Environmental Protection Network

(202) 656-6229
environmentalprotectionnetwork.org
info@environmentalprotectionnetwork.org

EPN Comments on New Active Ingredient Cyclobutrifluram
EPA-HQ-OPP-2022-0003
May 6, 2025

The Environmental Protection Network (EPN) harnesses the expertise of more than 650 former Environmental Protection Agency (EPA) career staff and confirmation-level appointees from Democratic and Republican administrations to provide the unique perspective of former regulators and scientists with decades of historical knowledge and subject matter expertise.

On April 21, 2025, EPA opened comments for the new active ingredient cyclobutrifluram. Cyclobutrifluram is used as a pesticide in or on cotton, romaine lettuce, soybean, ornamentals, and turf. EPN feels that the proposed decision needs additional thought and work to address shortcomings in the human health risk assessment and to improve the clarity and enforceability of the section of the labeling addressing how to minimize spray drift. Specifically, some statements in the risk assessment for human health are vague and lack scientific support. The explanation for reduction of the uncertainty factors for thyroid effects is not well supported in the document. The carcinogenicity study in rats lacks an explanation supporting the statement that the animals were 'adequately challenged' for carcinogenicity testing. In addition, much of the draft spray drift labeling is unenforceable, but other mandatory instructions amount to a "no drift" requirement that would be impossible to meet. EPN provides additional comments on the human health risk assessment for cyclobutrifluram and its subsequent labeling requirements below.

Suggested Changes to the Human Health Risk Assessment
The sentence on page 5, under exposure profile is grammatically incorrect and should read: "*Additionally, adults' short-term dermal and children's short-term dermal and incidental oral (post-application) exposures may occur from turf residues resulting from spray drift following applications to agricultural and/or non-agricultural areas.*"

The sentence on page 7 that reads, "The interspecies extrapolation factor can be reduced to 3X because this POD is based on thyroid disruption in adult rats, and they are known to be more sensitive to thyroid toxicity than adult humans due to differences in pharmacodynamics," is vague and lacking in details to support this conclusion. As a relevant example, this statement from the risk assessment for Triclosan is illustrative and the information regarding the thyroid aspect should be incorporated based on the available evidence for cyclobutrifluram:

> "Generally, in the absence of information on pharmacokinetics and/or pharmacodynamics, it is assumed that humans may be 10 times more sensitive than animals (10X interspecies uncertainty factor). With respect to thyroid effects, it is known that the rat is more sensitive than the human to perturbations in thyroid homeostasis based on the shorter half-life of T4 in rats (12-24 hours) compared to humans (5-9 days), and the lack of the high affinity binding protein thyroxine binding globulin in rats."

EPN thinks the meaning of 'adequately challenged' reads vaguely in the statement on page 7: "There are acceptable carcinogenicity studies in mice and rats in which rodents were adequately challenged to assess carcinogenic potential." The highest dose tested in this study did not seem to result in adverse effects, yet the statement is made that animals were 'adequately challenged.' EPN suggests clarifying the evidence

supporting this statement, and also modifying the classification sentence to say,*"Cyclobutrifluram is classified as 'Not Likely to Be Carcinogenic to Humans.' There are acceptable carcinogenicity studies in mice and rats in which no evidence of treatment related tumors was observed in either of these studies."* However, this classification needs to be supported by evidence that in fact, the doses used in the study were adequate but not excessive. It appears that higher doses could have been tolerated.

In the ADME section (4.2, page 17) EPN suggests clarifying the sentence: "With the [phenyl14C]-radiolabel, in whole blood following exposure to a single low dose, no sex differences were observed, and the peak concentration was reached after 30 minutes." This sentence is unclear, as it could relate to the peak blood concentration, peak plasma concentration, or another unmentioned concentration level. This suggestion also applies to the following sentence, "Following exposure to a single high dose, females reached peak concentration in whole blood 6X slower than males (12 vs 2 hours, respectively)." Unless EPA is willing to explain the basis for the difference in time to peak concentration between males and females, EPN recommends rewriting these sentences as "…*peak concentrations in whole blood were reached in females at 12 hours post-dosing, whereas peak whole blood concentrations in males were reached 2 hours post-dosing.*"

The sentence in paragraph 3, page 17 is vague: "Regardless of the dose level or exposure period, 6.5-18% of the administered dose (AD) was excreted in the urine and 76-92% in feces with nearly complete excretion by 48 hours post-dose (93-100%). These findings suggest rapid excretion of the parent compound and/or related metabolites." EPN suggests adding some detail (if true), such as "*In all dose groups, between 6.5-18% of the administered dose was excreted in urine, and 76-92% excreted in feces by 48 hours post-dose.*"

On page 70, in the summary of prenatal developmental toxicity study in the rat, a sentence reads: "The toxicokinetics of both cyclobutrifluram (SYN549522) and its metabolite SYN549104 were characterised by continuous exposure over 24 hours at all dose levels." EPN strongly recommends additional clarification as it is unclear what this statement means.

