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Review

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A comprehensive review of the regulation of fluorinated pesticide ingredients by the U.S. Environmental Protection Agency

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SUMMARY

Per- and polyfluoroalkyl substances (PFAS) have gained attention and been subject to public scrutiny due to concerns related to perceived health risks associated with high-profile chemicals within this class. However, the term "PFAS" is strictly related to the presence of specific structural features and describes a diverse class of chemicals with distinct chemical, physical, and toxicological properties. While different definitions of PFAS have been put forth, some are so broad that they include a number of chemicals that are already extensively regulated, such as fluorinated pesticide ingredients (FPIs), defined as pesticides that have at least one fluorine atom bonded to a carbon atom. The purpose of this review is to provide a comprehensive overview of FPIs, including clarity on the state and federal regulatory frameworks for all pesticides, discussion of PFAS definitions, an overview of the technical safety framework for FPIs, and overall regulatory considerations that can help avoid unnecessary alarm and potential burdens on critical activities that require pesticide use in the United States. All pesticides, including FPIs, are subject to extensive toxicological, ecotoxicological, environmental fate and residue chemistry data requirements; human health and ecological risk assessments; and post-market surveillance as required under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) in the United States. Pesticides are essential for the United States' food supply and safety, and overarching bans or restrictions of chemicals based on single molecular structural similarities are not reflective of scientific research or existing safety frameworks, and present unintended challenges and consequences, as seen in recent exemptions and amendments to already-enacted PFAS bans. In summary, it is critical to use specific and justifiable PFAS definitions to alleviate inadvertent and undesired impact on agriculture and innovation.

KEY WORDS: KeywordsPesticides, PFAS, EPA, FIFRA

HIGHLIGHTS

- Risk profiles of per- and polyfluoroalkyl substances (PFAS) for which the Environmental Protection Agency has established limits vary substantially.
- Pesticides are evaluated for hazards associated with high-profile PFAS.
- Broad-stroke PFAS bans may restrict pesticide use with no appreciable benefits to human health.

1. INTRODUCTION

There has been a considerable increase in public health interest and associated laws and regulations on the presence and use of per- and polyfluoroalkyl substances (PFAS) over the past decade.[1–3] This has been exemplified in the USA by the introduction of PFAS legislative bills in 40 of the 50 states between 2016 and 2023.[4] As public interest related to chemicals classified as PFAS has mounted, differences in state- and federal-level definitions of PFAS in broad stroke ban bills have become prevalent, presenting compliance and regulatory framework challenges for fluorinated pesticide ingredients (FPIs) as well as unintended practical consequences. The different definitions of PFAS currently in use by regulatory agencies and their potential impact on FPIs in the context of broad stroke bans are discussed further in Section 1.2.

The acronym "PFAS" has been used to define a broad class of synthetic chemicals characterized by multiple carbon–fluorine bonds. They include many subgroups with different structures

and properties. A recent commentary article, Donley *et al*. (2024), raised potential concerns about the extent of PFAS contamination of pesticide products, and touched on topics including the definition of PFAS and the manner in which FPIs are evaluated by the United States Environmental Protection Agency (EPA).[5] In the commentary, the authors apply a broad definition of PFAS – which goes beyond the definition used by the EPA – and call for the restricted use of products that fall into this category. However, they do not discuss the potential impacts on public health and agriculture that would result from these restrictions, nor acknowledge the processes already in place to ensure that the use of pesticides, including FPIs, does not present an "unreasonable risk to human health or the environment" as required by law.[6]

Pesticides encompass products ranging from herbicides, insecticides, and fungicides to anti-microbials. These products are used across various applications, including seed treatments, protection of growing crops, structural pest control, and sanitation and disinfection in public health and industrial settings. The considerations described in this manuscript could apply to other pesticide use patterns, such as the control of mosquitoes in residential areas, rodents in food processing or storage facilities, or the use of herbicides to control invasive plants in natural environments. Pesticides are a unique class of chemicals regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA); the requirements of which will be described in detail in Section 3. It should be noted that while FPIs are the focus of this manuscript, the regulatory requirements discussed here are applied to all pesticides, regardless of fluorination status.

The purpose of this review is to provide a comprehensive overview of FPIs, including clarity on the state and federal regulatory frameworks for FPIs, discussion of PFAS definitions, an overview of the technical safety framework for FPIs, and overall regulatory considerations that can help avoid unnecessary alarm and potential burdens on agricultural practices in the United States. It is critical that all stakeholders, from lawmakers to consumers, be provided full and accurate context on the safety and critical benefits of FPIs in the United States.

1.1 Regulatory background on FIFRA

In the United States, pesticides are regulated at the national level by the EPA under FIFRA. The original version of FIFRA was enacted in 1947, then heavily revised in 1972 to reflect its current form, which serves as the basis for current pesticide regulations.[7] FIFRA authorizes the EPA to regulate the use of pesticides within the United States, including requiring pesticides that are distributed or sold to be registered (licensed) by the EPA prior to distribution.[7] Note there are certain exceptions to this law, called minimum risk pesticides, that are not required to be registered, but this exception is not applicable to FPIs.[8] A key facet of FIFRA is that EPA needs to determine if the pesticide "when used in accordance with widespread and commonly recognized practice … will not generally cause unreasonable adverse effects on the environment."[9] The comprehensive human health and environmental data requirements required by EPA to make this determination for all pesticides – including FPIs – are further described in Section 3. In addition, states may impose their own additional regulatory requirements beyond the EPA requirements to allow for the use of pesticides in their respective jurisdictions.[10]

It is important to note that in addition to FIFRA, the FFDCA requires EPA to set tolerances (also known as maximum residue levels) for foods marketed in the United States.[11,12] Through human health risk assessments, EPA determines the toxicity of the FPI parent compound and its potential degradates to create health-based safety thresholds that inform the chemical residue tolerance level. In addition, the Food Quality and Protection Act (FQPA) amended FFDCA in 1996 and required EPA to consider the special susceptibility of children to pesticides, the aggregate risk exposure to a pesticide from multiple sources (e.g., food, water, and residential applications) and the cumulative risk for pesticides that share a common mode of action for toxicity.[13]

A typical pesticide formulation is composed of active ingredient(s) and the inert ingredients. EPA requires "extensive data requirements as outlined in 40 CFR 158" for both types of ingredients for pesticide registration.[14]

The active ingredient is defined by the EPA as the "chemical in a pesticide product that prevents, destroys, repels, or mitigates a pest, or acts as a plant regulator, defoliant, desiccant, or nitrogen stabilizer."[15] Essentially, the active ingredient is the substance that controls the pest. Every pesticide label is required to display the name and percentage by weight of each active ingredient within the pesticide.[16] Therefore, any pesticide with an active ingredient containing a fluorinated structure is readily disclosed to any stakeholder.

The inert ingredient is any other ingredient that is not the active ingredient, and these can include compounds that play an indirect role in the pesticide's performance, including, but not limited to, increasing penetrance of the active ingredient into the plant, preserving the active ingredient, and improving safety for the applicator.[17] Note that, in this context, the term "inert" should not be misconstrued as biologically or chemically inactive, and inert ingredients require their own human health and environmental information to be submitted to EPA prior to their use in a pesticide product (see Section 3 for more details). The active ingredient(s) and the inert ingredients in their entirety comprise the commercial formulation of the pesticide, and although the active ingredient and concentration are always disclosed, the inert ingredients are kept confidential from the public to preserve the commercial value of the formulation for the registrant as outlined in 7 U.S.C. 136e(d). Note that a lack of public disclosure on the pesticide label should not be conflated with a lack of safety data, as the approved use of an inert ingredient can only be made after the inert ingredient's safety profile is reviewed by the EPA.[18] Moreover, under EPA regulations, the inert ingredients need to be disclosed on the label if a determination is made "that such ingredient(s) may pose a hazard to man or the environment."[16] As described further in Section 3, inert ingredient toxicological, ecotoxicological, environmental fate, and exposure assessment data need to be submitted prior to approval by the EPA for use in pesticides. In summary, while inert ingredients do not require the same level of public disclosure on the label as active ingredients, they do require safety information to be submitted to

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and approved by the EPA *prior* to their use in marketed pesticide end-use products.

1.2 PFAS legislation in the states and definitions

As previously mentioned, state-level PFAS legislation has become widespread in the United States.[4] While some bills mention specific molecules, such as those for which EPA has established drinking water limits (discussed further in Section 2.1), many seek to limit the sale or use of PFAS as a class within specific product types (i.e., firefighting foam). These broad class-wide bans have been put forth with the intention of protecting the public from exposure to chemistries that fall into this category. The introduction of class-wide bans necessitates defining the molecular structure(s) that would result in inclusion as a PFAS.

