, occupational worker, and ecological risk assessments meet strict regulatory criteria (Gehen et al., 2019; Maienfisch & Stevenson, 2015). The US Environmental Protection Agency's (EPA) pesticide regulation process includes extensive data requirements from hundreds of studies on efficacy, human safety, environmental safety, metabolism, and residue analysis, and employs several levels of health-protective assumptions in safety assessments to ensure the most sensitive populations (e.g., infants and children) are protected. These regulatory evaluations are established to ensure approved use scenarios result in benefits and minimize risks. The whole process, starting from identifying

candidate molecules up to first sales of a pesticide product, can take over a decade, and registrants invest nearly 300 million U.S. Dollars for this process for a single active ingredient (Gehen et al., 2019). Additionally, EPA routinely re-evaluates active ingredients every 15 years to ensure they are fit/safe to stay registered considering any new scientific data/research available.

In this article, we describe the many facets of U.S. pesticide regulation, including a pesticide's registration-approval process mandated by statute and regulation to ensure the safety of pesticides entering the market and the re-evaluation and re-registration of those pesticides currently in the market. We focus on human safety, the data generated as required by the EPA's pesticide regulatory process and the potential risks being evaluated to ensure the safe use of pesticides, emphasizing the '*compounding health-protectiveness*' phenomenon inherent in the regulatory process. This phenomenon occurs when several layers of health protection are built into risk assessment paradigm, which compound to ensure all human sub-populations in the U.S. are protected from potential pesticide health risks We had previously published a commentary to discuss the same for environmental safety (Moore et al., 2021) and this current commentary is to complement that effort, focusing only on human safety.

2. Brief History of Pesticide Regulation in the U.S.

In the beginning of the 20th century, as the U.S. population grew rapidly and people migrated to urban areas, farmers faced pressure to significantly increase their crop yields. With great strides made in plant breeding, soil and water management, and pest control, the federal government realized the importance of, and the need to regulate, the burgeoning agriculture industry. In the mid-1900s, Congress enacted the Federal Food, Drug, and Cosmetic Act and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). These acts established food-quality standards that would be enforced by the federal government and provided the Secretary of Agriculture with the responsibility of overseeing pesticide use and addressing any concerns related to pesticide use in agricultural production. In 1970, the regulatory authority for FIFRA enforcement was moved from the Department of Agriculture to the newly created EPA, which established standards for pesticides in food and feed by assessing the potential impact of pesticide usage on environmental and human health through the Code of Federal Regulations Title 40 Part 180 (U.S. EPA 1996a; U.S. EPA 2002a; U.S. EPA 2020a). The EPA was also given the responsibility for regulatory oversight of the sale, distribution, and registration of pesticides; to determine and enforce Worker Protection Standards for pesticide applicators; to define instructions for the proper use, storage, and disposal of pesticides; to delineate the regulatory authority relegated to the states, in addition to strengthening enforcement and compliance mandates.

FIFRA codified that the 'pesticide label is the law': end users and sellers must comply with the directions on the label under full penalty of applicable law as the EPA has determined that the pesticide will not result in an unreasonable risk to human health or the environment when used as directed. To this end, the registration review process dictates that the label will clearly communicate the scope of the use of the pesticide, i.e., its use categorization; first aid statements; any precautionary statements and the directions for use. Both FIFRA and the Federal Food, Drug, and Cosmetic Act

require the EPA to also consider the benefits resulting from a pesticide's use relative to any potential risks to public health or the environment.

FIFRA has been amended through the years to grow into the regulatory process we know today (U.S. EPA 1988; U.S. EPA 1996b; U.S. EPA 2018a). As per FIFRA 1988, all registered pesticide active ingredients, manufacturing-use products, and end-use products are subject to re-evaluation every 15 years to determine whether they continue to meet the FIFRA standard for registration. This re-evaluation entails a comprehensive review of the scientific data supporting the pesticide registration to identify potential 'data gaps', i.e., information that is needed for the review, but is currently not available to the EPA. After data gaps have been identified, the EPA will issue a 'data call-in' to which the registrant must respond regarding their intention to fill the gaps by conducting new studies or citing existing data or choosing to voluntarily cancel the registration. Throughout this re-evaluation process, the EPA ensures transparency and requests public participation by review and comment. For example, the EPA seeks public comment at three important milestones during the pesticide reevaluation/reregistration process: the initial posting of the intent to reregister a pesticide; the posting of draft EPA human health and environmental risk assessments; and the posting of the Proposed Interim Decision, which presents proposed pesticide-use mitigations required as a result of those risk assessments (public comments can be uploaded using the following link: https://www.epa.gov/pesticide-reevaluation/opportunities-participate-pesticide-reevaluation).

In 1996, Congress passed the Food Quality Protection Act (FQPA) that requires the EPA to use risk assessment procedures for pesticides in food that employ a more holistic approach. During a pesticide's review, the EPA must consider: 1) all pesticides with a common mechanism of toxicity (cumulative risk); and 2) all pathways and routes of exposure, including oral, dermal, and inhalation exposure (aggregate risk) (U.S. EPA 1996b). Safety factors may be incorporated into the risk assessment to protect vulnerable populations, such as infants and children, when deemed appropriate. After assessing the cumulative and aggregate risk, EPA will only register a pesticide if there is 'a reasonable certainty of no harm'. FIFRA authorizes the EPA to take immediate action to suspend or cancel a pesticide registration if product use poses an imminent risk to human health or the environment. FQPA also codified the EPA requirement to review all previously established pesticide tolerances within 10 years of the passing of FQPA to ensure current safety standards have been met with pesticides registered prior to 1996.

In 2004, the Pesticide Registration Improvement Act updated FIFRA and created a fee-for-service system for pesticide registration applications and registration amendments, including approval for a new AI; a new use, such as a new food crop or lawns or home pest control; or a new product (the fees and the timelines for the review of submitted data are provided on the EPA website). To incentivize the development of 'safer' pesticides, the EPA has established a process for registration of so-called 'reduced risk' pesticides. The registrant may submit their reduced-risk case to demonstrate that the new pesticide poses less of a risk to humans or the environment than pesticides currently registered. The EPA reviews the case and, if compelling, will reduce the application fee and the timeline for registration, which

encourages development of increasingly safer pesticides.

3. Data Requirements for Pesticide Registration

The studies required in 40 Code of Federal Regulations (CFR) Part 158 provide the data-driven approach to identifying potential risks to the environment and humans (U.S. EPA 2021a). For study data submitted to support an active ingredient or pesticide product registration, the studies must be conducted under Good Laboratory Practice Standards (U.S. EPA 2020b) to ensure data quality, integrity and reproducibility mandated by 40 CFR Part 160. After the review of the submitted data, the Agency will grant registration of a pesticide product or, in the case of re-evaluation, either re-registers the pesticide or takes appropriate regulatory action, including restriction or outright cancellation of the product registration. The Federal government and FIFRA regulate the registration, distribution, sale, and use of pesticides, but states have the ultimate authority for compliance monitoring and enforcement of the pesticide label (U.S. EPA 2021a). A State in conjunction with the EPA may issue time-limited Experimental Use Permits to allow product testing under specific, regulated conditions, Special Local Needs registration that addresses a specific pest problem within a state, or Emergency Exemptions that address an urgent new pest threat, such as a new invasive pest species for which no acceptable control solution is available.

For the registration of a new active ingredient or end-use product, the EPA reviews the submitted data package and either grants registration or denies approval/registration. Denial of registration means that it is illegal to sell, distribute, sell or use the pesticide. In the case of reregistration, the EPA reviews the available data and determines whether the data are adequate to assess the 'reregisterability'. If not, a request for additional data is sent to the registrant, i.e., a data call-in, and a registrant can choose to: (1) rebut the EPA's conclusions; (2) conduct additional studies to satisfy or fill the data gap; or (3) voluntarily cancel the registration of the active ingredient, manufacturing-use product, and/or end-use product. If the registrant does not address the data gaps, registrations of end-use products may be cancelled by the EPA 'involuntarily' (as opposed to a voluntary cancellation initiated by the registrant).

The data required to support the registration of a pesticide are extensive and need to demonstrate the degradation, metabolism or dissipation of the pesticide in animals, plants, and soil; detectable residues (quantification of the pesticide and any relevant metabolites) of concern in crops and livestock animals; and the toxicity in animals and non-target species are required to meet the standards. These studies and the risk assessment methods to which they provide input will be discussed in the sections below.

