



CENTER FOR
FOOD SAFETY

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U.S. Environmental Protection Agency
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Mail Code 28221T
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RE: Docket ID: EPA-HQ-OPP-2021-0641
New Active Ingredient Isocycloseram

On behalf of itself and its 970,000 members and supporters, Center for Food Safety appreciates the opportunity to comment on EPA's proposed decision to register the new active ingredient, isocycloseram. Center for Food Safety (CFS) is a public interest, nonprofit membership organization with offices in Washington, D.C., San Francisco, California, and Portland, Oregon. CFS's mission is to empower people, support farmers, and protect the earth from the harmful impacts of industrial agriculture. Through groundbreaking legal, scientific, and grassroots action, CFS protects and promotes the public's right to safe food and the environment.

Isocycloseram is an isoxazoline insecticide that kills insects by blocking neurotransmission via allosteric binding to the gamma-aminobutyric acid (GABA)-gated chloride channel receptor. The manufacturing process for isocycloseram produces varying proportions of four stereoisomers. The manufacturer, Syngenta, has petitioned for registration of one technical and nine end-use formulations for a wide variety of agricultural and non-agricultural uses: cockroach gel bait, two seed treatment products, and five liquid concentrates for foliar application to a large range of crops. Syngenta has also petitioned for tolerances permitting residues of isocycloseram on a wide range of food crops.

HUMAN HEALTH CONCERNS AND HARMS

Toxicity of Numerous Metabolites and Degradates Goes Undetermined

Isocycloseram breaks down into a dizzying array of compounds in the digestive systems of mammals and other animals that are exposed to it, as well as in soils and in water. EPA lists

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36 such metabolites (EPA 8/2/22, Appendix A¹). Fully 24 of the degradates² are regarded as “major,” in that they each comprise greater than 10% of the amount of the original parent compound in various tests conducted to assess breakdown in living organisms or in abiotic systems (EPA 4/29/25, p. 30). Eleven of the 24 major degradates are identified as posing human health concerns in drinking water (Ibid.). The metabolites and degradates of isocycloseram in plants and livestock that EPA proposes to include in its human health dietary risk assessment together with parent isocycloseram are carefully listed in Table 5.1.4 (Ibid., p. 34).

However, despite the seeming precision of EPA’s treatment of these breakdown products, the Agency has very little information on them. It collected toxicological test data on only one, the dietary metabolite SYN548569, and the tests conducted on this single metabolite were extremely limited genotoxicity assays (EPA 4/29/25, p. 20). As detailed below, one of the genotoxicity assays suggests this metabolite could be carcinogenic – leading one to wonder what such testing, if it had been conducted, might have revealed about any of the other 20+ major degradates.

In the end, EPA had to concede that it was proceeding largely on the basis of guesswork. “Generally, the metabolites have similar structure as the parent isocycloseram, so are assumed to have similar toxicity to the parent compound” (Ibid., p. 33). Assumption rather than test data; toxicity *similar* to that of isocycloseram, rather than potentially *greater* toxicity.

Honey bees would object to the “similar toxicity” assumption. An isomer (SYN549106) of one metabolite, SYN549431, is four times more toxic to honey bees (*Apis mellifera*) than parent isocycloseram on an acute contact basis, and 1.5 times more toxic upon oral exposure (EPA 5/8/25, p. 34; Table 4-1, p. 36). There is no reason to think that thorough testing of the many degradates for potential human health impacts would not likewise yield results showing some were more toxic to humans than parent isocycloseram.

An additional concern is that residues of isocycloseram and its metabolites linger in the tissues of animals that ingest it. For instance, in one of several rat studies in which radiolabeled isocycloseram was fed to rats (single dose of either 3 or 50 mg/kg), scientists followed the tissue distribution and the rat’s elimination of radioactivity over time, with radioactivity a proxy for the presence of isocycloseram and its metabolites. Elimination of radioactivity was slow. After 1 week, most tissues retained quantifiable levels of radioactivity: 10-20% of the initial dose in male and 20-30% in female rats (EPA 4/29/25, p. 97). Any adverse effects of isocycloseram and its metabolites would be accentuated by this long residence and extremely slow elimination time; occupational users exposed repeatedly could even accumulate the pesticide in their tissues over a spraying season.