This is often the source of significant contention in the legislative process, as there is no universally accepted definition of PFAS.[19,20] In general, the acronym "PFAS" refers to chemicals with carbon chains that are "highly" (polyfluoroalkyl) or "fully" (perfluoroalkyl) fluorinated. Figure 1(a) and (b) includes two examples of fully fluorinated carbon atoms: (a) a terminal carbon atom with three fluorine atoms, and (b) a carbon atom with two fluorine atoms. In the states, definitions range from specifying structural characteristics to a vague "per- and polyfluoroalkyl substances," or even including no definition at all (Figure 1c). Fluorinated chemicals, including PFAS, have a range of physical

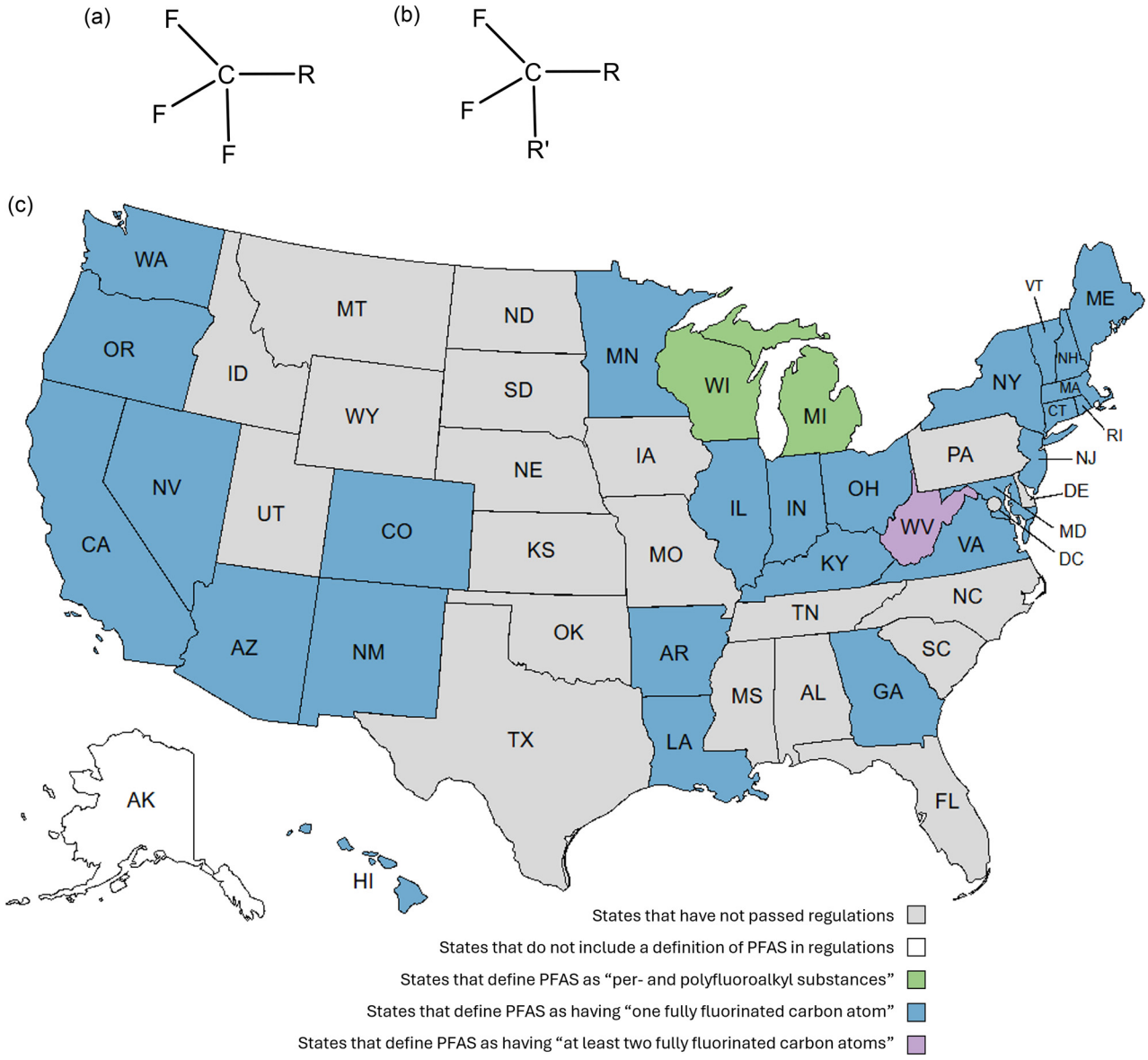


Figure 1. Fully fluorinated carbon atoms (a, b) and PFAS definitions cited in passed state regulations that restrict or prohibit the sale or use of products that contain PFAS (as of December 17, 2025) (c).

and chemical properties as well as toxicological characteristics. The variety that exists in these properties demonstrates that broad definitions of PFAS are only helpful insofar as delineating whether or not the above-mentioned chemical structures are present. Regardless, the definition of PFAS continues to evolve to reflect study and knowledge of these chemicals and can vary depending on the regulatory body and intended application of the regulation.[19] Generally, PFAS definitions referenced by regulatory and guidance authorities describe more specific structural characteristics than those described above.

1.2.1 One fully fluorinated carbon atom

The Organization for Economic Co-operation and Development (OECD) published a report in 2021 that included a revised definition of the PFAS class and guidance for using that definition in a regulatory context.[21] OECD's revised definition of PFAS broadened the scope of included chemistries and is inclusive of, with a few noted exceptions, any substance with at least one fully fluorinated carbon (–CF_3 or –CF_2–). OECD acknowledged that PFAS, as defined, is a "broad, general, non-specific term, which does not inform whether a compound is harmful or not" and only communicates structural similarities between compounds (i.e., presence of a fully fluorinated methyl or methylene carbon moiety).[21] OECD stated that its rationale behind the revision was to provide a general definition "from the chemical structure point of view" and that the definition "does not conclude that all PFASs have the same properties, uses, exposure and risks." OECD emphasized that its decision to broaden the definition is "not connected to decisions on how PFASs should be grouped in regulatory and voluntary actions."[21] OECD also makes the distinction between their general PFAS definition and user-specific working scopes of PFAS and emphasizes the importance of regulatory bodies and other stakeholders providing "context and rationale for selecting their PFAS working scope in order to provide transparency and avoid confusion by others."[21] In other words, OECD recommended using chemical-specific criteria or specifications as a starting point – not an end point – for regulatory or guidance purposes rather than their broad and general PFAS definition.

Despite OECD's emphasis on the need to develop specific definitions and scope for regulatory decision-making, many U.S. states have adopted broad OECD-aligned definitions for the regulation of PFAS without a clear rationale for doing so. This has largely been a result of public awareness of PFAS, concerns related to specific small-molecule PFAS (see Section 2), and an undifferentiated desire to reduce or eliminate the presence and use of PFAS generally. However, this adoption of broad definitions skips the due diligence of evaluating the specific chemical properties, uses, exposure, and risks of different PFAS as actually recommended by OECD.

Many states, including California, Maine, and Minnesota, define PFAS as "a class of fluorinated organic chemicals containing at least one fully fluorinated carbon atom" in regulations seeking to restrict or prohibit the presence of PFAS in consumer products.[22–24] The states that have utilized this broad definition of PFAS have not provided a rationale as to why this definition was chosen for regulatory purposes. In some cases, states have even gone beyond the OECD definition by stating that a "fully fluorinated carbon," "means a carbon atom on which all the hydrogen substituents have been replaced by fluorine," which would be inclusive of a single fluorine atom on a carbon atom with three covalent bonds to non-hydrogen atoms, such as a constituent of an aromatic ring.[25] Molecules with this type of feature were expressly highlighted in the OECD report as an example of what should not be designated as a PFAS under its definition. Some states have recognized the implications of utilizing a broad definition of PFAS and have more recently included lists of exempted product types and applications, as well as specific subsets of PFAS, and other amendments to PFAS restrictions. For example, in April 2025, New Mexico enacted a PFAS ban notable for its exemption of fluoropolymers – a subset of PFAS essential to a wide range of products across critical applications and industries.[26] Fluoropolymers are distinctive in their size and chemistry compared to other subsets of PFAS, and they are generally considered non-bioaccumulative and practically non-toxic.[27] New Mexico's PFAS ban also excludes a list of product categories and applications, including medical devices, semiconductors, and public health and water quality testing products. These developments underline the importance of further accounting for the low-risk toxicological profiles of fluoropolymers and other subsets of fluorinated chemistries. In addition, Minnesota has introduced several amendments to its PFAS ban, including for commercial and industrial products, and electronic and internal components of products.[28,29] These developments and amendments further underscore the challenges of implementing a broad definition of PFAS for regulatory purposes and demonstrate the need for data-driven and precise language when implementing chemical regulations.

Furthermore, Environment and Climate Change Canada and Health Canada's State of PFAS Report published in March 2025 cites OECD's 2021 PFAS definition and references the OECD 2021 report, stating that it may be necessary to consider more specific working definitions of PFAS by "combining the general definition of PFAS with additional considerations (e.g., specific properties or use areas)," which "may be beneficial when contemplating regulatory or non-regulatory approaches to reduce exposure."[30]

The regulatory implications of defining PFAS broadly are far more nuanced than a simple structural definition can capture. An independent panel of experts agreed that a broad definition of PFAS, such as the OECD 2021 definition, "needs to be refined for specific risk assessment goals" and acknowledged the importance of "subgroupings and the ability to group PFAS into more defined lists based on the problem formulation and regulatory context."[31] Even a published statement in support of defining PFAS using the OECD definition considered the difference between a chemical definition of PFAS and a definition used for regulatory purposes.[32] The authors recognized and acknowledged OECD's recommendation to adopt more specific PFAS definitions for regulatory purposes, stating that decision-makers should "[define] their own scope based on political and/or regulatory objectives, ideally with clear, transparent justification."[32]

1.2.2 Two or more fully fluorinated carbon atoms

At the federal level, the EPA acknowledges that they do not have one agency-wide definition for PFAS. EPA has issued several definitions of PFAS under different programs, depending on the program intention and application, and noted that *"[t]he term 'PFAS' has been used broadly for varying research and/or regulatory needs,"* and that more specific definitions may be needed for EPA programs that have distinct needs or purposes.[33] EPA has cited different PFAS definitions in regulation, including the Toxic Substances Control Act (TSCA) Significant New Use Rule (SNUR) for inactive pesticide ingredients, TSCA Section 8(a)(7) Reporting Rule, and EPA's Drinking Water Contaminant Candidate List (CCL). These definitions describe structural characteristics of fluorinated compounds and generally define PFAS as having at least two sequential or non-sequential fully fluorinated carbons.