4. Human Health Risk Assessment

In the U.S., the potential human health risks of a pesticide are determined by the EPA utilizing data on 1) health hazard identification, 2) hazard characterization through a dose-response assessment to identify the dose levels (exposure) required to elicit any health hazards, 3) human exposure assessment, which quantifies the expected human exposure to the pesticide based on intended use scenarios, and 4) risk characterization (U.S. EPA 2021b). The steps involved in the human health risk assessment process followed by the Federal Government are laid out by the National Research Council (NRC 1983). The key steps of the EPA's pesticide regulatory

human health risk assessment (HHRA) process are illustrated in Figure 1 below. In the risk-based regulatory system in the U.S., if the expected human exposures are sufficiently lower than the dose required to elicit a health hazard in the toxicology studies, it can be concluded that there is no meaningful risk to human health.

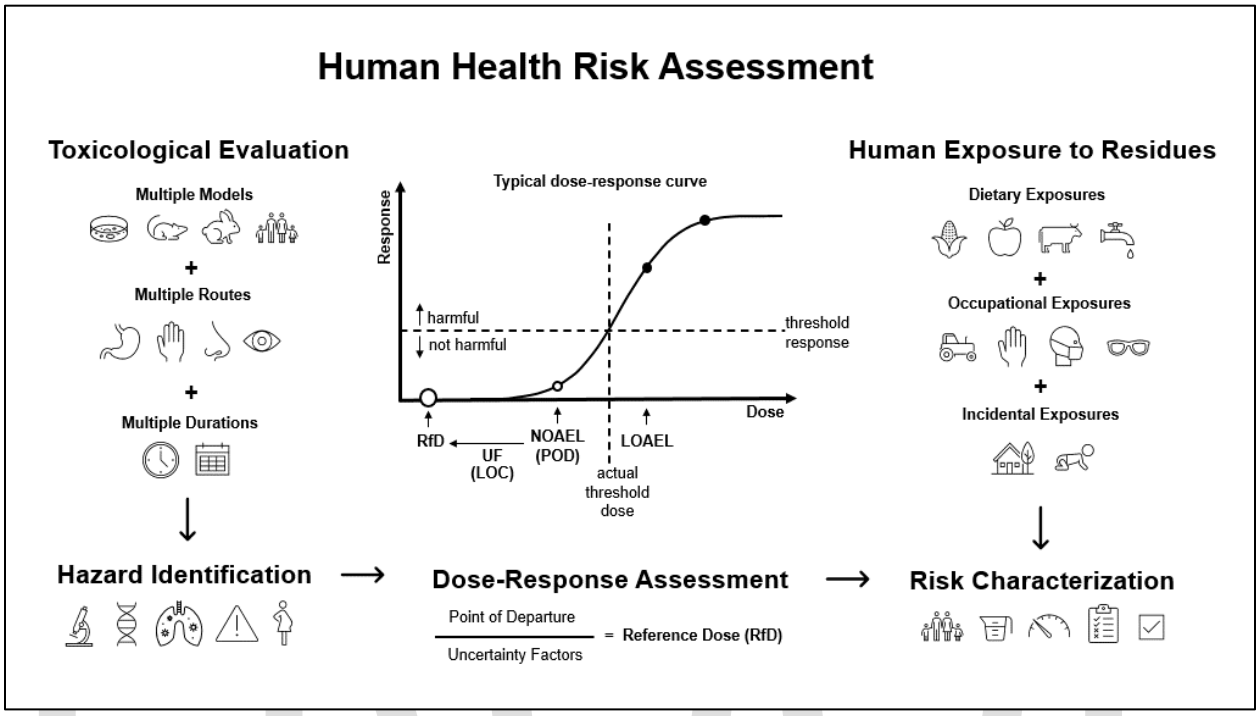

Figure 1. The key steps in the U.S. EPA's pesticide human health risk assessment process

4.1 Toxicological Evaluation

EPA toxicology data requirements for pesticides (found in 40 CFR Part 158, subpart F-Toxicology §158.500, and summarized in Table 1) include studies of various durations of exposure (acute, short-term, intermediate-term, or chronic/lifetime) and various routes of exposure (oral, dermal, inhalation, or eye contact), conducted according to standard test guidelines (U.S. EPA 2021c) and Good Laboratory Practice Standards. Most toxicology studies involve oral administration as a relevant route of exposure for agricultural products. In addition, certain studies are designed to examine specific health effects like neurotoxicity, developmental and reproductive effects (including birth defects and endocrine disruption), genetic toxicity, or carcinogenicity. Current data requirements for pesticides commonly rely on four species of laboratory animals (mice, rats, rabbits, dogs) which historically have been used as surrogate models for human safety testing. The conventional use of multiple species is thought to maximize the detection of potential health effects, since certain human-relevant effects may not be detected in every model species. However, it must be noted that animal testing should be used only when there are no acceptable alternatives. In the future, new technologies and alternative approaches are likely to provide the information necessary to protect human health and to further reduce or entirely replace animal testing (U.S. EPA 2019).

Table 1: Toxicology Data Requirements for a Food-Use Pesticide Active Ingredient

Type of Study	Data Requirements
Single Exposure (Acute) Testing	Acute oral toxicity - rat
	Acute dermal toxicity - rat
	Acute inhalation toxicity - rat
	Primary eye irritation - rabbit
	Primary dermal irritation - rabbit
	Dermal sensitization - mouse
	Delayed neurotoxicity (acute) - hen[CR]
	Acute neurotoxicity - rat
Short-term Repeated Exposure (Subchronic) Testing	90-day Oral toxicity - rodent
	90-day Oral toxicity - non-rodent
	21/28-day Dermal toxicity - rat
	90-day Dermal toxicity - rat[CR]
	90-day Inhalation toxicity - rat[CR]
	28-day Delayed neurotoxicity - hen[CR]
	90-day Neurotoxicity - rat
Long-term Exposure (Chronic) Testing	Chronic oral toxicity - rodent
	Carcinogenicity - two rodent species - rat and mouse preferred
Developmental Toxicity and Reproduction	Prenatal Developmental toxicity - rat and rabbit preferred
	Multigenerational reproduction and fertility effects - rat
	Developmental neurotoxicity[CR] - rat
Mutagenicity (Genetic Toxicity) Testing	*In vitro* bacterial reverse mutation assay
	In vitro mammalian cell assay
	In vivo cytogenetics - rat or mouse
Special Testing	Metabolism and pharmacokinetics - rodent
	Companion animal safety[CR]
	Dermal penetration[CR]
	Immunotoxicity - rodent

CR - Conditionally required study data

4.1.1 Hazard Identification

Based on the current data requirements, the first step is to identify any potential health effects attributable to the pesticide. In every toxicology study, any health effects observed in the exposed animals are compared to findings in concurrent control animals and, if appropriate, to the normal range of findings observed in historical control data. This comparison to control data is essential to distinguish any pesticide-related effects from background health effects commonly observed in a particular strain of animals.

Following identification of any pesticide-related health effects, further evaluation is then required to identify hazard based on two basic criteria:

- Which health effects are harmful (also known as *adverse*)? Some observed pesticide-related changes reflect

adaptative biological responses (e.g., to detoxify the pesticide and maintain homeostasis) and are mostly reversible with discontinued exposure, while others reflect adverse health effects (those that impair the performance of an organism or reduce its ability to respond to additional environmental challenges (Lewis et al., 2002). Although statistical tests can aid in the identification of pesticide-related effects, the toxicologist must consider that not all statistically significant differences are necessarily biological significant, and vice versa. Evaluating both statistical and biological significance and distinguishing adaptive from adverse effects in animal studies can be nuanced and requires expert judgment.

- Which adverse health effects are human-relevant? Although animal models share many biochemical and physiological processes with humans, not all adverse effects observed in animals are relevant to human health. It is important to consider the mode of action, or the sequence of events leading to the adverse effect, also known as an *adverse outcome pathway* (AOP). When the AOP could occur in humans, or if the AOP is unknown, the adverse effects in animals are assumed to be human-relevant and appropriate for HHRA. These human-relevant, adverse effects are sometimes called *critical effects* or *hazards*.

4.1.2 Dose-Response Assessment

Guideline toxicology studies must include a control group and at least three different exposure groups of increasing amounts (dosages) of the pesticide. The critical effects observed at each exposure level are known as the *dose-response*. The highest exposure level without any critical adverse effects is known as the No Observed Adverse Effect Level (NOAEL), and the exposure level where critical effects begin is known as the Lowest Observed Adverse Effect Level (LOAEL). The NOAEL is typically considered the threshold for a critical effect. In reality, the actual threshold occurs at some exposure level between the NOAEL and LOAEL. This actual threshold is sometimes called the benchmark dose (BMD) and can be estimated using mathematical modeling that incorporates the entire dose-response and variability in the dataset. Therefore, a calculated BMD may be considered a desirable refinement of the NOAEL.