Damage to the Male Reproductive System and Liver

EPA finds that the isocycloseram has a variety of adverse impacts on the male reproductive system and the liver. EPA found tubular degeneration in the testes and cellular debris and reduced sperm in the epididymides, as well as hepatocellular vacuolation, in a number of different studies (EPA 4/29/25).

¹ The count excludes stereoisomers of isocycloseram itself and of the metabolite SYN549431.

² Metabolite and degradate are used interchangeably, even though the former is technically the product resulting from transformation of a compound by a living organism, and the latter more commonly refers to the breakdown product in the environment.

Both male reproduction and the liver are extremely common targets for disruption by pesticides and other environmental toxins. Cumulative risk assessments are needed based on cumulative exposure to groups of compounds that affect the same organ or system in similar ways. EPA has done very little in this regard, still assessing pesticides like isocycloseram one at a time. The upshot is that thousands of individual safety thresholds are set for thousands of different chemicals, as if people were only exposed to one rather than many. Thus, there is seldom any consideration of cumulative exposure to similarly-acting compounds, which is far greater than exposure to any individual one, and the adverse effects this can have.

Interestingly, the Make America Healthy Again report correctly singles out this issue of cumulative exposure as the key to unravelling chemical-induced disease in America (MAHA 2025). Approaches to this daunting task have been laid out. For instance, Nielsen et al. (2012) have identified “cumulative assessment groups of pesticides” with groups broken down by the organ/system/tissue they affect, then further by type of effect on the give organ/tissue, down to groups of pesticides that share a common mechanism of toxic action. While this is a good start, the same approach needs to be broadened beyond pesticides to industrial chemicals and environmental toxins in general, for instance per- and polyfluoroalkyl substances (PFAS) and phthalates. Various PFAS are carcinogenic (testes and kidney), cause reduction in birth weight, trigger thyroid disease and/or impair the immune system; some phthalates are potent anti-androgens. These widespread contaminants should be assessed cumulatively with pesticides and other environmental toxins that have similar impacts, despite coming under the purview of different statutes and implementing regulations.

Center for Food Safety provides further exploration of this important topic in comments on EPA’s Cumulative Risk Assessment Guidelines for Planning and Problem Formulation (CFS 2023).

Beyond these harms acknowledged by EPA are many others that are given short shrift or ignored.

EPA Rejects Suggestive Evidence of Cancer Based on Deeply Flawed Animal Studies

EPA has entirely dismissed isocycloseram’s potential to cause cancer despite suggestive evidence of such, and in the absence of adequate animal biosassays required to make this important determination. EPA’s hazard descriptor, “not likely to be carcinogenic to humans,” requires “robust” evidence that isocycloseram does not pose a cancer hazard (EPA 2005, p. 2-57), a standard that is clearly not met.

First, isocycloseram and at least 13 of its 26 metabolites/degradates “produced plausible alerts for carcinogenicity and skin sensitization, and an equivocal alert for nephrotoxicity,” upon assessment by the Derek Nexus system (EPA 8/2/22, p. 4). DEREK is a knowledge-based expert system for prediction of the toxicity of chemicals that was developed by a consortium of representatives from the pesticide and drug industries, regulators and academics (Marchant 1996). DEREK is comprised of rules that associate structural features of a given chemical with a given toxicological effect, including carcinogenicity, mutagenicity, skin sensitization, teratogenicity, and neurotoxicity (Ibid.). EPA has previously relied upon DEREK to dismiss concerns for the carcinogenicity of certain chemicals in the absence of animal data (EPA 4/3/09, pp. 15-17). EPA makes no mention of these carcinogenicity alerts in its human health assessment, but rather only indicates that DEREK-based “alerts for the metabolite/degradeate were consistent with the parent compound analysis” for various compounds (EPA 4/29/25, pp.

32-33). The nature of the potential health threats flagged by DEREK were for some reason consigned to an obscure supporting document (EPA 8/2/22).

It is interesting to note that DEREK's prediction that isocycloseram is a skin sensitizer was correct (EPA 4/29/25, p. 23: isocycloseram "is a dermal sensitizer"). This was established via a well-established test in the mouse known as the local lymph node assay (LLNA) (Ibid., Table A.2, p. 56). This corroborating finding strengthens confidence in same system's prediction of the compound's carcinogenicity.