The TSCA PFAS definition includes chemistries with three structural characteristics: (1) R-(CF_2)-CF(R′)R″, where both the CF_2 and CF moieties are saturated carbons, (2) R-CF_2OCF_2-R′, where R and R′ can either be F, O, or saturated carbons, or (3) $CF_3C(CF_3)$R′R″, where R′ and R″ can either be F or saturated carbons; essentially encompassing chemistries with adjacent fully fluorinated carbons or fully fluorinated carbons separated by an oxygen or carbon atom.[34] EPA's rationale for the structure-based definition of PFAS is to focus "on substances most likely to be persistent in the environment," acknowledging that "the persistence of organofluoro compounds is more related to the density of C–F bonds within the molecule than to the existence of fully fluorinated carbons."[34] Furthermore, EPA also acknowledges that the definition does not include compounds with "a single fluorinated carbon, or unsaturated fluorinated moieties (e.g., fluorinated aromatic rings and olefins)" as these compounds "are more susceptible to chemical transformation than their saturated counterparts, and therefore, are less likely to persist in the environment."[34] EPA's PFAS definition cited in the CCL 5 published in 2022 is similar to the definition cited under TSCA, with an added limitation that the R groups cannot be hydrogen.[35] EPA states that this structural definition "captures PFAS known to occur in drinking water and/or source water" and includes "chemical intermediates, degradates, processing aids, and by-products of PFAS manufacturing."

EPA consistently highlights in their regulatory programs that utilizing a specific and direct PFAS definition relevant to the program's purpose and application is important. As mentioned in Section 1.1, EPA is required to ensure that the use of a pesticide will not pose an unreasonable risk to human health or the environment. The agency evaluates this through the review of extensive datasets as part of its human health and environmental risk assessments, which will be described in detail in Section 3. EPA has clarified that the "same standard applies to pesticides that contain a single fluorinated carbon."[36] The use of data-driven risk assessments allows the agency to regulate pesticides, including FPIs, according to measured versus assumed toxicological properties.

1.3 Review of fluorinated pesticide ingredients and definitions

Given the use of various definitions across non-specific PFAS restrictions introduced at the state level, it is helpful to see how many active and inert ingredients would be included under each definition. An evaluation of registered active and inert FPIs was conducted to determine how many FPIs meet the OECD and EPA TSCA definitions, utilizing EPA's System of Registries lists for active and inert pesticide ingredients, the Pesticide Product and Label System (PPLS), and the Knowtify pesticide database for active products.[37–40] All currently registered (as of July 30, 2025) active FPIs have 3 or fewer adjacent fully fluorinated carbons. Additionally, all but two of the inert FPIs have only one fully fluorinated carbon; the remaining ingredients are fluoropolymers (discussed in Section 1.2.1), with distinct physical characteristics. Of the 126 active and inert organofluorine FPIs (i.e., at least 1 carbon–fluorine bond), 45 (36%) do not meet either the OECD or EPA definition of PFAS and 76 (60%) have a single fully fluorinated carbon, satisfying only the OECD definition of PFAS. The remaining 5 (4%) FPIs, 3 active ingredients and 2 inerts, have more than one fully fluorinated carbon. The 2 inerts and 2 of the active ingredients meet the United States EPA TSCA PFAS definition. Active ingredients that meet this definition have 2–3 fully fluorinated carbons. As discussed, the 2 inert FPIs that meet the US EPA TSCA definition are classified as fluoropolymers. None of the FPIs, including those that meet either the TSCA or OECD PFAS definitions, include structural characteristics that would allow them to degrade or transform into long-chain (>6 fully fluorinated carbons) PFAS, like perfluorooctanoic acid (PFOA) or perfluorooctane sulfonic acid (PFOS).

2. CAUTIONS WITH GROUPING PFAS FOR REGULATORY PURPOSES

Fluorinated chemicals that fall under the "PFAS" umbrella, using either the OECD or EPA definitions, include thousands of molecules with unique structural, chemical, and physical properties. The PFAS structure-based classification does not account for the unique toxicological profiles and functions of the molecules included in this class; thus, it is appropriate to consider more specific or focused groupings of PFAS for risk evaluation and regulatory determinations. To this point, a recent publication from the EPA acknowledged that "the landscape of PFAS substances is substantially large and diverse" and requires a strategic approach to hazard and risk assessment.[41] Authors of the publication presented a grouping strategy based on structural characteristics for hazard assessments of PFAS, with the goal of establishing a category approach to PFAS data collection and assessment. This grouping strategy presents an opportunity to assess PFAS based on structural similarities, accounting for the variability in PFAS toxicological and environmental fate properties. The authors concluded that the approach presents a "robust foundation to aid EPA in addressing the significant challenges associated with evaluating the environmental and human health impacts of this class of chemicals."[41] A panel of experts in Anderson et al. stated that it is "inappropriate to assume equal toxicity/potency across the diverse class of PFAS" and that PFAS should be grouped based on risk and regulatory paradigm for purposes of human health risk assessment, not based on an overly simplified approach which only considers structure. These

published reviews underscore the importance of considering more specific grouping approaches for PFAS.

Overall, variability in PFAS molecular structures and associated functional properties needs to be carefully weighed to determine the safety profiles of individual PFAS. A small case example of variation is described in Section 2.1 for a subset of well-known PFAS.

2.1 Case example of toxicological and environmental property differences between targeted PFAS

For this example, "Targeted PFAS" is defined as PFAS for which EPA has considered regulating under the Safe Drinking Water Act via drinking water maximum contaminant levels (Table 1). In April 2024, EPA announced National Primary Drinking Water Regulations for six data-rich PFAS known to occur in drinking water: PFOA, PFOS, perfluorohexanesulphonic acid (PFHxS), perfluorononanoic acid (PFNA), hexafluoropropylene oxide dimer acid (HFPO-DA; also referred to as GenX), and perfluorobutanesulfonic acid (PFBS).[42] The Targeted PFAS presented in Table 1 are often grouped together based on their similarities in size, fluorinated chain length, and composition of alkyl chains with either sulfonic or carboxylic ends. Note that GenX (CAS RN 122499-17-6) has an exceptional structural formation with a non-linear chain with a fluoroether moiety (CF_2–O–CF–CF_3). The fluorinated alkyl chain commonality between these compounds is thought to contribute to their common functional properties of concern, such as toxicology, water solubility, and bioaccumulation. However, as detailed further, even this small sub-group of PFAS have distinct toxicological and environmental fate properties.

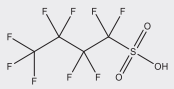
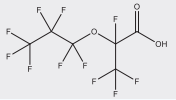
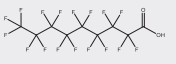
A commonly accepted mechanism of action for PFAS with fluorinated alkyl chains is liver toxicity due to their structural similarity to fatty acids, incorporation into the liver, and activation of proliferator-activated receptor alpha (PPARα) pathways.[43–45] Rats are typically more sensitive to PPARα than humans, and a common biological effect from PPARα activation observed in rat studies is an increase in liver weights.[44–46] However, there are distinct differences in liver effects even within this subgroup of Targeted PFAS as demonstrated with one published assessment evaluating a dose-response analysis on the effects of small- and long-chain PFAS on liver weights in male rats for comparable exposure durations (42–90 days).[46] This assessment developed relative potency factors (RPF) based on benchmark dose modeling applied uniformly across the different studies with PFOA having a RPF of 1.[46] A smaller RPF (<1) indicates the subject PFAS has a lower potency than PFOA (i.e., smaller impact on the liver at the same dose) and a larger RPF (>1) indicates the subject PFAS has higher potency than PFOA. The RPF findings for the other PFAS are presented in Table 1, and show a wide range of potencies with the short-chain PFBS having a RPF of 0.001 and the long-chain PFOS having a RPF of 2. This evaluation shows that even though this small subset of PFAS has high-level similarities in structural characteristics (i.e., alkyl chain, carboxylic or sulfonic head group), their potencies on a commonly recognized mechanism of action can differ by orders of magnitude. Given that FPIs will have a far more wide-ranging set of molecular structural characteristics than this small subset of PFAS, this mechanism of action evidence supports that fit-for-purpose toxicology evaluations for FPIs are far more appropriate than assuming similar toxicological similarities across FPIs. As discussed in Section 1.3, the maximum number of adjacent fully fluorinated carbons across all FPIs was three. It should be noted that short-chain PFAS (e.g., PFBS) show very little potency on liver effects relative to long-chain, which only further emphasizes the inappropriateness of grouping FPIs together based on a single structural similarity (i.e., fully fluorinated carbon).