Based on the dose-response across all of the toxicology studies conducted, the next step is to select *points of departure* (POD) for HHRA. A POD is an effect level (NOAEL, LOAEL, or BMD) that provides the most protective estimate of the threshold for the most relevant critical effect(s) for a given human exposure scenario or population. Several considerations can support the selection of an appropriate POD, including duration of exposure, route of exposure, species differences, life-stage sensitivity, human dosimetry, mode of action, or study data quality. As a result, a different POD may be selected for each exposure scenario.

Next, each POD is used to determine a human *reference dose* (RfD) or *level of concern* (LOC) for use in HHRA. A RfD is a maximum human exposure limit which cannot be exceeded, and a LOC is a minimum margin of exposure (MOE) between the POD and the expected human exposure. Both approaches ensure that allowed human exposures are acceptably lower than the POD such that there is no reasonable concern of adverse human health effects. The acceptable margin of safety between a POD and human exposure is

based on health-protective *uncertainty factors* (UF). These UFs typically are based on log units (10-fold) or half-log (~three-fold) and fall into three main categories:

- Variability: By default, a composite UF of 100X is used to adjust a POD based on animal data to a human RfD. This default 100X includes 10X for *interspecies variability* to account for differences between animals and humans, and 10X for *intraspecies variability* to account for human variability and sensitive populations. When additional data about these intrinsic sources of variability are available for a specific pesticide, it may be more appropriate to use chemical-specific, data-derived extrapolation factors rather than the default factors. Such data-derived extrapolation factors are often based on additional data about the toxicokinetics (the target tissue exposure that results from the pesticide circulating within the body) or toxicodynamics (the target tissue responses to this exposure). If it can be established that humans are less sensitive than the animal model in either of these parameters, the 10X interspecies UF could be reduced to 3X or even 1X. Similarly, if data are available for the most sensitive human population, it may be appropriate to reduce the intraspecies UF.
- Data adequacy: Additional default UFs may be applied to account for database uncertainties or inadequacies. One example would be a study where a NOAEL was not established (i.e., critical effects were observed at the lowest dosage tested). When a LOAEL is used as the POD rather than a NOAEL, the default approach is to apply up to an additional 10X UF for extrapolation; however, a viable alternative approach might be to estimate the NOAEL using BMD modeling. Additional UF may also be applied for extrapolation between different routes of exposure (e.g., oral vs. inhalation) or exposure durations (e.g., using a short-term POD for chronic risk).
- Protection of infants and children: The Food Quality Safety Act (U.S. EPA 1996b) requires EPA to apply an additional 10X safety factor for the protection of infants and children, unless the toxicology database adequately addresses any concerns for pre- and postnatal toxicity. If the POD for HHRA is based on effects in the most susceptible population, and there are no deficiencies in the database that raise concerns about sensitivity or exposure of the young, the default 100X UF is considered adequate to protect infants and children, and the FQPA factor can be reduced to 1X. (U.S. EPA 2002b).

If the total UF for a POD exceeds 3000X, the toxicology database would likely be considered inadequate for HHRA, and additional data would be required (U.S. EPA 2002c). For a POD based on adequate data with no uncertainties for life stage sensitivity, the default total UF would be 100X, and the human RfD would be the POD/100. For a margin of exposure approach (MOE = POD/human exposure), the total UF would become the LOC of 100. An RfD is expressed as mg of pesticide per kg of body weight, while a MOE is a unitless ratio of the POD to human exposure. The use of RfD and MOE for risk characterization will be further discussed in a later section in this commentary.

For potential carcinogenic effects, the dose-response could be 1) linear, in which case, a cancer potency factor (a

measure of cancer risk from a lifetime exposure to an agent) is derived as an estimate of toxicity; or, 2) non-linear, in which case, toxicity is estimated as a POD, which again follows a threshold-based approach for risk assessment (U.S. EPA 2000a; U.S. EPA 2005). In cases where human epidemiology and incident data are available on a pesticide being (re-) evaluated for continued registration, the EPA uses a standard framework (U.S. EPA 2016) to evaluate such observational studies and potentially inform the human health risk assessments. Epidemiology studies need to be evaluated carefully for their overall quality including study design, conduct, covariates/confounders consideration, exposure assessment, and the overall risk of bias before they can be utilized in risk assessments. Depending on the availability and the quality of pesticide epidemiology studies, they can play an informative role of potentially reducing uncertainty in pesticide risk assessments. In the hazard characterization step, epidemiology studies have the potential to inform on questions related to the relevance of animal models extrapolated to humans, when relevance is uncertain. With dose-response assessment, since epidemiology studies are inherently based on assumed real-world exposures, the uncertainty in extrapolation from high exposure levels in animal studies to human relevant exposure levels is reduced. They are also better in characterizing potential variability inherent in the population-level response than animal studies. In the US, the EPA follows a thorough and systematic review of available epidemiological data to inform their pesticide risk assessments (U.S. EPA 2016).

4.2 Exposure Assessment

In the EPA's risk-based regulatory framework, even if there is an identified hazard in toxicology tests, if the potential human exposure to the pesticide is expected to be lower than the levels at which the hazard can be elicited, minimal human health risks are to be expected. In general, the potential *exposure* to the pesticide is determined primarily based on its labeled directions for use (DFU) section in the registered label. The DFU specifies several parameters, including the crops allowed to be treated; methods, timings, sites, and frequency of application; maximum application rates; personal protective equipment (PPE) required for various operator activities; plant-back intervals, pre-harvest intervals, and restricted-entry interval; any other required mitigations; and drift management requirements. Using the above DFU information, targeted plant and livestock metabolism studies, crop and animal residue studies, and consumer and occupational exposure assessments are conducted by the registrant to assess potential human exposure, as part of the pre-registration approval data requirements of the EPA.

4.2.1 Metabolism Studies and Environmental Fate Studies

When a pesticide is applied to a location and crop depending on the chemistry of the pesticide, several different degradation and fate processes may occur. These include 1) uptake of the pesticide into the primary and rotational crops, which are then consumed by humans as raw agricultural commodities or processed food and/or as feed by livestock; 2) sorption of the pesticide to soil; 3) pesticide dissolution and/or run-off into surface and ground water; as well as 4) metabolism or breaking down of the pesticide in these different environmental compartments to one or more metabolites. To understand the potential human exposure to a pesticide, all of these potential pesticide environmental fate processes need to be comprehensively studied. The EPA's

metabolism and environmental fate data requirements include several required and some conditionally required studies that aim to understand the metabolism of the pesticide in crops and livestock, as well as the fate of the pesticide and any related metabolites in the environment. These studies provide key exposure information including an estimate of total residues and major components of metabolite residues in the edible raw agricultural commodities and livestock commodities. Another important aspect of studies is to define metabolic pathway for the pesticide in ruminants, poultry and plants. Finally, these studies provide data to establish rotational intervals and/or rotational crop restrictions based on residue uptake levels and whether field trials for rotational crops are needed. These studies are conducted under Good Laboratory Practice Standards with ^{14}C radiolabeled test substances (for analytical identification and accuracy).

In general, requirements in these study guidelines enable rigorous assessment of the possible pathways of the pesticide and any relevant metabolites' exposure to humans. These include,

- For crop metabolism studies, a minimum of three diverse crops (root vegetables, leafy crops, fruits, pulses and oilseeds, and cereals) that support the intended use pattern of the pesticide are dosed at the maximum application rate allowed in the DFU. If the metabolic pathway in three diverse crops studied is similar, the metabolism in other crops groups can be assumed to be similar. If dissimilar, a unique definition of residue will be defined for each crop type based on the metabolism study results.
- Studies on confined rotational crops are conditionally required for uses of pesticides on food crops. For rotational crop studies, representative rotational crops are planted at three appropriate rotational intervals or plant back intervals. The rotational intervals selected should be based on the expected agricultural use for the active ingredient and typical rotational practices and the rotational crops should be representative of each of the multiple crop groups listed in the DFU.
- If the pesticide is to be applied to livestock feed crops, or is intended for treatment of livestock, then a comprehensive set of livestock metabolism studies also are required. Livestock studies are needed to elucidate the absorption and disposition of active ingredients whenever pesticide use may lead to residues entering the human food chain. Livestock metabolism studies are generally carried out on ruminants (goats) and poultry (laying chickens). Typically, one lactating goat and eight laying hens are used per test substance.
- In addition to the crop and livestock metabolism studies, a high temperature hydrolysis study may be required to establish whether the nature of the residue in the processed commodities is different from that in the raw agricultural commodity.
- Several environmental fate studies including those that help determine the concentration of the pesticide (and any relevant metabolites) in surface and ground water are also required.

The key metabolism and environmental fate studies that are required or conditionally required under 40 CFR part 158 (U.S. EPA 2020c) are shown in Table 2 below.