Second, an *in vitro* genotoxicity assay demonstrated that a dietary metabolite of isocycloseram (SYN548569) causes increased micronuclei to form in human lymphocytes in a concentration-dependent manner (Ibid., p. 66). Micronuclei are aberrant structures in the cytoplasm of cells that are caused by DNA damage or genomic instability, which in turn can give rise to cancer and other diseases; the micronucleus assay is one of the most widely used tests to assess carcinogenic potential (Sommer et al. 2020). DEREK analysis of the metabolite in question (SYN548569) produced two of the three alerts (carcinogenicity, skin sensitization, nephrotoxicity) noted above for isocycloseram and 13 of its metabolites/degradates (EPA 8/2/22, p. 4); one of the two alerts is likely to be carcinogenicity, because later in the same document EPA states with respect to SYN548569 that "alerts for the metabolite were consistent with the parent compound analysis..." (Ibid., p. 9). If carcinogenicity is one of the two alerts, this would constitute a second piece of evidence in support of isocycloseram's carcinogenic potential via exposure to its dietary metabolite, which is formed by metabolism of ingested isocycloseram and detected in the liver of lactating goats and laying hens, and in the liver and kidney of lactating cows (Ibid., pp. 5-6).

In light of this evidence suggestive of carcinogenicity, EPA should have ensured that the animal bioassays intended to explore this potential hazard were sound, and scrutinized all available data for possible signs of carcinogenic potential. Unfortunately, the Agency did not do this.

In an 80-week mouse carcinogenicity study, "various neoplastic and non-neoplastic causes of death were reported" (EPA 4/29/25, p. 88); "neoplastic" refers to the abnormal and excessive growth of a tissue that is known as a tumor, which can be cancerous [malignant] or benign. Unfortunately, EPA neither identifies the type of tumors found in these mice nor gives any explanation as to why it regarded them as unrelated to isocycloseram, much less what other factors might have been responsible for them. Likewise, EPA claims there was no treatment-related increase in tumor incidence among surviving animals.

EPA concedes that male and female mice in both the mid- and high-dose groups (≥ 7 mg/kg bw/day³) experienced "plasmacytosis/plasma cell infiltration in the lymph nodes (most notably the mesenteric lymph node), spleen, and thymus" (Ibid., p. 88). Plasmacytosis is an unusual increase in plasma cells [antibody-producing cells] in the bloodstream or other tissues;⁴ when it occurs in lymph nodes, it can signify a normal immune response to an infection (lymphadenopathy, or swollen lymph nodes) or be a sign of malignant lymphoma (Xie et al. 2016). EPA maintains that: "**At the doses tested** [t]he plasmacytosis was not associated with an increase in the incidence of lymphoid tumors, lymphomas, or leukemias," but regarded it as

³ This abbreviation means milligrams [of isocycloseram] per kilogram body weight per day, and is often shortened to mg/kg/day.

⁴ https://taylorandfrancis.com/knowledge/Medicine_and_healthcare/Hematology/Plasmacytosis/.

a “non-adverse immune response” to isocycloseram (EPA 4/29/25, p. 88, emphasis added).⁵ EPA leaves ample reason to doubt its conclusion that isocycloseram does not cause cancer, particularly lymphomas or other immune system cancers.

First, “the doses tested” in the mouse study were not anywhere near high enough to constitute a legitimate test of isocycloseram’s carcinogenic potential. Three groups of mice were administered isocycloseram at daily doses of either 2, 7 or 23/24 (M/F) mg/kg bw/day for 80 weeks, and compared to an untreated control group. EPA found no adverse effects in any group of mice, even those fed the highest dose, which was designated the no-observed adverse effect level (NOAEL). A legitimate rodent carcinogenicity trial must incorporate a highest dose that “elicit[s] signs of toxicity without substantially altering the life span due to effects other than tumors,” while even “intermediate-dose level[s] should be spaced to produce a gradation of toxic effects,” and only the lowest dose should not have toxic effects (EPA 1998a, p. 4). In other words, the study was “non-guideline,” “because no LOAEL⁶ was identified ... and the animals were not dosed up to the limit dose” (EPA 4/29/25, p. 89). The upshot is clear. An entirely new mouse carcinogenicity is called for, one in which the high dose of the already conducted study becomes the low dose of a new study, with both intermediate and high doses considerably higher, as per EPA Cancer Test Guidelines (EPA 1998a). This is particularly necessary given that ***the high dose of 23/24 mg/kg/day (M/F) is less than 2.5% of the “limit dose” of 1,000 mg/kg/day.***⁷

The rat chronic toxicity/carcinogenicity study had the same deficiency, with the high-dose group receiving just 7/9 mg/kg/day (M/F) (Ibid., pp. 67-68). It is not surprising that EPA did not find any isocycloseram-related tumors, given the incredibly low doses administered, which were less than 1% of the limit dose. This rat study should be also be repeated at substantially higher doses.