With regards to toxicological risk assessment endpoints, EPA has identified a range of critical effects and key points of departure (PODs) for Targeted PFAS that would also indicate these compounds do not share the same apical health outcomes (see in Table 1).[47–52] Note that the differences in PODs for Targeted PFAS can vary by orders of magnitude. It is recognized that EPA's identification of critical health effects for Targeted PFAS is controversial in the scientific community.[53,54] An example is the use of vaccine antibody titer changes observed in epidemiological studies for risk assessment for PFOA that may not represent a true adverse outcome because the clinical consequences remain uncertain, and the biological mode of action data needed to evaluate human relevance and plausibility are lacking.[55–57] Furthermore, the studies reviewed by EPA across these six PFAS vary significantly in terms of test system and methods for a given toxicological outcome, preventing the ability to conduct focused potency evaluations across different critical effects. Nonetheless, the wide variation of key critical effects and toxicological thresholds derived by EPA for these Targeted PFAS only further supports that the presence of a fully fluorinated carbon is uninformative for inferring potential biological activity.

From an environmental perspective, fate and transport of PFAS in the environment and biological systems depend greatly on structural characteristics like chain length and functional groups. In general, bioconcentration factors (BCFs) of PFAS tend to increase with increasing fluorinated chain length, indicating a greater potential for bioaccumulation.[58] However, structural features like the head groups (sulfonic and carboxylic acids) and other non-fluorinated components of PFAS also significantly impact variability in bioconcentration as well as biotransformation and half-lives in organisms.[58] Within the Targeted PFAS, log BCFs for an aquatic species differ by several orders of magnitude, ranging from 0.9 (PFOA) to 3.6 (PFOS), both straight-chain chemistries with 7 and 8 fully fluorinated carbons, respectively, but different head groups, and 0.61 for GenX, a fluoroether compound (see Table 1).[59] Similar to the variability in toxicological thresholds and critical effects, the differences in BCFs within the Targeted PFAS support the point that a simple fluorinated structural component cannot inform on the environmental fate and behavior of a class of diverse chemistries.

The Targeted PFAS offer a useful case study in why simply grouping chemicals together based on a single structural feature does not reflect the underlying scientific data on similarities and differences, even for PFAS that share common physical and chemical characteristics such as physical state, water solubility, persistence, and molecular size. Despite being similar in size, fluorinated chain length, and being comprised of alkyl chains with either sulfonic or carboxylic ends, the toxicological and environmental fate characteristics of the Targeted PFAS vary.

Table 1. Differences in toxicological and environmental properties of Targeted PFAS.

Chemical name	Perfluorobutane sulfonic acid	Hexafluoropropylene oxide dimer acid	Perfluorohexane sulphonic acid	Perfluorooctanoic acid	Perfluorooctane sulfonic acid	Perfluorononanoic acid
Acronym	PFBS	HFPO-DA-GenX	PFHxS	PFOA	PFOS	PFNA
CAS number	45187-15-3	122499-17-6	355-46-4	335-67-1	1763-23-1	375-95-1
Chemical structure						
Key structural moieties	Sulfonic acid head Fully fluorinated carbons[4]	Carboxylic acid head Fully fluorinated carbons[5] Fluoroether	Sulfonic acid head Fully fluorinated carbons[6]	Carboxylic acid head Fully fluorinated carbons[7]	Sulfonic acid head Fully fluorinated carbons[8]	Carboxylic acid head Fully fluorinated carbons[8]
Potencies on common mechanism of action[a]						
Relative potency factor (increase in liver weights)	0.001	0.06	0.6	1	2	10
EPA risk assessment						
Critical effects	Endocrine	Hepatic	Developmental, immune	Immune, developmental, cardiovascular	Developmental, cardiovascular	Developmental[b]
Points of departure (HED in mg/kg-bw/day)	0.095	0.01	1×10^{-8}	3×10^{-7}	1×10^{-6}	2×10^{-7}
Bioconcentration factors[c]						
Log BCF	1.35 ± 0.84	0.61	1.30 ± 0.9	0.93 ± 1.15	3.18 ± 0.68	2.16 ± 0.78

[a]Bil et al.[46]
[b]Draft information; EPA has not finalized the toxicity assessment for PFNA.
[c]Burkhard[59]

Grouping molecules with a high degree of structural dissimilarity, such as FPIs, with Targeted PFAS under a broad, simple definition of PFAS to predict or regulate human and environmental risk is inappropriate. These lessons gleaned from review of the Targeted PFAS data indicate that the current EPA approach of using a case-by-case detailed examination of FPI toxicological, ecotoxicological, environmental fate, and exposure parameters to determine overall risk is essential.

3. EXISTING REGULATORY REQUIREMENTS FOR FLUORINATED PESTICIDE INGREDIENTS

Section 2 described the underlying technical issues with grouping the Targeted PFAS under the same definition for the purposes of risk assessment. There are also distinct regulatory considerations regarding how FPIs are regulated, compared to other PFAS compounds such as the Targeted PFAS. As discussed in Section 1.1, FPIs are regulated under FIFRA, while the manufacturing and distribution of Targeted PFAS have historically been regulated under TSCA. Chemicals regulated by TSCA are highly diverse and used in a wide range of applications. The regulatory requirements of TSCA in relation to chemicals that are classified as PFAS by the EPA have been reviewed previously.[1–3] The regulatory requirements outlined under FIFRA for evaluating the safety of FPIs are extensive and comprehensive, especially with respect to the typical concerns associated with the Targeted PFAS discussed above. As such, the purpose of this section is to provide a review of the substantial number of required safety studies generated for FPIs and risk assessment determinations that have to be considered and accepted by EPA prior to FPIs being marketed in the United States. A workflow overview of the extensive toxicological, ecotoxicological, environmental fate and residue chemistry data requirements; human health and ecological risk assessments; and post-market surveillance that is required for FPIs is shown in Figure 2.

3.1 All pesticides, regardless of fluorination status, are regulated under FIFRA

The issues typically associated with the Targeted PFAS mentioned above are comprehensively evaluated for FPIs in the robust and transparent premarket approval framework mandated under FIFRA. All conventional pesticides, including FPIs, have defined mandatory data requirements to evaluate the safety of that pesticide, and these data are required to be submitted and reviewed by regulators. Based on that knowledge, regulators need to make a safety finding *before* the pesticide can be marketed in the United States (40 CFR § 150–189). These include mandatory studies for toxicology, ecotoxicology, environmental fate, and residue chemistry of an FPI, which are then integrated into comprehensive evaluations of potential health and environmental risks and to provide for an informed regulatory decision on the use of the FPI as detailed in Figure 2.

One of the often-noted concerns related to some of the Targeted PFAS is the potential insufficiency of the data to determine their safety prior to their initial use, which in some cases dates back decades. FPIs have been subject to extensive health and safety testing requirements since the late 1970s, at which time the EPA required new pesticides to undergo extensive testing *prior* to being marketed in the United States. For example, in 1978, EPA published the rules for pesticide toxicology data requirements that are still in force today, including required evaluations of repeated-dose subchronic and chronic toxicity, developmental toxicity, reproductive toxicity, genetic toxicity, and carcinogenicity.[60] Moreover, even several decades ago, there was recognition that specific test guidelines needed to be followed to ensure the scientific robustness of the required studies. This resulted in requirements such as conducting tests in both male and female experimental animals, and in different life stages to address potential sex-specific and developmental susceptibility of pesticide effects.[60] Regulation of pesticide safety was further enhanced with the FQPA in 1996, which included requiring EPA to evaluate the special susceptibility of children to pesticides by applying an additional tenfold safety factor, evaluation of aggregate exposure to pesticides from dietary, drinking water and residential exposure, and requiring EPA to consider cumulative exposure to pesticides that have common mechanisms of action.[61] Lastly, it should be emphasized that FQPA is a strict health-based standard in which EPA is required to ensure a "reasonable certainty of no harm" for all pesticides used in food commodities.[62]

In summary, safety testing requirements for FPIs under FIFRA are extensive, and these requirements have been enforced for decades by the EPA for any FPIs marketed in the United States that have the potential for human or environmental exposure. This practice has helped ensure that no FPI is placed on the market prior to the generation of a sufficient dataset that would allow a regulator to make an informed decision on their potential risk to human and environmental health. Further discussion of how safety data for FPIs is generated, and specific testing data requirements for toxicology, ecotoxicology, environmental fate, and residues for FPIs are provided below.

3.2 Overview of reliability and validity testing requirements for FPI safety studies

Like all conventional pesticides, studies required for FPIs need to be conducted by testing laboratories in compliance with good laboratory practice (GLP) regulations and internationally accepted standardized testing protocols.[63] The standard process for a company registering a new active FPI in the United States is to either conduct the study in their own laboratories or sponsor the mandatory studies at an external contract research organization. One often cited concern for industry-sponsored studies is potential bias,[64] and this bias is, in part, addressed through regulatory GLP requirements enforced by regulators as well as regulatory requirements to conduct specific study procedures recognized by public health agencies as having validated safety endpoints for a chemical.