Table 2: Metabolism and Environmental Fate Studies for a Food-Use Pesticide Active Ingredient

Type of Study	Required Information and Tests
Metabolism Studies	Primary Crops
	Livestock
	Confined Rotational Crops
	High Temperature Hydrolysis
	Absorption, Distribution, Metabolism and Excretion
Environmental fate studies	Hydrolysis
	Aqueous Photolysis
	Aerobic Mineralization in Surface Water
	Soil Metabolism – Aerobic and Anaerobic
	Aquatic Sediment Degradation – Aerobic and Anaerobic
	Adsorption/Desorption
	Soil Photolysis – Dry and Moist Layers
	Ready Biodegradability

4.2.2 Crop and Animal Residue Studies

Once the metabolism and potential fate of the applied pesticide is determined in agricultural commodities and livestock, the next key step in the human exposure assessment process is the quantification of the pesticide and any relevant metabolites that are potentially available for exposure, following the label-directed use of the pesticide. FIFRA mandated crop and animal residue study data requirements include several required (and some conditionally required) studies aimed at assessing the potential pesticide exposure to general consumers and occupational workers through consumption of crop commodities, animal commodities, as well as contacting pesticide residues on crop foliage and turf during occupational or recreational activities.

In general, the residue and animal study guidelines provide a comprehensive and scientifically rigorous dataset to evaluate exposure to humans. These include:

- The analytical chemistry method developed to identify pesticide residues must be specific to the pesticide, validated to work in multiple (relevant) biological matrices, accurate, precise, and repeatable at the determined Limit of Quantitation (LOQ).
- Storage stability studies are mandated and ensure that the residue levels detected in crop residue studies are accurate representations of what residue levels would be expected from a specific pesticide use on a particular crop.
- Crop field trials are performed at the maximum intended pesticide rate per application and per year, the maximum number of applications, the minimum interval between applications, and the minimum preharvest interval. Crop samples are not washed or brushed clean in any way to allow for the detection of worst-case residue levels. This provides a worst-case scenario and is intended to ensure that exposure is not under-estimated.

- When using crop field trial residue data which are non-quantifiable (i.e., lower than the LOQ), the EPA uses the LOQ or the numeric limit of detection as the residue values in the exposure assessment, thereby further contributing to conservatism in the assessment (U.S. EPA, 2000a).
- Tolerance or the maximum residue level of a pesticide, which is the legally established highest amount of allowable residue on a specific crop, is estimated following the Organization for Economic Co-operation and Development guidelines (OECD, 2016). This is estimated using the 95th percentile of the residue distribution from crop field trials. This level of conservatism is intended to overestimate the residue levels on all possible crop commodities consumable by humans or livestock. For this reason, actual residues are unlikely to exceed tolerances levels set on crop commodities.
- Separate animal feeding studies may be required to determine residue levels in meat, milk and egg commodities that may be consumed by humans. Transfer factors for the animal commodities in conjunction with the residue levels from the crop field trials are used to calculate an animal dietary burden to be used in the dietary exposure assessment.
- Field accumulation trials are used to determine the amount of residue uptake into rotational crops planted after the application and harvest of a pesticide product to the target crops. These data will determine whether a plant back restriction will be applied to the label, or an inadvertent tolerance will need to be set for any crops not on the label.
- Dislodgeable foliar residue (DFR) and turf transferable residue (TTR) studies are conducted to determine the magnitude and longevity of available (dislodgeable) pesticide residues found on crop and turf leaf surfaces after application of a pesticide product according to the directions for use.

The crop and animal residue related studies that are required (or conditionally required) under 40 CFR part 158 (U.S. EPA 2020c) are shown in Table 3.

Table 3: Crop and Animal Residue Studies for a Food-Use Pesticide Active Ingredient

Type of Study	Required and Conditional Information and Tests	
Residue Chemistry	Residue analytical method	Crop field trials
	Multiresidue method	Processed food/feed
	Storage stability data	Proposed tolerances
	Nature of residue: plants, livestock	Field accumulation in rotational crops^{CR}
	Food handling^{CR}	Meat/milk/poultry/eggs^{CR}
	Dislodgeable Foliar and Turf Transferable Residues^{CR}	

CR - Conditionally required study data

Once all the required fate, metabolism, and crop and animal residue data are generated, the next step is to assess worst-case potential exposures to consumers and occupational workers. The goal of the exposure assessment process is to 1) thoroughly evaluate the different routes (i.e., oral, dermal, inhalation) and pathways (i.e., dietary, residential, occupational) by which a pesticide (and its residues) that is used according to a registered label's DFUs can reach all potential human sub-populations and 2) conservatively quantify the potential exposure of a pesticide to human sub-populations for different durations, as applicable, to then be compared with the health-protective POD to arrive at an estimate of potential health risk. The comprehensive exposure assessment methodology including the key *health-protective* assumptions involved in the methodology are discussed in the following sections.

4.2.3 Consumer exposure assessment

The general consumer in the U.S. can potentially be exposed to a pesticide through dietary, drinking water, recreational, and residential pathways. The EPA mandates that potential dietary and residential exposure to all life stages of the U.S. human population, from infants to seniors aged 99 years are evaluated, as applicable (U.S. EPA 1996b). In general, the EPA uses a tiered approach for assessing consumer exposure, with low-tier or screening-level assessments typically using several worst-case and highly conservative assumptions. When a candidate pesticide passes this worst-case scenario, there is a high degree of certainty regarding no adverse health risk to the consumer. Failing a low-tier assessment doesn't necessarily indicate an actual adverse health risk; rather, it substantiates the need for a high-tier, refined risk assessment. A high-tier assessment utilizes more realistic assumptions to evaluate exposure, while still maintaining the overall health-protective approach (U.S. EPA 2000a; U.S. EPA 2001a).

4.2.3.1 Dietary and drinking water exposure

The U.S. EPA's regulatory model uses two types of data to comprehensively estimate dietary and drinking water exposure: 1) pesticide residue(s) in and/or on food; and 2) food consumption data of a representative U.S. subpopulation (U.S. EPA 2012a). Data on pesticide residue(s) in/on food are obtained as discussed in the above sections, while the food consumption data used is from the EPA's What We Eat in America - Food Commodity Intake Database based on the nationally representative National Health and Nutrition Examination Survey of food and beverage consumption data which provides realistic estimates of what actual people ingest over a two-day time period (U.S. EPA 2021c).

The dietary and drinking water assessment approach as required by the EPA (U.S. EPA 2000a) uses several health-protective model assumptions, including:

- Low-tier deterministic acute dietary assessments assume worst-case tolerance-level residue values, worst-case processing factors for processed commodities, and assuming one hundred percent of the crop is treated by the pesticide; in these cases, the 95th percentile of any modeled sub-population's exposure is used for assessing risk, which will result in unrealistic overestimates of the percentile of the population at risk (U.S. EPA 2000a; U.S. EPA 2000b).

- Middle-tier deterministic acute dietary assessments use somewhat more realistic residue data (for example, field trial residues and empirical processing factors generated from processing studies), while higher-tier probabilistic acute assessments use even more realistic residue data (for example, Pesticide Data Program residue monitoring data) and percent crop treated values, but the health-protective standards are still maintained by requiring the use of 99.9^{th} percentile of any modeled sub-population's exposure for assessing risk.
- Drinking water concentrations used in the consumer model are usually an over-estimation based on maximum labeled pesticide use rate and frequency and the use of worst-case chemical fate and transport parameters in modeling the pesticide concentrations in different environmental matrices (Moore et al., 2021).
- It is assumed that 100% of pesticide residues that are ingested by consumers are absorbed systemically and that none is excreted without toxicologic effect.
- When calculating livestock dietary burden (to estimate human exposure through milk, meat and eggs) it's assumed that most, if not all, of what the animal is eating is treated with the pesticide being evaluated, which is also highly conservative.
- Potential exposure to sensitive population including infants, children, women of child-bearing age and seniors are evaluated separately to make sure that they are safe.

4.2.3.2 Residential and other non-occupational exposure

In addition to the dietary pathway, the other potential pathways for exposure of a general U.S. consumer to pesticides are the residential and the recreational/non-occupational pathways. These include exposure from pesticide application to areas such as lawns and turf, gardens and trees, indoor environments, drift from agricultural applications, etc. The EPA requires the use of its Standard Operating Procedures (SOPs) for evaluating such pesticide exposures to different sub-populations, as applicable (U.S. EPA 2012b). As required by FQPA, each pesticide must be evaluated through all exposure routes and pathways for each scenario in which it is intended for use, thereby mandating a thorough evaluation for each scenario. The health-protectiveness in the approach can be based either on the underlying choice of inputs or the exposure assessment model and its assumptions:

- Most input data used in residential assessments are high-end point estimates from scientifically well-accepted data distributions, such as the exposure factor's handbook (U.S. EPA 2011) or peer-reviewed scientific publications. For example, arithmetic means or maximum values from population-level survey data are used for inputs such as body weight, deposited and transferable residues, residential activity durations, transfer coefficients, hand-to-mouth frequencies among children, etc. These multiple conservative input values, when combined, provide worst-case exposure estimates that are health-protective.
- The EPA uses the simple model to represent scenarios throughout the residential SOPs, with simplifying assumptions that are highly health-protective (U.S. EPA 2012b). For example, with the indoor environment

post-application exposure, the SOP assumes that all the applied pesticide is available for inhalation, and that all the applied pesticide settles onto the floor and is available for dermal exposure, i.e., no pesticide dissipation is accounted for. Such assumptions, combined with the choice of input data, together make sure that exposure is over-estimated to be protective of the general public.