Second, comparisons to the carcinogenicity of closely related compounds also weigh in favor of isocycloseram’s carcinogenic potential. EPA utilized the toxicological data on two such related compounds – broflanilide and fluxametamide – to support waiving otherwise required studies on isocycloseram.⁸ EPA classified broflanilide as “likely to be carcinogenic to humans” and fluxametamide as having “suggestive evidence of carcinogenic potential” in separate evaluations (EPA 10/17/20, p. 21; EPA 12/11/20, pp. 9, 11). These two compounds not only have the same mode of action as isocycloseram, they also share 55% and 76% structural similarity to it, respectively (EPA 12/6/22, p. 6, ft. 3).

Critically, the evidence for the carcinogenicity of these closely related compounds came from studies that employed appropriately high doses that approached the limit dose of 1,000 mg/kg/day: 709 mg/kg/day in the case of a study on broflanilide, which caused found Ledyidg

⁵ EPA then confusingly contradicts itself, maintaining that “[w]hite blood cell counts and related parameters were unaffected by isocycloseram administration” (Ibid.), never explaining why plasma cells (a type of white blood cell) increased if not due to isocycloseram and any damage it caused.

⁶ LOAEL = lowest observed adverse effect level. Properly conducted animal studies establish both an exposure level without toxic effects (NOAEL) and the next higher dose, the LOAEL (EPA 1/31/25).

⁷ The limit dose for any given test is the dose that need not be exceeded, even if it does not, as otherwise prescribed for a high dose, elicit signs of toxicity without substantially altering the life span due to effects other than tumors.

⁸ EPA waived studies on isocycloseram’s inhalation toxicity, immunotoxicity and developmental neurotoxicity based on evaluations of these two related compounds, which it found did not exert these specific toxic effects (EPA 12/6/22). Accordingly, evidence that they cause other toxic effects such as cancer must be weighed in an assessment of isocycloseram.

cell (testicular) tumors in male rats (EPA 10/17/20, pp. 69-70⁹); and 899 and 877 mg/kg/day in studies on fluxametamide, which caused thyroid tumors in male rats and liver tumors in male mice, respectively, at these doses (EPA 12/11/20, p. 9).

Clearly, adequately dosed studies of isocycloseram in at least two animal models (e.g. rat and mouse) are urgently required to determine the carcinogenic potential of this pesticide, for instance, whether or not the plasmacytosis/plasma cell infiltration of the lymph nodes, spleen and thymus are a low-dose indicator of lymphomas or other cancers that would manifest at higher doses (Xie et al. 2016). As discussed further below, plasmacytosis and other immune system effects were found in several other studies.

Developmental Toxicity, Birth Defects

There is also suggestive evidence that isocycloseram is a developmental toxin, meaning that fetal exposure *in utero* or infant exposure via breast milk could cause lasting damage to the developing human at the stage of growth when it is most vulnerable to disruption.

First, the DEREK analysis of isocycloseram and its metabolites identified one (SYN551324) as a potential developmental toxin, and produced equivocal alerts for teratogenicity for six others - SYN549433, SYN549554, SYN550455, SYN550602, SYN551113 and SYN551190 – based on glucocorticoid receptor activity (EPA 8/2/22, p. 4).

Second, scientists with the Australian Pesticides and Veterinary Medicines Authority (APVMA) who reviewed toxicology studies on isocycloseram found that it caused a rare skeletal malformation in a rat developmental study. Pregnant rats dosed with just 15 mg/kg/day isocycloseram produced two fetuses in two separate litters with bifid sternum (APVMA 2022, p. 12). Bifid sternum is a rare congenital anomaly resulting from a fusion failure of the sternum; in humans, surgery is called for to protect the heart and major blood vessels from trauma, to improve respiratory dynamics, and for aesthetic reasons.¹⁰ The Australian reviewers were confident that isocycloseram caused this birth defect, as evidenced by their establishment of the acute reference dose (ARfD) for women of child-bearing age on the basis of this study (Ibid., p. 13).¹¹ The critical consideration here is that isocycloseram caused a birth defect in rats, not the nature of the defect, since isocycloseram's developmental toxicity may well manifest differently in humans.