GLP regulations for pesticides in the United States mandate that testing to support the safety of a pesticide needs to be based on reliable and well-documented studies as part of a laboratory quality assurance system.[63] For example, all testing data records and raw materials for a given study need to be maintained by the testing laboratory. Any deviation from the protocol needs to be documented for review, and the impact of that deviation on the

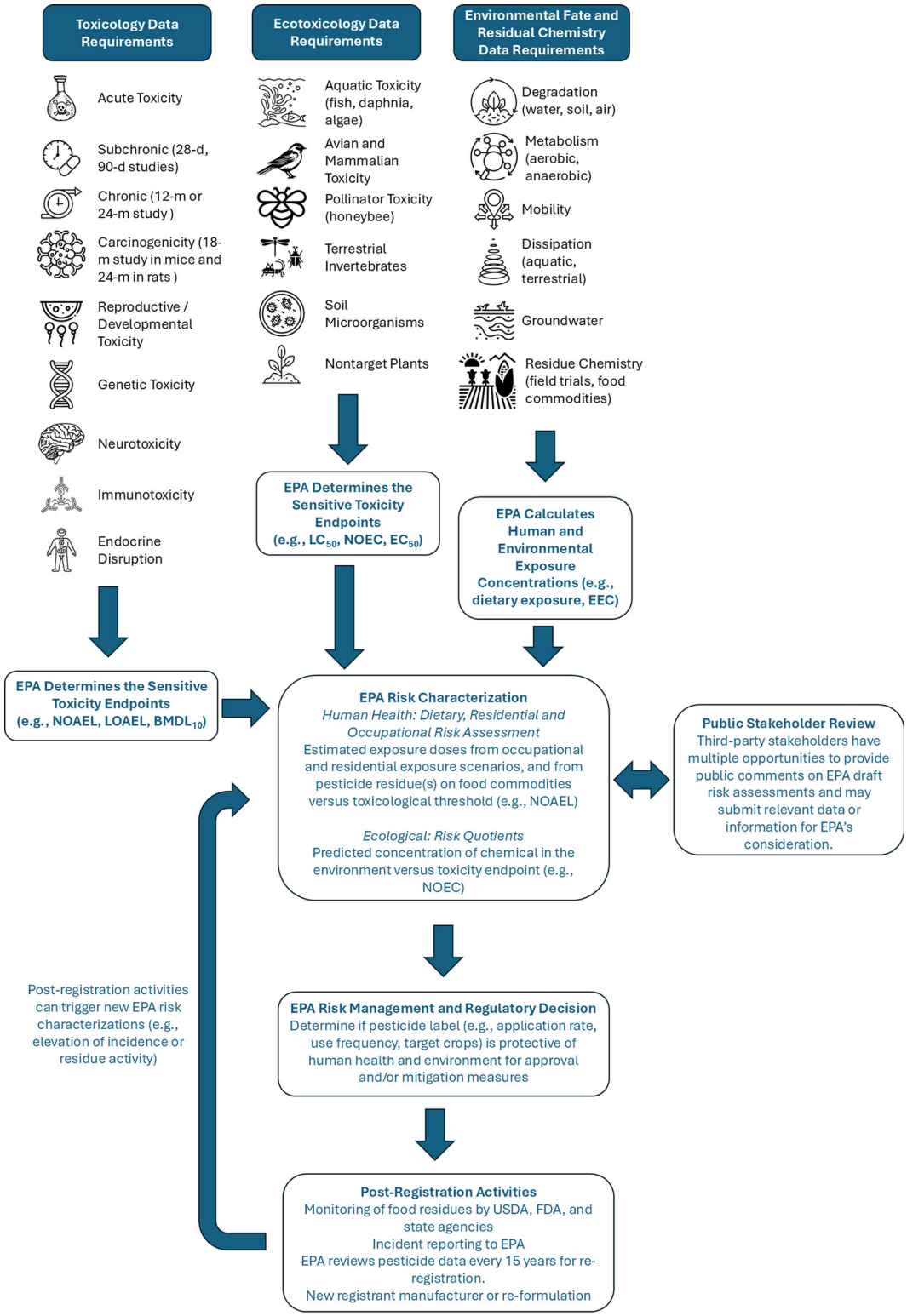


Figure 2. Overview of EPA's toxicology, ecotoxicology, environmental fate, and residue chemistry data requirements, risk characterization, and risk management process for FPIs.

study's conduct and interpretation must be detailed.[63] The EPA's access to the underlying raw data and detailed methodological information is critical to ensure that the analyses supporting the risk determination can be independently verified and reproduced.

EPA maintains a strict GLP compliance monitoring program that is enforced through inspections and investigations by agency inspectors, and in which violations can result in fines, prohibition of the laboratory from engaging in safety testing, and criminal charges in severe cases.[65] It should be noted that academic science research itself does not have an equivalent universal GLP compliance program.[66,67] Although EPA has access to substantial data submitted by pesticide registrants, agency policy guidance states that EPA is expected to consider relevant published literature alongside registrant-submitted data when making pesticide regulatory decisions (discussed further in Section 3.6).[68,69]

While GLP requirements address the reliability of the data, pesticide testing guidelines address whether studies and study designs are fit-for-purpose, i.e., whether the required study accurately informs the short-term or long-term health and environmental risks of exposure to a pesticide. EPA has an approved list of testing guidelines for pesticides that address toxicology, ecotoxicology, environmental fate, and residue chemistry studies.[70] Furthermore, the United States is part of the OECD, which is an organization that is responsible for preparing, reviewing, and updating chemical test guidelines.[71] The OECD has a multilateral agreement called the OECD Mutual Acceptance of Data (MAD) system, which ensures any member state, including the United States, must accept studies conducted in accordance with OECD testing guidelines.[72] OECD testing guidelines undergo periodic reviews and updates by public health agency experts in member countries to ensure they adhere to contemporary best-scientific practice.[73] Furthermore, as scientific research improves the methods needed to detect potential health risks, new OECD testing guidelines are generated after an extensive review of the new method.[73]

EPA also has an advisory Pesticide Program Dialogue Committee (PPDC) established by the Federal Advisory Committee Act that develops "practical, protective approaches for addressing pesticide regulatory policy, program implementation, environmental, technical, economic, and other policy issues" and reviews proposed modifications "to OPP's current policies and procedures, including the technical and economic feasibility of any proposed regulatory changes to the current process of registering and reevaluating pesticides."[74] The topics that PPDC covers are varied but can include better approaches to address endangered species, review potential new approach methods to replace animal testing, and implement pesticide resistance management.[75–77] PPDC is a useful process that allows for external stakeholder input to improve the reliability and validity of testing requirements.

For specific product registration, the EPA allows for applicants to engage in pre-application meetings (also known as pre-submission meetings), which allow the EPA to provide technical clarity to registrants on the appropriate testing data requirements.[78,79] This provides an opportunity for EPA to develop rigorous study designs with registrants that are responsive to potential agency concerns and provide guidance to registrants on new state-of-science methods for testing such as new approach methodologies (NAMs).[80]

Lastly, there are product chemistry requirements to control the physical and chemistry requirements of the final pesticide product.[81] This includes data requirements on the description of the starting materials for production, the production and formulation processes, discussion of impurities, and certified limits for active and inactive ingredients. All of these key properties need to be accounted for in the test material used for pre-marketing testing to ensure that the EPA has relevant safety data reflective of the final marketed product. Furthermore, some required controlled properties, for example, water solubility, partition coefficient, and vapor pressure can be informative for downstream environmental testing parameters and/or modeling environmental fate parameters.[82] Finally, some other physical and chemical properties can also inform on simple safety considerations of the pesticide such as flammability, explodability and corrosion characteristics which may influence storage requirements or use of personal protection equipment. Overall, by requiring FPIs to have multiple product chemistry data requirements helps ensure the reliability of pre-market testing, allow for development important modeling parameters for environmental fate determination, human safety controls, and post-market enforcement.

3.3 Overview of toxicology data requirements for FPIs under FIFRA

The human health toxicology data requirements for all active ingredients – fluorinated or not – include evaluations of critical hazards that have been associated with high-profile legacy fluorinated chemicals such as PFOA and PFOS. This includes studies conducted in multiple species, over varying exposure durations and routes, and evaluations of diverse endpoints such as immunotoxicity, neurotoxicity, developmental and reproductive effects, carcinogenicity, and endocrine disruption.[83,89,90] These studies follow either EPA Test Guidelines or OECD Test Guidelines that are validated and accepted by regulatory agencies to critically assess each of the named hazards. For example, the active ingredient data requirements include two lifetime experimental animal exposure studies, one in mice and one in rats, in which up to 40 distinct tissue sites can be evaluated for any potential chemical-induced increase in tumor formation or other non-neoplastic effect.[84] Hazards identified amongst the EPA "Targeted PFAS" are endocrine and development toxicity.[47,49,50] As such, it is worth noting that developmental- and endocrine-associated endpoints are already a part of the required battery of studies for fluorinated active ingredients, including, but not limited to, organ weight and histopathological evaluations of multiple endocrine tissues (e.g., thyroid, ovaries, testes), sexual organ maturation in developing males and females, and reproductive capacity.[61,85–87]

Fluorinated inert ingredients with food uses have the same endpoint requirements as the active ingredient, i.e., evaluations of immunotoxicity, genotoxicity, neurotoxicity, developmental and reproductive effects, carcinogenicity, and endocrine disruption.[88] Unlike the data requirements for fluorinated active ingredients, the EPA does allow for their inert ingredients review to include

the consideration of non-animal testing methods such as data from structural analogs or quantitative structure activity relationships models to evaluate reproductive or carcinogenic effects.[18] Note that this alternative approach still undergoes EPA review, and if a structural analogue approach is taken, EPA requires "a scientific discussion as to why the surrogate data is relevant/adequate for read across/bridging to the subject chemical," and an insufficient explanation or rationale can be rejected.[18]

Guideline repeated-dose toxicity studies have strict dosing requirements to ensure revelation of any potential human health hazard for an FPI. Experimental animals need to be administered a range of doses, with the default required maximum oral dose of 1,000 mg chemical per kilogram bodyweight per day (mg/kg bw/day). This equates to a 60 kg (132 lb) person ingesting ~12 teaspoons of that chemical every day, which far exceeds any realistic incidental exposure scenario for any FPI.[85,86] Exceptions to this approach are made for chemicals that cannot be administered at a rate of 1,000 mg/kg bw/day due to overt toxicity. In such cases, it is required that the chemical be tested up to the maximally tolerated dose, i.e., the dose just below that at which overt toxicity (e.g., mortality, morbidity, or severe clinical signs) is observed.[85,86] This required dosing regimen approach ensures that any potential human health hazard for FPIs is readily revealed to regulators during human health review and appropriate safety thresholds are applied for risk assessment to conservatively protect against any adverse effect.