It is to be noted that the EPA acknowledges that their SOPs are conservative and are designed to be health-protective (U.S. EPA 2012b).

4.2.3.3 Aggregate and cumulative exposures

As mandated by the FQPA act of 1996 (U.S. EPA 1996b), the EPA evaluates consumer risks from aggregate exposure to the same pesticide (through different routes/pathways such as food, water, and residential uses) as well as cumulative exposures to groups of pesticides sharing the same mechanisms of toxicity, on a case-by-case basis. A pesticide can only be registered in the U.S. if the aggregate and cumulative risks are acceptable at the proposed label use rates (U.S. EPA 2001a; U.S. EPA 2002d). These evaluations also follow a tiered-approach and employ the health-protective assumptions described thus far. Key health-protective assumptions include:

- In the aggregate exposure assessment, the same individual is assumed to be exposed to both the worst-case dietary exposures and worst-case residential exposures at the same time, which is highly unlikely.
- In the cumulative exposure assessment, the assumption of tolerance-level residues on all crops and the assumption that 100 percent of a crop grown in the U.S. is treated by every chemical in a common mechanism group is represents an unrealistic worst-case scenario, but is clearly health-protective.

4.2.4 Occupational worker exposures

Occupational workers who handle pesticides constitute the other key population mandated by the EPA to be protected from identified hazards posed by pesticides. This includes field handlers, re-entry workers, post-harvest commodity treatment workers, and seed treatment workers. Unlike consumers, these workers are directly involved in handling pesticide products based on label DFUs. Hence, the EPA and other stakeholders have worked together to generate data from surveys and real-world exposure studies to identify and quantify potential worker dermal and inhalational exposures to pesticides. The EPA Exposure Advisory Council's guidance documents for assessing risks to each broad category of occupational worker are shown in Table 4 below (U.S. EPA 2001b; U.S. EPA 2021d; U.S. EPA 2021e; U.S. EPA 2022a; U.S. EPA 2022b; U.S. EPA 2018b). These provide the standard methods and health-protective assumptions for assessing pesticide exposure for any occupational activity. The key determinants for occupational exposure are: 1) formulation type; 2) application equipment and worker activity types; 3) the personal protective equipment worn by the worker; 4) standard values for area treated with a pesticide/pesticide amount handled; and 5) standard values for unit exposure (microgram of pesticide available for exposure for every single pound of pesticide handled).

Table 4: The U.S. EPA's Current Guidance for Different Occupational Worker Risk Assessments

Occupational Worker Type	Relevant U.S. EPA Guidance Document
Field handler	ExpoSAC* policy 9.1, Occupational Pesticide Handler Unit Exposure Surrogate Reference Table
Re-entry worker	ExpoSAC policy 3
Seed treatment worker	ExpoSAC policy 14 and 15.2
Post-harvest commodity treatment	Assessment of Occupational Exposure for Post-Harvest Commodity Pesticide Treatments

**Scientific Advisory Council for Exposure*

The EPA's approach to assess exposure and risk to the different occupational worker scenarios include several health-protective assumptions as listed below:

- The unit exposure is the basis for occupational handler exposure assessment, and it is derived from various worker exposure study data approved by the EPA to be health-protective (U.S. EPA 2021d; U.S. EPA 2022a). These worker exposure data are based on comprehensively conducted and peer-reviewed passive dosimetry worker exposure studies aggregating dermal exposures from the worker's face, neck, arms, head, and the torso, as well as the potentially inhaled exposures.
- The EPA requires the use of arithmetic mean unit exposure values from worker exposure study data distributions, which is almost always greater than the 50th percentile of the underlying data (exposure distributions are typically right skewed, dominated by a few high individual exposure datapoints, while most of the individual exposure datapoints are below the mean).
- Another adjustment the EPA uses in determining unit exposures from worker exposure data is the Method Efficiency Adjustment, whereby if the measured hand wash, face and neck wipe exposures contribute between 20 and 60 % of total exposure, a default doubling of the hand wash, head and neck wipe pesticide exposure measures to the total exposure measure is required by the EPA. This adjustment is to account for inefficiency in the removal of pesticide residues from skin and is again health-protective.
- In some cases, the EPA uses an fRA (fold relative accuracy) correction factor to correct for variability in the worker unit exposure estimates, owing to the high spread of the individual worker data points for a worker scenario unit exposure. If the fRA benchmark value is determined to be greater than 3-fold, an automatic multiplier fRA correction factor is added to the unit exposures.
- The EPA requires the use of typical to high-end values for daily area treated by a worker or amount of product handled by a worker in a day in the exposure calculations. In the real world, not every worker is expected to always be involved in such high levels of activity, for example, the assumptions that an aerial applicator will treat 1200 acres of high acre field crops per day or a groundboom applicator will treat 200 acres of high acre field crops per day are worst-case high-end values and not expected from a typical worker (U.S. EPA 2001b).

- In most cases, for liquid application, it is assumed that 100% of the pesticide available for inhalation is absorbed into the operator's systemic circulation. However, the particle size distribution of the applied pesticide droplets determines the availability for inhalation and medium to coarse droplet sizes are expected to settle quickly and not be inhaled. Even when such sized droplets are inhaled, due to their size, they mostly get deposited in the upper respiratory tract and cleared by the muco-ciliary escalator system and not all the inhaled particles enter the systemic circulation.
- The use of worst-case dermal absorption factor (between the concentrated product and diluted product) for modeling dermal exposure is supposed to be health-protective
- It is assumed that the re-entry workers do not wear any PPE and hence more susceptible to dermal exposures, whereas in reality, some workers might wear PPE for re-entry activities
- If chemical-specific DFR and TTR data are not available for re-entry worker exposure, health-protective default values for day zero DFR (25% of application rate) and day zero TTR (1% of application rate for liquids and 0.2 % of application rate for solid formulations) and daily dissipation rate (10%) are assumed. Chemical-specific DFR and TTR studies are waived only if the MOE resulting out of the default assumptions is higher than the LOC by a factor of four and 10 respectively, for DFR and TTR studies to be waived (U.S. EPA, 2012c). Thus, the health-protective standards are still maintained in the exposure assessment process when chemical-specific DFR and TTR data are not available.

Together, these worst-case assumptions ensure that the pesticide exposure to an occupation worker is over-estimated for use in the risk assessment, thereby the worker's risk estimate, if acceptable, is protective of the worker's health. In addition to the health-protective operator exposure and risk assessment methods employed by the EPA as described above, the agency also mandates agricultural worker protection standards, under 40 CFR part 170 (U.S. EPA 2020d), which are aimed at mitigating exposure and preventing any unreasonable adverse effects among farmworkers and their families, pesticide handlers, and any other people (including vulnerable populations such as minority and low-income populations) who might be on or near the agricultural establishment.

So far, we have described in detail how estimates of the potential hazard and exposure to a pesticide are derived, while being comprehensive, conservative (often worst case), and thereby *health protective*. The next two sections explain how these are combined to characterize potential risk to humans, and the resulting compounded nature of health-protective assumptions in this whole process mandated by the EPA to register and use a pesticide.

4.3 Risk Characterization

In general, the EPA utilizes margin of exposure (MOE) to estimate/characterize risk, i.e., to integrate the hazard and exposure information, and to describe the resulting potential risk of using a particular pesticide as directed by the label (U.S. EPA, 2001a). For each potential exposure scenario (dietary, residential, and occupational handler) and for each potential exposed human sub-population (depending on use scenario and the sub-population's potential for exposure from that use scenario), the

margin of exposure is calculated by dividing the *health-protective* estimate of the potential 'hazard' by the *health-protective* estimate of potential 'exposure'. This number is then compared with the level of concern (LOC), which is an estimate of total potential uncertainty in the estimates of hazard (calculated by multiplying all health-protective safety/uncertainty factors). The exposure level for any scenario is considered acceptable only if the MOE is greater than the LOC. In evaluating consumer exposures, MOEs from different pathways (dietary and residential) are combined before comparing with the LOC, to account for aggregate risks. In cases where carcinogenicity is a potential outcome, when the dose-response is linear, the cancer potency factor is multiplied by the estimated average human exposure to arrive at risk in terms of probability of developing cancer following a lifetime of exposure (U.S. EPA 2005); when the dose response is non-linear, a threshold-based MOE approach will be used to characterize risk.