The EPA reviewed what is likely to be the very same rat developmental study. The registrant sponsoring the study is the same in both cases: Syngenta. The mid- and high doses cited in the brief Australian review document – 7.5 and 15 mg/kg/day (APVMA 2022, p. 12) – match those in the study reviewed by EPA (EPA 4/29/25, pp. 83-84). Whether or not it is the same study (if so, Australian scientists identified birth defects apparently overlooked by EPA reviewers), this evidence of isocycloseram's developmental toxicity, combined with the DEREK expert system's flagging of seven metabolites for potential developmental toxicity (1) or teratogenicity (6), casts grave doubt on EPA's argument that isocycloseram does not have developmental toxicity.

⁹ Note that the high dose is also designated 15000 ppm, which is the concentration of broflanilide in the rat's diet, and which translates to 709 mg/kg bw/day for male rats, given the amount of chow they consume.

¹⁰ [https://www.annalsthoracicsurgery.org/article/S0003-4975\(99\)01206-0/fulltext](https://www.annalsthoracicsurgery.org/article/S0003-4975(99)01206-0/fulltext).

¹¹ The acute reference dose is the safety threshold (maximum dose regarded as safe for humans) for single (acute) exposures. Like Australian authorities, EPA understands that a single exposure to a developmental toxin during a critical period of fetal development can induce birth defects; therefore, EPA also sometimes utilizes developmental toxicity studies to establish acute reference doses for pesticides (EPA 1998b, p. 2).

We say argument because EPA itself reached no conclusion on this matter, owing to the fact that the prenatal developmental toxicity studies, like the cancer studies discussed above, were severely underdosed, and thus in violation of EPA Test Guidelines for this type of study (EPA 1998c). EPA freely concedes that “the rat and rabbit definitive developmental studies did not test up to the limit dose and there is a potential for *susceptibility at higher doses...*” (EPA 5/6/25, p. 19, emphasis added), for which reason these two studies were both classified as “non-guideline because no LOAEL was identified in the study, and the animals were not dosed up to the limit dose” (EPA 4/29/25, p. 84-85). A key attribute of a developmental toxin is that it exerts adverse effects on the fetal or infant organism¹² at doses lower than those that cause harm to the maternal animal. This increased “susceptibility” [of the fetus/infant] vis-à-vis the mother is what EPA maintains might have been found if the rat and rabbit studies had been properly conducted “at higher doses,” potentially “up to the limit dose.” EPA’s Prenatal Developmental Toxicity Study Test Guidelines specify that “the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity but not death or severe suffering” and that “[t]he highest dose tested need not exceed 1,000 mg/kg/day,” defined as the “limit dose” (EPA 1998c, p. 2).

Finally, fluralaner, the compound found to have the greatest (80%) structural similarity to isocycloseram (EPA 8/2/22, p. 4), as well as sharing its mode of action, is a developmental toxin. According to a recent Safety Data Sheet (Fluralaner SDS 2024), fluralaner caused skeletal and/or visceral malformations in two rabbit developmental toxicity studies, and adverse neonatal effects and postimplantation loss in a two-generation rat study (Fluralaner SDS 2024, p. 9). It thus carries the hazard statement “Suspected of damaging the unborn child” (Ibid., p. 1).

A weight of the evidence assessment suggests that isocycloseram is likely a developmental toxin. First, Australian authorities identified clear birth defects in fetuses of maternal rats dosed with isocycloseram. EPA’s expert knowledge system, DEREK, identified structural features in seven metabolites of isocycloseram typical of developmental toxins/teratogens. A closely related compound is classified as suspected of causing birth defects. EPA itself cannot conclude with any confidence that isocycloseram does not cause birth defects due to severely underdosed studies that violate EPA Test Guidelines, and freely concedes that “there is a potential for susceptibility [adverse effects on the fetus] at higher doses” that should have been administered, but were not, in the studies in question.