Immunotoxicity effects have been identified by EPA as a key toxicological hazard for PFOA and PFOS, though the relevancy of its scientific basis for EPA's identification is controversial.[89–92] As such, it is worth clarifying that immunotoxicity data are generated from the default required studies for FPIs, and therefore, sufficient FPI immunotoxicity information is available during regulatory review.[86,93] For example, the required subchronic and chronic repeated-dose guideline studies include multiple assessments of immunotoxicity markers, including organ weights and histopathological evaluation of immune tissues (e.g., thymus, spleen, and bone marrow), and evaluations of white blood differential cell counts (e.g., neutrophils, lymphocytes, and eosinophils).[84–87] As noted before, these studies are designed to test chemicals at high doses or near the maximum tolerated level to reveal any potential hazard. Therefore, a compound that specifically interacts with immune system receptors is expected to be revealed at those elevated exposure levels. Furthermore, if there is an immunotoxicity signal for an FPI, the EPA has a data requirement for an additional immunotoxicity test that evaluates an antibody response to a T-cell-dependent antigen.[93] In summary, immunotoxicity information is evaluated and considered by regulators for all FPIs, and if a concerning signal is determined from the initial immunotoxicity endpoints, the FPI would be required to have a T-cell-dependent antigen test.

Note that the immunotoxicity test is not required if the baseline required studies do not suggest that the active ingredient triggers immunotoxicity responses, and registrants must submit a study waiver request to be reviewed by EPA.[93,94] Study waiver requests are a recognized tool by EPA Office of Pesticide Programs' Hazard and Science Policy Council to help reduce the need for animal testing, saving hundreds of thousands of animal lives, while increasing efficiency in the human health risk assessment process.[95] Waivers for this study and others are granted only when there is sufficient evidence indicating that the study would not significantly contribute to public health protective decision-making. The use of a study waiver is guided by objective criteria and does not imply an omission in assessing the effect. The comprehensive toxicology dataset generated by the required testing allows EPA to fully evaluate all relevant hazards and apply sensitive toxicological threshold endpoints for risk assessment. In summary, FPIs have an extensive evaluation of all relevant human health hazards from multiple toxicology studies, which are submitted to and reviewed by the EPA *prior* to marketing of the FPI within the United States.

3.4 Overview of FPI ecotoxicology data requirements under FIFRA

The ecotoxicology data requirements for FPIs include studies for multiple non-target organisms, including birds, mammals (typically sourced from the toxicology data requirements), aquatic organisms (e.g., fish, invertebrates, and algae), pollinators (e.g., honey bees), and terrestrial plants.[96–98] These studies follow either EPA Test Guidelines or OECD Test Guidelines that have been validated and accepted by regulatory agencies to critically assess each of the named hazards. For example, in a guideline avian dietary toxicity study, young northern bobwhite quails (*Colinus virginianus*) and mallard ducks (*Anas platyrhynchos*) are administered dosed diets up to 5,000 ppm for up to 5 days and evaluated for body weight, food consumption, and clinical toxicity.[99] Further ecotoxicology testing is conducted as a tiered process, with higher-tiered testing required based on results of lower-tiered tests. For example, if the required guideline honey bee acute contact study results in an acute LD_{50} of <11 μg per bee, and there is reason to believe that honey bees may be exposed to the pesticide, a more in-depth guideline honey bee study is triggered.[100,101] In the escalatory guideline study, honey bees are exposed to the pesticide applied at its maximum rate to treated foliage, and the mortality and behavior of the bees are monitored.[102]

Fluorinated inert ingredients have ecotoxicity data requirements similar to the active ingredients, including evaluations of aquatic, avian, and invertebrate endpoints.[18] Unlike the data requirements for active ingredients, EPA allows for inert ingredient submission to include the consideration of non-animal testing methods, such as EPA's validated Ecological Structure Activity Relationships (ECOSAR) Class Program to fulfill these data requirements.[18,103]

Lastly, registration of an FPI requires EPA to consider the impact of the FPI application on endangered species and their critical habitats. There is both an informal Endangered Species Act consultation during the pre-registration process (i.e., new use or new compound being considered), a preliminary risk assessment during the registration review process and a formal Endangered Species Act consultation during final risk assessment and proposed decisions.[104,105] This is an additional due diligence consideration for FPIs to ensure sufficient protection of endangered species and their critical habitats.

In summary, FPIs have extensive assessment of all relevant ecotoxicological hazards for multiple receptors, including birds,

honey bees, fish, plants, and endangered species, which are submitted to, and reviewed by, the EPA *prior* to marketing of the FPI within the United States.

3.5 Overview of FPI environmental fate and residue chemistry data requirements under FIFRA

Members of the abovementioned "Targeted PFAS" are often nicknamed "forever chemicals" due to their persistence in the environment. The production of some of these compounds – beginning in the 1940s – predates the establishment of EPA by over 20 years. This, combined with their longevity in the environment, led to their widespread detection in drinking water long before the EPA became aware of their persistence or hazard profile.[106,107] In sharp contrast, conventional pesticides such as FPIs have strict environmental data requirements that include evaluations of the degradation, metabolism, mobility, dissipation, and food commodity residue *prior* to being marketed in the United States. EPA approves FPIs only when it has "determined that there is 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" as has been required by law since the amendment to the FFDCA by the FQPA in 1996.[108]

Note that tracking of an FPI's environmental fate does not end with the parent compound but is pursued to its potential metabolites and environmental degradates. EPA requires registrants to conduct studies for the purposes of evaluating the exposure to pesticide compounds, including metabolites and degradates, in or on treated crops, in animals fed those crops, and in the environment.[109,110] In this context, a metabolite is defined as a compound formed through a biological process in animals, and a degradate is defined as a compound formed through environmental action. These chemicals have the potential to remain as residues on the target crops and therefore have the potential for environmental or human health exposure. EPA addresses this critical concern for FPIs under FIFRA by first understanding what residues may occur and identifying any residue of concern, which is defined as an "active ingredient and its degradates for which risk is assessed, based on known or assumed toxicological and exposure concerns."[111]

The tracking of any potential residues from an FPI is extensive. First, environmental fate studies are used to understand the general breakdown of the FPI in different mediums, which include, but are not limited to, hydrolysis in water, photodegradation, and aerobic and anaerobic metabolism in soil.[112–114] Even further, parent compounds are radiolabeled and then applied to representative crops, and then the radiolabel of the parent compound or its metabolite/degradates are tracked through to the harvested food or feed commodity[110,116] Furthermore, these types of assessments would include the potential of any FPI-related residue being concentrated through processing.[115] Residues of concern in feeds also undergo this type of tracking to determine residues of concern in meat, milk, poultry, and/or eggs, depending on the intended use of the FPI.[110,116,117] Moreover, if there is any trigger or potential concern for groundwater exposure, such as the use of an FPI for aquatic use patterns, a study is required to track residues.[109,118] For drinking water evaluations, the EPA derives upper-bound estimates of potential pesticide concentrations in surface- and ground-waters, and also validates predictions against available water monitoring data for registered pesticides.[119,120] Residue data can also address human exposure occupational and residential data requirements following application of a pesticide at a given site.[121] Depending on the use scenario, this may include testing for dislodgeable foliar residue and turf transferable residues, soil residue dissipation, and indoor surface residue dissipation.[121]

Once a metabolite or degradate is characterized or identified, the potential for mammalian or ecological toxicity and environmental persistence and bioaccumulation is evaluated.[111] Note that part of EPA's investigation into a degradate's potential persistence, especially if there is absence of direct experimental environmental fate data on the degradate, includes evaluating other chemicals of similar structure, and therefore if any degradate derived from an FPI contains similarities to persistent compounds, this will automatically be flagged for review.[111] Further, additional testing may be required for compounds to determine if metabolites or degradates are more toxic, less toxic, or of equal potency compared to the parent compound in terms human health effects (e.g., general toxicity, target organ effect, or potential for carcinogenicity) or ecotoxicity (e.g., toxic to fish, invertebrates, algae, and honey bees).[111] If, for example, an FPI degradate is more toxic or persistent than the parent compound, that degradate could require its own full toxicology, ecotoxicology, and environmental fate dataset as presented in Figure 2.

Before allowing the use of a pesticide on food/feed crops, there is a tolerance or maximum residue limit set by the EPA, which is "the amount of pesticide residue allowed to remain in or on each treated food commodity."[122] This tolerance can be set for either active or inert ingredients. It is critical to note that although a tolerance for an FPI on a given food is solely based on the residues that may occur following legal use of the pesticide product, the establishment of that tolerance has taken into consideration aggregate exposure from all foods, drinking water, and potential residential exposures.[108] Therefore, the pesticide registration process ensures that exposure to an FPI via multiple routes remains below applicable safety limits.