5. Compounding Health-Protectiveness

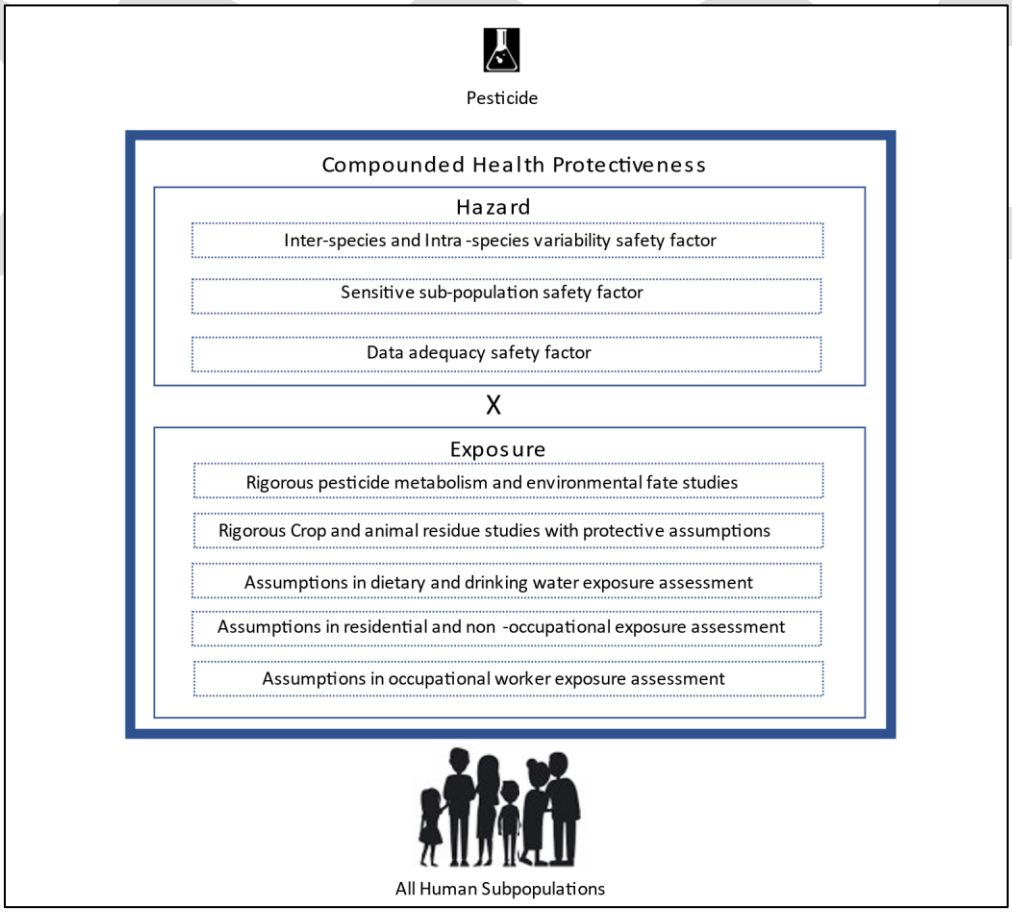

Figure 2: Illustration of the layers of safety leading to compounded health-protectiveness in the U.S. EPA's pesticide HHRA process

The EPA's pesticide HHRA process has several layers of conservatism and protection built into the hazard and exposure assessment steps, which compound to protect all human sub-populations in the U.S. from pesticide health risks as illustrated

in Figure 2. Hazard identification assumes human relevance unless the weight of evidence demonstrates otherwise, even for marginal hazards at high doses far exceeding realistic human exposures. Dose-response assessment selects a dose where no hazard was observed in the most sensitive animal species tested and divides that dose by UFs to derive a human RfD or LOC. Exposure assessment for each use scenario assumes worst-case human exposures to avoid underestimation. These health-protective assumptions compound and overestimate pesticide exposure, and in turn, the estimated risk. If a pesticide risk assessment which strictly follows the current comprehensive and stringent FIFRA regulatory framework results in an MOE that is greater than the LOC, with all the inherent health-protective assumptions, this demonstrates that the pesticide when used according to its EPA-reviewed and approved label directions, "will not generally cause unreasonable adverse effects or harm to humans."

6. Discussion

As illustrated in this commentary, the strength of the EPA's pesticide regulation process lies in the comprehensive methods and health-protective assumptions used to evaluate potential human health risks from pesticides. With U.S. consumers, the key route of potential exposure is through consumption of commodities treated with a given pesticide and any residues in drinking water. Regulatory field trials, by nature of their study design, present a worst-case representation of residue levels that can be expected in crop commodities following pesticide application. The US Department of Agriculture Pesticide Data Program (PDP), provides national pesticide residue monitoring of fresh produced and processed goods with an emphasis on those consumed by infants and children (USDA, 2015). The PDP has collected residue data for 30 years to help enable the EPA to assess real world dietary exposure to pesticides. Over the last five years, <2% of PDP samples had pesticide levels above an established tolerance on a given year, and less than 9% had detections when a tolerance wasn't established. A previous analysis of the 2010 PDP data had shown that the expected consumer chronic exposures to the 10 most frequently detected pesticides in the commodities thought to be of most concern were all negligible (CAST, 2019; Winter & Katz, 2011). However, it should also be noted that the PDP program has a variable detection limit; hence the interpretation of the data should be done carefully. With acute dietary assessments, a recent comprehensive collaborative effort led by the World Health Organization with regulators from across the world, including the U.S. EPA also concluded that the general population is adequately protected. Probabilistic acute dietary assessments (including 38 pesticides and data from eight countries) were conducted using real-world regional pesticide residue monitoring data and it was demonstrated that even with the worst-case assumption that 100% of the crops were treated with each pesticide in question, there was no appreciable risk to human sub-populations, including children, in the U.S. and seven other countries (Crépet et al., 2021). Residential use is the other potential pathway for consumer exposure to pesticides. The EPA's residential SOPs for consumer residential exposure assessment already use health-protective methods and assumptions to cover for any uncertainty in the risk estimation. The compounding health-protectiveness of the U.S. regulatory system demonstrated in this commentary ensures that the registered uses of pesticides are safe to U.S. consumers.

Occupational workers are required to follow the pesticide label instructions for

PPE, permissible application rates and methods, safety precautions, mitigation options and best practices to reduce or prevent any harm to workers. The robust worker exposure study data and methods used in the EPA Exposure Advisory Council's guidance documents for assessing risks to occupational workers include several health-protective assumptions as discussed earlier in the commentary and consistently over-estimate occupational workers' potential exposures. Health-protective layers of safety are consistently seen throughout the EPA's methods for estimating exposure for occupational worker activities. Together with the EPA's stringent worker protection standards (WPS), these measures are designed to ensure there is no harm to workers. In addition to the aforementioned safety standards and precautions for consumer and occupational workers, the EPA regularly reviews public health incident data for each registered pesticide active ingredient from various sources, including the U.S EPA's Office of Pesticide Programs Incident Data System; the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health; the Sentinel Event Notification System for Occupational Risk-Pesticides; the Agency-sponsored National Pesticide Information Center; and California's Pesticide Incident Surveillance Program databases. These reviews classify any human incidents into low, moderate, high severity and, in rare cases, reported deaths. Based on the severity of human incidents and the trend of incidents over time, the EPA may require changes in label language including potential mitigation measures to restrict unintended exposures, increased PPE, enhanced visual warning signs on labels (U.S. EPA 2021f). In some cases, the EPA may classify a pesticide as a Restricted-Use-Pesticide (U.S. EPA 2021g). In summary, throughout the EPA's pesticide regulatory process, the assumptions and procedures in place consistently over-estimate both hazard and exposure, thereby evaluating risks to humans through a conservative and *health-protective* lens. The EPA is required to re-evaluate the safety of registered pesticides every 15 years, considering all new safety data that are available since the time of the initial registration. When registering and re-registering a pesticide, the EPA is required by law to holistically evaluate both the potential economic, social, and health benefits and potential health risks to the U.S. population and the environment (U.S. EPA 1994). At every stage of the pesticide regulatory process, there is an opportunity for the general public to participate by providing comments on study findings. In addition to this safety evaluation system, the EPA also encourages registrants to develop and submit new 'reduced risk' pesticides for registration. If the registrant demonstrates evidence that a new pesticide can significantly reduce the potential risk (to humans and/or the environment) relative to any existing registered alternatives, the submission is given preference over other non-reduced risk submissions. (U.S. EPA 2021h).