EPA Waived Immunotoxicity Study Despite Suggestive Evidence of Immune System Effects

The finding that isocycloseram triggers an immune response is not limited to the plasmacytosis/plasma cell infiltration of lymph nodes, spleen and thymus in the 80-week mouse study discussed above. Leucocyte (white blood cell) counts increased in response to administration of isocycloseram in many of the animal studies, including the 28-day oral rat study, the 28-day dermal rat study, the 90-day oral mouse and 90-day oral rat studies (EPA

¹² We include infant organism because some developmental toxicity studies (unlike these, which were ended during pregnancy, with only fetuses examined for birth defects) continue through birth into the early infant stages, during which time the infants may be exposed to the test compound in breast milk.

4/29/25 at 69, 72, 79-80 and 82). In each case, EPA dismissed the results as either non-adverse or within the historical control range.¹³

Scientists with the Australian Pesticides and Veterinary Medicines Authority (APVMA) who reviewed toxicology studies on isocycloseram also noted immune system reactions in response to isocyclosporam administration, noting “lymphocytic leucocytosis” in the 28-day oral rat study and “leucocytosis” in the 28-day dermal rat study (APVMA, p. 11). APVMA characterized the immune system response in the 80-week mouse study (discussed above in the Cancer section) as “lymphatic and non-lymphatic plasmacytosis,” and utilized this adverse effect to establish the Acceptable Daily Intake (ADI), which is equivalent to EPA’s chronic reference dose (both values indicate the maximum presumably safe level of daily exposure over a lifetime) (APVMA at 12-13).

Interestingly, APVMA noted that “[n]o data were available on immunotoxicity,” which prevented it from determining whether or not isocycloseram was adversely affecting the function of “T- and B-cell[s],” critical classes of immune system cells. As explained above, aberrant immune system responses can be indicators of lymphomas or other blood-borne cancers.

It is thus unfortunate that EPA chose to waive the immunotoxicity study on isocycloseram, which is otherwise required of all pesticides used with food crops (40 CFR 158, Subpart F, 158.500: Toxicology data requirements table, see last entry). And EPA granted the waiver on faulty grounds (unless otherwise noted, see EPA 12/6/22, pp. 7-8, for the following discussion). EPA’s < 1 page rationale for the study waiver is based in part on supposed negative findings for a number of parameters in other studies, comprising the isocycloseram database. These supposed negative findings include “Hematology indicators (WBC changes),” despite ample evidence of isocycloseram’s elicitation of marked changes in white blood cell (WBC) parameters in numerous animal studies, as discussed above. Another parameter for which EPA claimed negative findings was “organ weight indicators (spleen, thymus),” ignoring the Agency’s own identification of higher spleen weights in male and female mice, which correlated with microscopic changes in this organ (lymphoid cellularity), in the 90-day oral toxicity study (EPA 4/29/25, p. 80). Otherwise, EPA bases the waiver on its observation that two pesticides related to isocycloseram (broflanilide and fluxametamide) evinced immunotoxicity only at doses close to or above the limit dose, or not at all. The toxicological data on isocycloseram suggesting possible immune system toxicity obviously trumps whatever findings were made on different pesticides, and demands more intensive investigation and clarification with a study designed specifically to explore immunotoxicity.

¹³ Historical controls are control (untreated) groups of animals from entirely different studies. The incidence of a particular adverse effect in a control group (i.e. proportion of animals manifesting it) is the baseline for “spontaneous” (i.e. unexplained) occurrence of the adverse effect (here, abnormally high white blood cell counts), against which the incidence of that effect in the treatment groups is compared. All of the isocycloseram studies have concurrent control groups, which provide the best measure of “spontaneous” incidence of a particular adverse effect. The range in incidence of the adverse effect in control groups from previously conducted (historical) studies provides additional but less relevant context for assessing whether an adverse effect in the current study is treatment-related or not. EPA frequently misuses historical control group data to discount adverse effects that are significantly elevated in the treatment groups relative to the concurrent control of the study in question.

Waiver of Developmental Neurotoxicity Test Not Justified

EPA also waived the conditional requirement for a developmental neurotoxicity (DNT) study. The Agency's rationale for this waiver is essentially that two different studies (acute and subchronic) designed explicitly to detect neurological impairment of **adult** animals did not turn up signs of such impairment; and that the acute and subchronic neurotoxicity studies on two related pesticides (broflanilide and fluxametamide) did not show adult neurotoxicity (see EPA 12/6/22, pp. 8-9, for the following discussion). This rationale misses the mark for several important reasons.