In summary, EPA has substantial data requirements to address the environmental fate and residue chemistry of any potential FPI parent compound and metabolites/degradates of concern that have the potential for human health or environmental exposure *prior* to the FPI being marketed in the United States (Figure 3).

3.6 Overview of FPI risk assessment and post-market enforcement under FIFRA

The toxicological, ecotoxicological, environmental fate, and residue data collected for FPIs is integrated by EPA into an overall risk assessment that integrates hazard identification (i.e., what adverse health effects are identified by the available data), dose response assessment (i.e., at what level of exposure are the adverse health effects observed), and exposure assessments (i.e., what populations are exposed to the pesticide, and at what dose and duration).[123] Note that a hazard is something that has the potential to harm an individual whereas the risk

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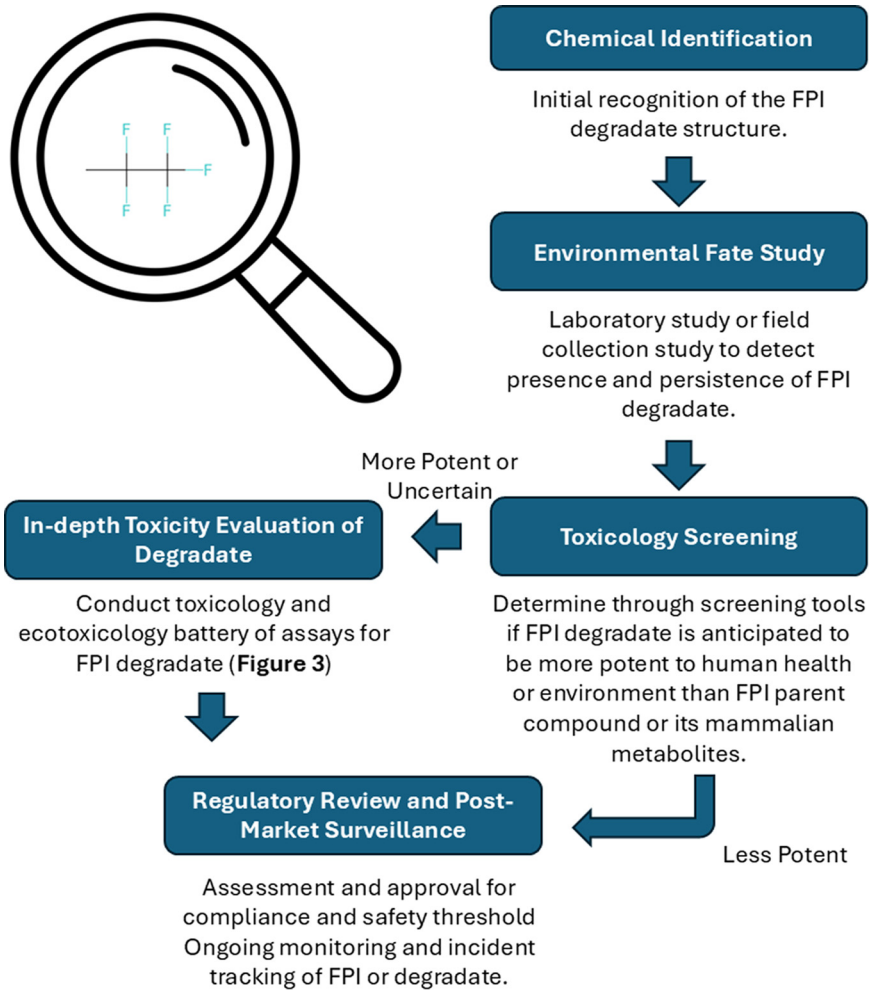

Figure 3. Overview of FPI degradate analysis.

is the likelihood of a hazard causing harm.[124] Many natural and synthetic compounds have the potential to harm cells or the body at some theoretical dose level.[125,126] It is also not unusual that artificial laboratory conditions and unique experimental animal physiology can lead to health outcomes that would otherwise not be observed in humans under realistic exposure conditions.[127–129] A risk managed approach weighs actual exposure against a human-relevant toxicity threshold to manage real-world risks effectively and avoids unjustified restrictions or bans on beneficial substances.

EPA guidance for risk assessment emphasizes four critical principles of transparency (i.e., explicitness in the risk assessment process), clarity (i.e., free from obscure language and is easily understood), consistency (i.e., conclusions of the risk assessment characterized in harmony with other EPA actions), and reasonableness (i.e., risk assessment based on sound judgment).[123]

The transparency of the decision-making for Targeted PFAS has been subject to criticism in the past.[106] In contrast, during the registration of a new FPI or one that would entail a changed use pattern, EPA is required to open a public docket for comments on the application, which allows for external stakeholder input.[130] With regards to clarity and consistency, EPA publishes technical guidance documents to help applicants and the public understand the standardized best-scientific practices that EPA is implementing to regulate pesticides, including items such as waivers from animal testing, application of uncertainty factors, physiologically-based pharmacokinetic modeling, and advance inhalation dosimetry models.[131–136] These technical documents allow for stakeholders to understand the science driving regulatory decisions and provide a foundation for further research to enhance the efficiency and protectiveness of regulatory science.

The EPA risk assessment addresses all use patterns proposed for an FPI, their associated exposure scenarios, and provides risk estimates (e.g., Margins of Exposure) that allow the agency to make risk management decisions.[123] Human exposure data is required for pesticides.[137] As discussed in Section 3.5, residue data information helps to determine potential exposure for workers or bystanders following application of a pesticide, and this data may even lead to re-entry restriction requirements to a

treated area to be placed on the label. Furthermore, EPA publishes guidance documents with specific algorithms to determine exposure estimates and these algorithms account for a variety of different occupational and residential exposure scenarios with allows for harmonization and transparency of agency decision-making.[138,139] These algorithms are able to calculate an exposure dose based on the use scenario and label use directions for comparison to the derived toxicity threshold that is protective of all relevant health risks.[138,139] In summary, FPI's are carefully examined within use-specific occupational and residential scenarios to account for potential health risks.

The results of the risk assessment and management process also establish tolerance levels for the FPI for relevant food commodities, and an approved label for the pesticide product that ensures exposure to the FPI's resulting from application under federal law would not result in adverse effects. Importantly, even after an FPI is approved for marketing, vigilant monitoring of tolerance levels for pesticide residues in food is conducted by the United States Food and Drug Administration (FDA) and United States Department of Agriculture (USDA). This post-market surveillance ensures that EPA receives contemporary data regarding the FPI residues, and this information informs any potential future EPA risk evaluation for a given FPI.

The FDA is responsible for the national pesticide residue monitoring program for the purpose of enforcing "tolerances for domestic foods shipped in interstate commerce and foods imported into the United States."[140] The latest FDA regulatory residue monitoring report (posted in September 2024) noted that the FDA "monitors a broad range of domestic and import commodities for residues of ~750 different pesticides and selected industrial compounds."[140] Furthermore, the FDA also carries out focused sampling surveys for specific commodities or pesticides of special interest as well as monitoring of pesticide residues as part of its Total Diet Study, which is an ongoing program that monitors contaminants and nutrients in the average US diet.[140,141]

Note that the FDA's default limit of analytical quantification for enforcement is 0.01 parts per million (or 10 parts per billion).[140] The limit of analytical quantification is analogous to detecting 25 mL of chemical content (just over half a shot glass) in an Olympic-sized swimming pool, which holds 2.5 million liters of water (660,000 gallons). Furthermore, the FDA has released annual reports of the results of its pesticide residue monitoring program since 1994, which include the sample analytical data.[142] In the latest reported survey (2022), "FDA found that 96.2% of domestic and 89.5% of import human foods were compliant with federal standards," which indicates a high degree of compliance with EPA-set tolerances.[140]

The USDA conducts its own independent pesticide monitoring program known as the Pesticide Data Program (PDP), which designs its sample selection "to obtain a statistically valid representation of the U.S. food supply," with a special focus put on foods most likely to be consumed by infants and children.[143] The PDP is supported at the federal level by the EPA and the FDA, but also at the state level, including California, Colorado, Florida, Maryland, Michigan, New York, Ohio, Texas, and Washington.[143] PDP samples are obtained near the "point of consumption and are prepared emulating consumer practices (e.g., washing, peeling)." Fruit and vegetable samples are analyzed for almost 600 pesticides (including FPIs), metabolites, and degradates using multi-residue methodology. This allows for the realistic assessment of co-occurrence (the presence of more than one pesticide on a food sample). As of 2021, it contained "42 million residue data points that pair an individual pesticide residue with a food commodity."[144] The latest report for the calendar year of 2023 noted that "99 percent of the samples tested had residues below the tolerances established by the EPA with 38.8 percent having no detectable residue," which again indicates a high degree of compliance with EPA-set tolerances.[143]

Adverse effects that may be related to exposure to a pesticide should be reported to either the FPI registrant or directly to EPA. Registrants who receive these reports are required to share them with the EPA within the timeline outlined under FIFRA.[145] While incident reports are reviewed by EPA as they are received, all registered FPIs are also subject to a full registration review every 15 years. It is at this time that the agency evaluates any published literature related to an FPI (such as epidemiology studies), in addition to requesting additional testing requirements instituted following the original registration.

In summary, the EPA's risk assessment and management process that sets tolerances and approves pesticide labels in conjunction with extensive post-market surveillance programs ensures that FPIs continue to be carefully evaluated for potential human health and environmental risks after their initial registration.