A frequent issue with pesticide risk perception is the detection of some pesticides and/or pesticide metabolites in blood or urine of the U.S. population, as seen in the U.S. Centers for Disease Control and prevention's National Health and Nutrition Examination Survey biomonitoring data. As part of this effort, pesticides have been monitored in biological samples of a representative sample of the noninstitutionalized U.S. civilian population since 1988. While such data are very helpful in providing a snapshot of the body burden of a chemical at any point in time, spot biomarker concentrations should be treated with caution as they do not represent

average or peak exposure levels and there is a high potential for measurement error. Such detections of pesticides or their metabolites cannot be directly interpreted as evidence for or against public harm or adequacy of the EPA's regulatory process. Especially with pesticides, which typically have short half-lives in the human body, making meaningful exposure and risk extrapolations from single biomarker measurements is tenuous. Additional models are required to link the measured biomarker levels to external exposures in a causal framework. The use of 'biomonitoring equivalents', which are defined as levels of chemicals/metabolites in the biological media that correspond to exposure at a guidance level (such as the human Rfd discussed), has been proposed as a viable approach to use human biomonitoring data to inform policy decisions. This is a scientific area which requires further advancements in the design and methods of analysis, and interpretation of the resulting data, before they can be meaningfully incorporated in pesticide HHRA and regulatory decisions (Sobus et al., 2015; Hays et al., 2007).

Previous and ongoing scientific arguments against the adequacy of the EPA's pesticide regulatory process to protect humans exist. For example, Bruce et al., 2022 argue that the regulatory process only evaluates the pesticide active ingredients and does not evaluate the end-use formulated product which contain other inert ingredients including surfactants, dyes, antifoaming agents, and adjuvants. The authors suggest that these ingredients are assumed to be benign, but there is concern that the together with these, the final formulated pesticide product might be more hazardous than the pesticide active ingredient itself. However, the EPA has been actively evaluating the toxicity of inert ingredients before their use in formulated pesticide products since 1987. The EPA has also started reassessing tolerances for such ingredients, following the same general principles of minimum safety requirements that active ingredients are evaluated on (U.S. EPA 2022c). Evaluation of health risks posed by exposure to chemical mixtures is mandated by the FQPA act and on a case-by-case basis, the EPA uses previously published risk assessment methods to evaluate and characterize risks from chemical mixtures (U.S. EPA 2022d).

Another criticism is that the EPA primarily uses the data provided by the registrants to conduct safety evaluations and arrive at risk assessment conclusions. The authors suggest that with the perceived inherent conflicts of interest, the EPA's pesticide risk assessment process is compromised. (Boone et al., 2014). As we have described so far in the commentary, the data provided by the registrants follow rigorous Good Laboratory Practice Standards to ensure data quality, integrity, and reproducibility; and the laboratories that conduct such studies are audited by the Agency periodically as well. Additionally, the continuous improvement process built-in to the regulatory process ensures that any new pertinent data, regardless of the source, that corroborates or contradicts the original data used in safety evaluations are treated equally and evaluated similarly to inform the ongoing human health risk assessments and related policy decisions. For example, most, if not all, the published environmental epidemiological studies of pesticides are of non-industry origin and the EPA evaluates them in a transparent and rigorous way to inform their human health risk assessments.

In general, it should be acknowledged that no system is perfect; however, the pesticide regulatory process is continuously improving along with advances and new findings in science. As we have demonstrated with our brief history of the

pesticide regulatory system in the U.S. and the advancements in the mandates and methods employed by the EPA over the years, the current regulatory system is designed to be rigorous at any point in time, carefully weighing risks against benefits, and continuously improves to ensure the protection of human health. The U.S. government's pesticide regulatory framework can be considered a classic example of risk-benefit balancing for the greater good of the population. A familiar example of daily risk-benefit analysis involves modern transportation and infrastructure, like cars, airplanes, or bridges, that have the potential to result in serious harm or even death. One possible approach to eliminate the human health risk would be to completely avoid all use of these modern conveniences, but clearly this would have extreme economic, societal, and personal impacts. An alternative approach is to investigate the sources of potential hazard and to identify safety measures that significantly lower the risk of harm. Modern transportation and infrastructure safety has evolved over time to incorporate several health-protective measures like seatbelts and other safety features, maintenance, mandatory safety inspections, government regulations and traffic laws, and education. These risk management strategies have greatly and demonstrably increased safety over time to ensure that the benefits continue to outweigh the risks. Similarly, the HHRA process and resulting label requirements for pesticides ensure that actual human exposures remain orders of magnitude lower than doses that resulted in no harmful health effects in animal studies. Most importantly, the EPA's pesticide regulatory framework ensures the benefits of these essential modern agricultural tools far outweigh any risk to human health. It is the combined responsibility of all stakeholders involved—registrants, growers, regulators, consumers, and agricultural workers—to maintain this risk-benefit balance for the public good.

7. Conclusion

The current U.S. EPA's pesticide regulatory framework is comprehensive, science-based, rigorous, continuously improving, transparent and is unlikely to underestimate risk to ensure the protection of human health. Balancing potential unintended risks through mitigations and strict enforcement, while reaping the economic, health, and social benefits of pesticide use will be key to sustainably serve the growing world population into the future.

8. Declaration of Conflict of Interest

The authors of this paper are employees of Syngenta Crop Protection LLC. No Syngenta pesticide products are promoted in this paper. Rather, the focus is on the pesticide registration process in the United States. No other conflicts of interest exist for the authors of this paper.

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10. References

Boone, M. D., Bishop, C. A., Boswell, L. A., Brodman, R. D., Burger, J., Davidson, C., Gochfeld, M., Hoverman. et al. (2014) Pesticide regulation amid the influence of industry. Bioscience 64(10):917–922

Bruce, A. B., Borlu, Y., Glenna, L. L. (2022). Assessing the scientific support for U.S. EPA pesticide regulatory policy governing active and inert ingredients. Journal of Environmental Studies and Sciences. J Environ Stud

Sci. https://doi.org/10.1007/s13412-022-00788-4

Council for Agricultural Science and Technology (CAST). (2019). Interpreting Pesticide Residues in Food. Issue Paper 66. Retrieved from https://www.cast-science.org/publication/interpreting-pesticide-residues-in-food/

Crépet, A., Luong, T. M., Baines, J., Boon, P. E., Ennis, J., Kennedy, M., Massarelli, I., Miller, D., Nako, S., Reuss, R., Yoon, H. J., & Verger, P. (2021). An international probabilistic risk assessment of acute dietary exposure to pesticide residues in relation to codex maximum residue limits for pesticides in food. *Food Control*, *121*(August 2020). https://doi.org/10.1016/j.foodcont.2020.107563

Food and Agriculture Organization. (2009). Declaration of the World Summit on Food Security. Retrieved from https://www.fao.org/fileadmin/templates/wsfs/Summit/Docs/Final_Declaration/WSFS09_Declaration.pdf

Food Quality Protection Act. (1996). Food Quality Protection Act of1996, Public Law 104-170

Gehen, S., Corvaro, M., Jones, J., Ma, M., & Yang, Q. (2019). Challenges and Opportunities in the Global Regulation of Crop Protection Products [Review-article]. *Organic Process Research & Development*, *23*, 2225–2233. https://doi.org/10.1021/acs.oprd.9b00284

Hays, S. M., Becker, R. A., Leung, H. W., Aylward, L. L., Pyatt, D. W. (2007). Biomonitoring equivalents: a screening approach for interpreting biomonitoring results from a public health risk perspective.Regul Toxicol Pharmacol47:96-10917030369

Lewis, R. W., Billington, R., Debryune, E., Gamer, A., Lang, B., & Carpanini, F. (2002). Recognition of Adverse and Nonadverse Effects in Toxicity Studies. *Toxicologic Pathology*, *30*(1), 66–74. https://doi.org/10.1080/01926230252824725

Maienfisch, P., & Stevenson, T. M. (2015). Modern agribusiness - Markets, companies, benefits and challenges. *ACS Symposium Series*, *1204*, 1–13. https://doi.org/10.1021/bk-2015-1204.ch001

Moore, D. R. J., Mccarroll-butler, C. A., Avanasi, R., & Chen, W., White, M. & Brain R.A. (2021). Regulatory Science How Protective to the Environment is the Pesticide Risk Assessment and Registration Process in the United States ? *Journal of Regulatory Science*, *9*(2), 1–20.

National Research Council. 1983. Risk assessment in the federal government. Managing the process. National Academy Press, Washington, DC.