First, isocycloseram's toxic mode of action – blocking neurotransmission at GABA-gated chloride channel receptors – is neurological. On first principles, then, an especially hard look is needed to ascertain whether this insecticide can affect human neurology at any lifestage, given the conservation of such GABA receptors across animal species.

Second, the developing nervous system of a fetal human being is worlds apart from the mature nervous system of an adult, and far more sensitive to chemical disruption during critical windows of development, which can have permanent adverse consequences “that may be quite unlike the chemical's effects in an adult nervous system,” explaining why “regulatory agencies have promulgated testing guidelines for DNT.”

Third, isocycloseram did show evidence of neurotoxicity, contrary to EPA's blanket assertion that “no indications of neurotoxicity were observed within the isocycloseram database” (Ibid., pp. 8-9). EPA itself contradictorily concedes that male dogs fed isocycloseram at 80 mg/kg/day experienced “slight body tremor and vomiting,” clear neurological symptoms. Moreover, elsewhere EPA noted that in neurobehavioral functional observations made in the subchronic (13 week) rat study, male rats fed just 22 mg/kg/day isocycloseram experienced a 17% lower forelimb grip strength, but the Agency somehow regards this neurobehavioral loss of more than 1/6th of grip strength as not adverse (EPA 4/29/25, p. 69).

Fourth, the apparent lack of adverse neurological effects in the subchronic neurotoxicity study must be viewed in light of its extremely low dosing – with a high dose of just 25/33 mg/kg/day (M/F), versus a limit dose for this study that is >30-fold higher: 1,000 mg/kg/day (EPA 8/2/22, p. 9).

EPA should demand both immunotoxicity and DNT studies before deciding whether to register this insecticide.

EPA Celebrates Study Waivers and Decision-Making Without Critical Data

An expose from several years ago revealed the extent to which the EPA's Office of Pesticide Programs (OPP) waives studies that would otherwise be required (see Lerner 2021 for the following discussion). From December 2011 to May 2018, OPP granted 972 requests to waive toxicity studies at the request of manufacturers, 89% of all requests made: 90% of developmental neurotoxicity waiver requests were granted, and an astronomical 97% of those for waiving immunotoxicity tests. These high figures are perhaps not surprising given that pesticide manufacturers BASF, Corteva and Syngenta helped EPA draft the waiver guidelines. EPA does not appear to grant these waivers grudgingly; on the contrary, in 2018 OPP held a party to “celebrate reaching 1000 studies waived! There will be cake....” (Lerner 2021).

Making decisions in the absence of critical data does not inspire confidence in either the competence or honesty of EPA's pesticide division.

ENVIRONMENTAL CONCERNS AND HARMIS

Environmental Fate

Isocycloseram is moderately persistent in soils, with aerobic soil metabolism half-lives ranging from 56-293 days, and field dissipation half-lives of 4 to 382 days. This means that half an initial amount of isocycloseram present in soils persists for up to a year, depending on soil type, pH and other factors. Because isocycloseram is also slightly to hardly mobile in soil, levels could under certain circumstances build up over time. When isocycloseram does break down, it forms 24 major degradates (with “major” signifying that the degradate comprises 10% or more of the initial amount of parent compound). The degradates generally have considerably greater persistence than parent isocycloseram. Dissipation rates of the six degradates that EPA regards as “residues of concern” are estimated to be many-fold longer than the parent compound, up to several years for 50% to dissipate (EPA 5/8/25, Table 5-2, pp. 43-45).

Isocycloseram also has a high bioconcentration factor in fish, ranging from 823 to 982 L/kg-wet weight fish (EPA 5/6/25, p. 27). This means that fish accumulate isocycloseram in their tissues to levels that are 823 to 982 times higher than its presence in the surrounding water.

Organisms at Risk

Isocycloseram is extremely toxic to multiple taxa. Chronic exposure to just 0.0042 micrograms per bee (equivalent to 4.2 billionths of a gram) per day increases adult honey bee deaths by 15%. Chronic exposure of honey bee larvae to 11 billionths of a gram per day causes a 21% increase in larval deaths, a 61% increase in pupal deaths, and a 79% reduction in adult emergence (Ibid., p. 29). The risk quotients for larval and adult honey bees range from 180 to 1,537), meaning that estimated environmental exposure exceeds the safety threshold by 180 to 1,537 times. While acute risks (effects from a single exposure) are less pronounced, the risk quotients still range up to 23 and 54 for larvae and adults, respectively. As noted earlier, contact with one of the few degradates for which EPA has experimental data is four times more lethal to honey bees than contact with parent isocycloseram.