Regarding the thyroid effects and selection as the POD, EPN is curious as to why the thyroid effects are observed in the reproduction toxicity study at lower doses from dietary exposure compared to the 90-day oral dietary study in rats. No thyroid effects are observed from oral gavage exposures in rats. EPN is curious if this aspect has been considered in the risk assessment. NOAEL and LOAEL values in the 90-day oral study were 187/204 and 51/59 mg/kg/day respectively, while in the reproduction toxicity study of almost the same exposure duration, the LOAEL and NOAEL values were 43/53 and 9/11 mg/kg/day respectively. Is there an explanation for this between the two studies, that use the same effect for the LOAEL?

In the summary of chronic toxicity/carcinogenicity study in rats on page 76, EPN suggests clarification of the statement, "The animals were adequately challenged to assess carcinogenic potential." Similar to what has been mentioned above, it is unclear what 'adequately challenged' refers to and we suggest adding more detail here and throughout the risk assessment.

Labeling Requirements

The "Labeling Requirements" section of the draft Decision Document contains several groups of proposed labeling text; one of these, addressing "Spray Drift Management," needs significant changes. Specifically, EPA should require the applicant to revise this text to eliminate an impossible "no drift" requirement. EPN strongly recommends that EPA require the labeling to include a requirement that "no harm" result from drift. If that is done, the labeling text addressing application parameters can remain as is. If EPA removes

the "no drift" text, but the agency does not replace it with a requirement that drift causes "no harm," EPA should require the applicant to amend the text concerning application parameters to make them enforceable.

EPN agrees with policy experts who have long favored the use, where appropriate, of "performance standards" – requirements that tell people what results their actions must achieve – over the use of "design standards" – requirements that tell people what actions to take (or not to take). According to policy experts, performance standards should be used to regulate situations both: 1) where there is an objective, measurable, and acceptable outcome that the regulated community should meet; and 2) there are different ways to achieve that outcome. Leaving the regulated community discretion about how to meet a performance standard encourages innovation and efficient operations. Moreover, performance standards automatically make enforcement priorities focus on significant outcomes that matter, not on behaviors that may not be meaningfully related to outcomes.

Performance standards, however, are not always appropriate. Experts say regulators should turn to design standards when there is no practical way to achieve the desired outcome, for example because the measures necessary to produce the outcome are inordinately expensive. In those cases, regulators should decide what behaviors are reasonable and require the regulated community to adopt the specified behaviors. Even when using design standards, experts advise against making them mandatory when they would unnecessarily lock the regulated community into a specific technology that may become outmoded. At the same time, regulators should recognize that design standards which are not mandatory can be ignored and thus may not produce the desired improvements in outcomes.

Using this conceptual framework, a spray drift use direction in pesticide labeling can be categorized as being either a "design standard" – i.e., text discussing how to apply the product in a way that would lessen the amount of drift, but that does not establish a limit on the amount of drift that results from application – or a "performance standard" – i.e., text that instructs the user about how much drift is allowed, but that leaves the applicator discretion about how to apply the product. In addition, a standard can be either mandatory and enforceable, or advisory and unenforceable.

The draft Spray Drift Management labeling text the current proposal is lengthy and contains a mix of performance standards that are impossible to meet, a few enforceable design standards, and many unenforceable design standards. EPN believes this draft spray drift labeling will probably be sufficient for most use situations. It seems fairly likely there will be no risks of concern when a user follows the recommendations regarding application parameters to minimize spray drift. However, if, a user ignores the advisory language and drift results in damage, many parts of the proposed labeling text are currently worded in ways which would make it unlikely that EPA could successfully pursue a violation of FIFRA sec. 12(a)(2)(G) or that a state or tribal government could win a "misuse" case under their laws and regulations. If users realize that the spray drift labeling is largely unenforceable, they will be less likely to follow it. At the same time, there are two specific statements that seem to establish an absolute "no drift" standard for off-target sites. If enforcement authorities focus on this language, they risk over-reaching – bringing enforcement actions that deserve low priority or that should not be pursued at all.

Looking first at the "no drift" performance standards in the labeling, EPN believes that pesticide labeling should not categorically prohibit all drift. As a simple matter of physics, some drift beyond the treated site is always theoretically possible and in practice often occurs at low, non-harmful levels. Yet the draft labeling would make it illegal to allow even a single molecule of the product to drift beyond the boundaries of the

treated site. The draft text states: "THE APPLICATOR IS RESPONSIBLE FOR AVOIDING OFF-SITE SPRAY DRIFT." The draft text also states: "DO NOT apply this pesticide when the product may drift to non-target areas (i.e., residential areas, bodies of water, known habitat for threatened or endangered species, or non-target crops)." Pursuant to this wording, if residues of the product are found to have drifted onto any location other than the treated site, it would appear the user could be found to have violated the requirement to "avoid[ ] off-site spray drift." Likewise, a user would be guilty of "misuse" if he allowed any level of product residues to drift into a "residential area[ ], bod[y] of water, known habitat for threatened or endangered species, or non-target crops."