Organisation for Economic Co-operation and Development. (2016). OECD document on crop field trials. OECD Environment, Health and Safety Publications, Paris, 2016. Retrieved December 1 2021 from https://one.oecd.org/document/ENV/JM/MONO(2011)50/REV1/en/pdf

Popp, J., Hantos, K. (2011). Studies in agricultural economics. No. 113. *Stud Agric Econ*, *113*, 47–66.

Popp, J. (2011). Cost-benefit analysis of crop protection measures. *Journal Fur Verbraucherschutz Und Lebensmittelsicherheit*, *6*(SUPPL. 1),

105–112. https://doi.org/10.1007/s00003-011-0677-4

Sobus, J. R., DeWoskin, R. S., Tan, Y., Pleil, J. D., Philips, M. B., George, B. J., Christensen, K., Schreinemachers, D. M., Williams, M, A., Cohen-Hubal, E. A., Edwards, S. (2015). Uses of NHANES Biomarker Data for Chemical Risk Assessment: Trends, Challenges, and Opportunities. Environ Health Perspect 123: 919-927; doi.org/10.1289/ehp.1409177.

United States Department of Agriculture. (2015). Pesticide Data Program. Retrieved December 1 2021 from https://www.ams.usda.gov/sites/default/files/media/PDP%20factsheet.pdf

United States Environmental Protection Agency. (1988). EPA History: FIFRA Amendments of 1988. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1 2021 from https://archive.epa.gov/epa/aboutepa/epa-history-fifra-amendments-1988.html#:~:text=The%20Federal%20Insecticide%2C%20Fungicide%20and%20Rodenticide%20Act%20(FIFRA)%20governs,sold%20or%20distributed%20in%20commerce

United States Environmental Protection Agency. (1994). The role of BEAD in pesticide regulation. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1 2021 from https://nepis.epa.gov/Exe/ZyPDF.cgi/200001EH.PDF?Dockey=200001EH.PDF

United States Environmental Protection Agency. (1996a). Summary of the Federal Insecticide, Fungicide, and Rodenticide Act. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1 2021 from https://www.epa.gov/laws-regulations/summary-federal-insecticide-fungicide-and-rodenticide-act

United States Environmental Protection Agency. (1996b). Summary of the Food Quality Protection Act. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1 2021 from https://www.epa.gov/laws-regulations/summary-food-quality-protection-act

United States Environmental Protection Agency. (2000a). Available information on assessing exposure from pesticides in food- A User's guide. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1 2021 from https://www.regulations.gov/document/EPA-HQ-OPP-2007-0780-0001

United States Environmental Protection Agency. (2000b). Choosing a percentile of acute dietary exposure as a threshold of regulatory concern. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1 2021 from https://www.epa.gov/sites/default/files/2015-07/documents/trac2b054_0.pdf

United States Environmental Protection Agency. (2001a). General Principles For Performing Aggregate Exposure And Risk Assessments. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1 2021 from https://www.epa.gov/sites/default/files/2015-07/documents/aggregate.pdf

United States Environmental Protection Agency. (2001b). Science advisory council for exposure policy 9.1.

Standard values for daily acres treated in agriculture. U.S. Environmental Protection Agency, Washington, D.C.

United States Environmental Protection Agency. (2002a). Summary of the Federal Food, Drug, and Cosmetic Act. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/laws-regulations/summary-federal-food-drug-and-cosmetic-act

United States Environmental Protection Agency. (2002b). Determination of the appropriate FQPA safety factor(s) in tolerance assessment. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/sites/default/files/2015-07/documents/determ.pdf

United States Environmental Protection Agency. (2002c). A review of the reference dose and reference concentration processes. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/sites/default/files/2014-12/documents/rfd-final.pdf

United States Environmental Protection Agency. (2002d). Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/sites/default/files/2015-07/documents/guidance_on_common_mechanism.pdf

United States Environmental Protection Agency. (2005). Chemicals Evaluated for Carcinogenic Potential by the Office of Pesticide Programs. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from http://npic.orst.edu/chemicals_evaluated.pdf

United States Environmental Protection Agency. Exposure Factors Handbook 2011 Edition (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-09/052F, 2011.

United States Environmental Protection Agency. (2012a). Exposure Models: DEEM-FCID/Calendex/SHEDS. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/deem-fcidcalendex-software-installer#models

United States Environmental Protection Agency. (2012b). Standard Operating Procedure for Residential Exposure and Risk Assessment for Pesticides. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedure-residential-exposure

United States Environmental Protection Agency. (2012c). Guidance for Requiring/Waiving Turf Transferable Residue and Dislodgeable Foliar Residue Studies. U.S. Environmental Protection Agency, Washington, D.C. 2012.

United States Environmental Protection Agency. (2016). Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic &

Incident Data in Risk Assessments for Pesticides Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf

United States Environmental Protection Agency. (2018a). PRIA Overview and History. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/pria-fees/pria-overview-and-history#pria4

United States Environmental Protection Agency. (2018b). Assessment of Occupational Exposure for Post-Harvest Commodity Pesticide Treatments. U.S. Environmental Protection Agency, Washington, D.C. 2012

United States Environmental Protection Agency. (2019). Directive to Prioritize Effects to Reduce Animal Testing. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/sites/production/files/2019-09/documents/image2019-09-09-231249.pdf

United States Environmental Protection Agency. (2020a). PART 180—Tolerances and exemptions for pesticide chemical residues in food. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.govinfo.gov/content/pkg/CFR-2020-title40-vol26/pdf/CFR-2020-title40-vol26-part180.pdf

United States Environmental Protection Agency. (2020b). PART 160—Good Laboratory Practice Standards. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.govinfo.gov/content/pkg/CFR-2020-title40-vol26/pdf/CFR-2020-title40-vol26-part160.pdf

United States Environmental Protection Agency. (2020c). PART 158—Data requirements for pesticides. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.govinfo.gov/content/pkg/CFR-2020-title40-vol26/pdf/CFR-2020-title40-vol26-part158.pdf

United States Environmental Protection Agency. (2020d). PART 170—Worker protection Standard. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.govinfo.gov/content/pkg/CFR-2020-title40-vol26/pdf/CFR-2020-title40-vol26-part170.pdf

United States Environmental Protection Agency. (2021a). Pesticide Registration Manual. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/pesticide-registration/pesticide-registration-manual

United States Environmental Protection Agency. (2021b). About Pesticide Registration. U.S. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/pesticide-registration/about-pesticide-registration

United States Environmental Protection Agency. (2021c). The U.S. EPA's What We Eat in America - Food Commodity Intake Database, 2005-2010 (WWEIA-FCID 2005-10). Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from

https://fcid.foodrisk.org/#

United States Environmental Protection Agency. (2021d). Occupational Pesticide Handler Unit Exposure Surrogate Reference Table. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/sites/default/files/2021-05/documents/occupational-pesticide-handler-unit-exposure-surrogate-reference-table-may-2021.pdf

United States Environmental Protection Agency. (2021e). Science Advisory Council for Exposure(ExpoSAC) Policy 3. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/sites/default/files/2021-03/documents/usepa-opp-hed_exposac_policy_3_march2021_0.pdf

United States Environmental Protection Agency. (2021f). OPP Report on Incident Information: The Baseline. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://archive.epa.gov/pesticides/ppdc/web/pdf/session10-finalrpt.pdf

United States Environmental Protection Agency. (2021g). Restricted Use Products (RUP) Report. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/pesticide-worker-safety/restricted-use-products-rup-report

United States Environmental Protection Agency. (2021h). Conventional Reduced Risk Pesticide Program. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/pesticide-registration/conventional-reduced-risk-pesticide-program

United States Environmental Protection Agency. (2022a). Standard Operating Procedures (SOPs) for Seed Treatment. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/system/files/documents/2022-01/exposac-policy-14_seed-treatment-exposure-data.pdf

United States Environmental Protection Agency. (2022b). Standard Values for Amount of Seed Treated and/or Planted Per Day. Environmental Protection Agency, Washington, D.C. Retrieved December 1, 2021 from https://www.epa.gov/system/files/documents/2022-01/exposac-policy-15_amount-seed-treated-planted.pdf

United States Environmental Protection Agency. (2022c). PRN 97-6: Use of Term "Inert" in the Label Ingredients Statement. Environmental Protection Agency, Washington, D.C. Retrieved November 1, 2022 from https://www.epa.gov/pesticide-registration/prn-97-6-use-term-inert-label-ingredients-statement

United States Environmental Protection Agency. (2022d). PRN 97-6: Developing Relative Potency Factors For Pesticide Mixtures: Biostatistical Analyses Of Joint Dose-Response. Environmental Protection Agency, Washington, D.C. Retrieved November 1, 2022 https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=66273

Winter, C. K., & Katz, J. M. (2011). Dietary exposure to pesticide residues from commodities alleged to contain the

highest contamination levels. *Journal of Toxicology*, *2011*(6). https://doi.org/10.1155/2011/589674