4. DISCUSSION: BENEFITS AND RISKS

It is typical for high-profile PFAS to be discussed in the biomedical, academic, and regulatory literature solely from the viewpoint of health consequences from incidental human or environmental exposure. However, leading these types of discussions with molecular features inevitably leads to skewed public perception of fluorinated chemistries in general and avoids the more nuanced data-driven consideration of benefits against controlled risks. The utility of fluorination is made evident by the fact that 107 pharmaceuticals, including essential medicines such as levofloxacin (Levaquin) and fluoxetine (Prozac), meet the OECD definition of PFAS, and 337 pharmaceuticals have at least one fully fluorinated carbon.[146] Similarly, fluoropolymers (e.g., polytetrafluoroethylene) are critical components of medical devices, including implants that monitor electrophysiology equipment, with little evidence of adverse events associated with the use of polytetrafluoroethylene reported in the literature.[147,148] FDA further defended the safety and use of fluoropolymers in medical devices, noting the agency's continued evaluation and monitoring of the use of these materials in medical devices based on available scientific information.[149] FDA noted "[t]he PFAS used in medical devices are not the same as those identified as being potentially harmful to people in other contexts" and concluded that "FDA's evaluation is that currently there is no reason to restrict their continued use in devices."[149]

Fluorination serves specific purposes in an agrochemical context. For example, in some cases fluorination may confer molecules with increased stability under environmental conditions.[152]

Agrochemicals cannot be stored under controlled conditions, such as refrigeration or protection from sunlight, once applied. They must remain active in the environment long enough to be effective, but not persist in the field beyond when they are needed. The atomic properties of fluorine allow it to mimic hydrogen atoms that interact with enzyme active sites while resisting biochemical transformation.[150] These properties contribute to the selective targeting of plant and insect metabolic pathways while reducing off-target species effects.[151–153] Metered increases in stability and altered metabolic properties both have the potential to impact the toxicological profile of these molecules. Moreover, EPA even notes for compounds with single fluorinated carbons that "Many of the uses of these pesticides are reduced risk compared to other product uses currently on the market."[36] As discussed in the previous section, the environmental persistence and toxicity of these FPIs and their degradants are evaluated extensively prior to their approval for use. In summary, fluorination serves specific purposes, has been a critical tool in the development of advanced chemistries, and, in the FPI context, is the subject of an extensive system and highly protective safeguards against adverse human health and environmental effects.

Similarly, it is essential to consider the benefits of FPIs in general against the controlled risks when prioritizing regulatory actions. One useful review describes 26 primary benefits of pesticides, which include improved crop/livestock yields and quality, improved shelf life of produce, and reduced fungal toxins.[154] Food security is a significant public health issue recognized by multiple public health agencies, with crop losses due to pests and disease recognized as a major obstacle in achieving this.[155] One study published in 2019 estimated pest- and pathogen-based global loss estimates per crop of 21.5%, 30.0%, 22.6%, 17.2%, and 21.4% for wheat, rice, maize, potato, and soybean, respectively.[156] Providing farmers with safe and effective tools can increase production, and increase the availability of affordable and healthy fruit and vegetable produce for the global population while minimizing microbial health outbreaks. Pesticides used outside of an agricultural setting serve as vital tools for controlling human and animal disease vectors (e.g., mosquitoes, ticks, etc.) and prevent the establishment or spread of invasive species in managed natural areas.

Strategic pesticide use has become significantly more refined with joint industry and public health agency support for the adoption of Integrated Pest Management (IPM). IPM encourages the long-term, sustainable and judicious use of pesticides along with other agricultural practices such as crop surveillance and monitoring, optimal water management, and improvements in cultivation techniques.[157–159] Managing and preventing pest resistance to pesticides is an essential part of IPM to help maintain efficacy. Resistance management dictates that pesticides with different modes of action be used sequentially to prevent the establishment of resistant pest populations. The significance of this is that in agricultural settings, farmers must use multiple products that vary in mode of action to manage pressures from weeds, insect pests, and bacterial or fungal diseases.

As introduced in Section 1.3, restricting FPIs only using OECD's PFAS definition would impact over 60 active FPIs with numerous uses, including food crops and food crop sites as well as other plants and vegetation, industrial and feed crops, and non-agricultural sites. Specifically, FPIs are approved for critical agricultural uses for crop development and pest management. The functional uses of FPIs that fit this definition are diverse and wide-reaching. As summarized in Table 2, FPIs fall into several pesticide categories, including herbicides, insecticides, and fungicides, that are approved for the management of numerous pests, including weeds, insects, fungi, mites, and parasites that can impact crops. For example, in the herbicide group (29 FPIs), there are over 1,200 unique approved pest uses today. It has been estimated that increasing global temperatures will only increase the threat of pest persistence and activity in the future.[160] With increased potential impact of crop disease and pesticide resistance on food supply, it is important to have options and strategies available, including pesticides like FPIs, that are approved for numerous pest uses.[161,162] In addition, FPIs are utilized in the development and production of many domestic crops, including several of the top-produced crops in the United States such as corn, soybean, sorghum, and wheat.[163] Farmers must consider factors such as crop specifications, intended commodity markets, geographical location, growth stage, and, of course, specific pest protection needs and price point when selecting the right product to suit their needs. Considering the multidimensional factors that enter into the pesticide selection process, the availability of and ability to choose from a range of effective pesticides for specific uses and situations is essential.

Table 2. Approved pest uses for active FPIs in the United States.

Pesticide type (number of included FPIs)	Number of approved pest uses[a]
Herbicide (29)	1,215
Insecticide (19)	1,136
Fungicide (15)	515
Regulator (2)	–
Miticide (1)	16
Nematicide (1)	9
Rodenticide (1)	23
Algaecide (1)	12

[a]Approved pest uses for FPIs that meet the OECD definition of PFAS were obtained from the Knowtify database. The total number of approved pest uses for each pesticide type includes those that are listed in Knowtify for active products for each FPI.

Recognition of the extensive system of highly protective safeguards governing pesticide approval and use, as well as their status as a critical tool for agricultural production, provides a strong rationale for the standardization of regulations for FPIs on the national and state levels. As detailed in Section 3, conventional pesticides, including FPIs, undergo extensive premarket toxicological, ecotoxicological, environmental fate, and residue chemistry data review, and active post-market surveillance and monitoring to ensure human and environmental safety, as shown in Figure 2. Therefore, it is inappropriate and misguided to regulate these data-rich chemistries under the broad umbrella of wide-reaching PFAS bans.

As described in Section 3, there are significant and transparent existing safeguards within the FPI registration and surveillance process. This includes a comprehensive understanding of toxicological and ecological properties and tracking the environmental fate of FPIs and their degradates, to harvested raw and processed food commodities, and continued post-market public health monitoring. This process is undertaken by the EPA in a transparent manner that allows all public stakeholders to provide input into the risk assessment and risk management process. Therefore, the standardization of regulations for FPIs on the national and state level will not be expected to come at any increased health or environmental cost but rather at the recognition of these existing safeguards for the use of FPIs and benefits of supplying farmers with a wide array of tools to safeguard sustainable agricultural production. In response to a bill that would restrict FPIs in Maine, a farmer representative group submitted testimony stating that restricting the sale of "1/3 of the number of registered pesticides in Maine" using a one-carbon definition would "not decrease the volume of pesticides used," but may instead result in "[increased] pesticide use … and [increased] toxicity."[164] The consequences of overregulating FPIs through the use of broad PFAS regulatory actions risk reducing the availability of many active ingredients important to the production of a wide variety of crops without providing any increased level of protection to human health or the environment.

EPA has taken several targeted and science-based actions regarding the possible presence of PFAS in pesticides. These actions include an analytical report for impurities in specific insecticides in 2023 in response to a peer-reviewed publication reporting the detection of PFAS in certain products.[165,166] EPA confirmed through an agency-validated approach that the end-use products in question did not contain any PFAS above the method detection limits (0.2 parts per billion).[166] EPA has also released validated analytical methodologies to evaluate these types of claims going forward, including whether there may be PFAS impurities that have leached from fluorinated high-density polyethylene containers.[167–169] Finally, in 2022 EPA removed 12 ingredients for *nonfood* use that contained fluorinated structures from the current list of approved inert ingredients.[170] As part of this announcement, EPA was clear that the ingredients could be reconsidered with submission of technical data specific to each ingredient; however, this has not been pursued and these ingredients are not used in any registered pesticide product, regardless of intended use.

The current federal regulatory framework for evaluating FPIs utilizes highly protective safeguards to prevent adverse effects on human health and the environment. Considering the potential adverse consequences of regulating a wide range of product categories, like pesticides, under broad PFAS bans, there is a critical need for harmonizing federal and state PFAS rulemaking to alleviate undesired and unintentional impacts on essential industries. Recent state-level regulatory developments and amendments to PFAS regulations demonstrate the challenges encountered in attempting to use a broad definition of PFAS for regulatory purposes, and highlight the need for precise, data-driven language when implementing chemical regulations. If regulatory bodies consider adopting PFAS bans or restrictions it is important that they refine broad PFAS definitions for regulatory purposes by considering additional criteria or specifications that distinguish chemistries, uses, and risk profiles; as suggested by OECD and reiterated by other regulatory agencies. EPA utilizes a science and risk-based approach to evaluate and address concerns related to PFAS in pesticides, ensuring that pesticide products are safe for human health and the environment when used as directed. Additional state-specific restrictions lacking scientific grounding would only serve to complicate the regulatory landscape without offering appreciable benefits to protecting human health or the environment.

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