EPN strongly recommends replacing the draft spray labeling statements which are impossible to meet with the following text: "Do not apply this product in a manner that results in spray drift which causes harm." In contrast to the current "no drift" text, to enforce this use direction, it would not be sufficient to establish a violation simply to detect the presence of the product on a non-target site; enforcement would also need to show such drift caused "harm." EPN considers this alternative performance standard objective, measurable, and appropriate. Drift which causes any type of harm beyond the treated site is a problem, and it is appropriate to prevent such drift. "Harm" is also an objective, measurable concept. Drift which damages property or non-target animals, plants, or people is harmful. Property damage could include causing a neighbor's crop to violate a tolerance requirement or organic status or reducing the crop's quality or yield. It could also include damaging ornamental plants or causing illness in pets or livestock. Drift that contaminates water at levels unsafe for consumption or recreational use is also harmful. EPN notes that the state of Indiana has long had a regulation applicable to drift of pesticide sprays that is effectively comparable to our recommended labeling requirement.

EPN notes that, apart from the two performance standards quoted above, the other 25 use directions concerning spray drift are all design standards – text that addresses application parameters or other factors that could affect the amount of off-target drift, but not the impacts of such drift. Only 4 of the other 25 specific use directions in the Spray Drift section are clearly enforceable:

Spray Drift Management

. . .

iv. DO NOT apply when the wind speed is greater than 10 mph or during periods of temperature inversions.

b. Ground Applications

i. Apply with the nozzle height recommended by the manufacturer, but no more than 3 feet above the ground or crop canopy unless making a pasture or rangeland application, in which case applicators may apply with a nozzle height no more than 4 feet above the ground.

ii. For all other applications, applicators are required to use a medium or coarser droplet size (ASABE S572.1).

. . .

h. Wind

. . .

ii. Note: Local terrain can influence wind patterns. Leave a 25-foot buffer downwind

of the application to avoid drift to non-target areas

EPN notes that to enforce these labeling provisions would be extremely difficult. To establish a violation, the enforcement authority would need to have evidence which could be gathered only through direct observation of the application process. Otherwise, it would be nearly impossible to prove the wind speed, release height, or droplet size of the application. Since enforcement personnel almost always learn of spray drift incidents only after they occur, EPN expects these use directions would never be the basis for an enforcement action.

The balance of the draft spray drift text is advisory, meaning that an applicator who did not follow the labeling recommendations could not be found to have violated the "misuse" provisions of federal, state, and tribal law. The 21 spray drift directions are unenforceable due to two types of recurring deficiencies. First, most of these flawed use directions employ terms that are vague and subjective. For example,

ii. DO NOT apply when conditions favor drift beyond the target area.

. . .

d. Controlling droplet size

i. An effective way to reduce spray drift is to apply large droplets. Use the largest droplets that provide target pest control.

. . .

g. Temperature and Humidity

i. When making applications in hot and dry conditions, use larger droplets to reduce effects of evaporation.

A user could plausibly argue the conditions did not "favor" drift, even when drift occurred. Similarly, a user who used a smaller droplet size could argue it was necessary for the "largest pest control" or that the conditions were not sufficiently "hot and dry" to justify using a larger droplet size. Indeed, "larger droplets" is not defined. Other statements contain similarly undefined terms that would give the user very broad discretion about what actions, if any, they were required to take. Second, other text is phrased as statements that do not impose any duty at all on the user. For example, the draft labeling states:

ii. The interaction of many equipment- and weather-related factors determines the potential for spray drift.

. . .

i. Drift potential is lowest when wind speeds are 10 mph or less. However, many factors, including droplet size, pressure, and equipment type determine drift potential at any given wind speed.

. . .

iv. Applicators need to be familiar with local wind patterns and terrain that could affect spray drift.

None of these "use directions" instructs the user on a specific behavior they must follow. If the agency does not adopt our suggestion to require the applicant to add the following statement – "Do not apply this product in a manner that results in spray drift which causes harm." – EPN recommends that EPA reexamine the spray drift labeling carefully to determine which design standards should be mandatory and then require the applicant to revise them, if necessary. Currently, only the wind speed and downwind buffer are mandatory for all applications; the release height and droplet size restrictions are required only for ground applications. At a minimum, EPN believes the labeling should make mandatory any application parameter that EPA's spray drift assessment assumes users will follow.

Conclusion

EPN respectfully requests that EPA not finalize the registration of cyclobutrifluram products as proposed. As explained in more detail in these comments, both the human health risk assessment and the draft labeling have significant deficiencies that should be reevaluated. While EPA may eventually conclude the cyclobutrifluram products do meet the statutory standard for registration, the information in the record accompanying the proposal does not currently support such a conclusion. EPA will not have an adequate record until EPA has more comprehensively analyzed and fully explained its analysis of the potential risks to human health and has examined whether the labeling reflects the assumptions about use on which that assessment is based.