Isocycloseram is also very highly toxic to aquatic invertebrates, with acute and chronic risk quotients ranging up to 86.4 and 413, respectively, for those in the water column (Ibid., p. 29).

Birds and mammals are at risk from isocycloseram-treated rapeseed (canola), with risk quotients up to 19.8 and 16.1, respectively (Ibid., p. 30).

As a relatively new compound, there are few independent studies on isocycloseram’s environmental risks. One study assessed isocycloseram’s toxicity to the boll weevil and two of its natural enemies: the ladybird beetle (*Eriopis connexa*) and a parasitoid wasp (*Bracon vulgaris*), and concluded that isocycloseram was highly toxic to all three; while another insecticide that was assessed, ethiprole, was highly toxic to boll weevil while far less injurious to this pest’s natural enemies, and thus would be a far less damaging choice (Lira et al. 2024).

Presumed Benefits

EPA's "benefits" assessment is largely limited to comparing isocycloseram to what it regards as the most likely alternatives to it: chemical insecticides that are also highly toxic to non-target organisms (EPA 5/6/25, pp. 35-36). Lacking is any comparison of the efficacy and non-target effects of isocycloseram in comparison to less toxic biologically-based controls. For instance, EPA points to tarnished plant bug as an important pest controlled by isocycloseram, one that is often controlled by multiple insecticide applications over the course of a year (e.g. in cotton). Repeated use of this sort is what leads to rapid evolution of resistance in target pests. EPA welcomes isocycloseram as a tool to control pests resistant to other insecticides, but nowhere addresses how the repeated use of those insecticides fostered the resistance isocycloseram is now supposed to overcome, nor how isocycloseram resistance is likely to rapidly evolve given the unsustainable use of such pesticides that is endemic to industrial agriculture. In any case, EPA needs to consider biologically based control methods. One such tool is a parasitic wasp (*Peristenus digoneutis*) that preys upon (parasitizes) tarnished plant bug nymphs, and which has had some success in controlling this pest in New Hampshire (Eaton 2016). Other alternatives that EPA must consider are the plethora of green pesticides that are being developed for myriad uses, and which generally speaking cause far less harm to non-target organisms (Song et al., 2024).

MITIGATIONS

EPA's mitigations are unlikely to provide much protection for non-target organisms, especially for the invertebrates (terrestrial and aquatic) that are particularly at such high risk from this extremely toxic insecticide. For instance, EPA estimates that runoff mitigations may reduce risks to aquatic invertebrates by about one order of magnitude, a likely overestimate given the paltry 2 points of mitigation that EPA proposes, and the largely useless label language instructing farmers not to apply during rain. Even if true, the estimated mitigation effect would not be sufficient to provide much benefit given the very highly toxic nature of this insecticide to these organisms (risk quotients ranging into the hundreds, as noted above).

We take particular exception to EPA's failure to ban aerial application for all uses, given the well-known fact that spray drift extend far greater distances from the sprayed field, and at far higher concentrations, than when the pesticide is sprayed with ground equipment. EPA says it has prohibited aerial application for all crops except those that are among the most widely planted in America: corn, soybean, cotton and potato. Permission to aerially spray corn and soybean is especially perverse, in that these crops are little plagued by insect pests in the first place, and many alternatives exist in those few situations where some control might be called for, especially in the case of corn. EPA's rationale of countervailing "high benefit" for these crops is highly suspect, and almost certainly based on the self-interested representations of Syngenta, anxious to secure the widest possible use of its new product. We would note that Australian authorities banned aerial applications of this same insecticide, with no exceptions.

Otherwise, EPA's mitigations mainly involve the usual ineffective language on labels. For instance, EPA's label-based "advisories" to protect pollinators from dust generated from abrasion of isocycloseram-treated seed coatings during planting is likely to have zero impact, since farmers rarely apply the seed coating, often have little choice of untreated seed, and will

use whatever expensive planting equipment they already own, irrespective of whether it generates more or less toxic dust.

Conclusion

For all of the reasons discussed above, we urge EPA to reject the proposed registration decision for isocycloseram.

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