NRDC NATURAL RESOURCES DEFENSE COUNCIL

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Developmental and Reproductive Toxicants Identification Committee,
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Sacramento, California 95814

Submitted electronically at https://oehha.ca.gov/comments

**Comments from the Natural Resources Defense Council (NRDC)
To The Office of Environmental Health Hazard Assessment (OEHHA)
on its list of chemicals to be considered at the December 10, 2020, meeting
of the Developmental and Reproductive Toxicant Identification Committee**

Dear Members of the Developmental and Reproductive Toxicants Identification Committee (DARTIC):

Thank you for the opportunity to provide comments. NRDC is a national, non-profit environmental organization of lawyers, scientists, and other professionals. NRDC presents these comments on behalf of our over three million members and online activists, including about 400 thousand members in California. NRDC does not have any financial interest in the topic of these comments.

We urge the DARTIC to recommend that the following pesticides be prioritized and moved forward:

- Glyphosate and its salts
- Neonicotinoid pesticides ("neonics")
  - Acetamiprid
  - Clothianidin
  - Imidacloprid
  - Thiamethoxam

We believe that the scientific evidence base supports the listing of these pesticides as developmental and reproductive toxicants under Proposition 65, based on the information presented in the OEHHA report, Prioritization: Chemicals Identified for Consultation with the Developmental and Reproductive Toxicant Identification Committee, October 2020 (herein referred to as the "OEHHA Prioritization report"), and additional information in these comments.[1]

[1] Prioritization: Chemicals Identified for Consultation with the Developmental and Reproductive Toxicant Identification Committee, Oct 2, 2020. Available at https://oehha.ca.gov/proposition-65/crnr/announcement-developmental-and-reproductive-toxicant-identification-committee-0.

GENERAL COMMENTS – GLYPHOSATE AND ITS SALTS

Evaluation of glyphosate and its salts is somewhat complicated by the fact that the epidemiological studies (predominantly case control and cohort studies) are of exposures to formulated herbicide products that contain glyphosate and other ingredients (called 'glyphosate-based products,' GBP), whereas the preponderance of laboratory animal studies are from oral administration of glyphosate technical (no other product ingredients). As it is the goal of Proposition 65 to provide a warning so that Californians can make informed decisions to protect themselves and their families, exposure to both the pure active ingredient (glyphosate technical) and glyphosate formulations are relevant. Moreover, reproductive, developmental, and endocrine effects are reported in animal studies of glyphosate technical, and in both human and animal studies of glyphosate formulations (see ATSDR 2020, Figs. 2-1, 2-2), further supporting the inclusion of all studies.[2]

GENERAL COMMENTS - NEONICS

OEHHA should include neonic seed treatments in its evaluation, which may account for as much as half the amount of neonics used in California

The OEHHA Prioritization report systematically and substantially underestimates of the amount of neonic pesticides used in California. This is because it relies solely on data from the California Department of Pesticide Registration's (CaDPR) Pesticide Use Reporting (PUR) database. The PUR database largely does not track neonics used as coatings on crop seeds—the largest single use of neonics nationwide. This is because CaDPR, like the federal EPA and Canadian regulatory agencies, does not directly regulate or track pesticide-treated seeds as "pesticides."

The table below compares the amount of neonics that the OEHHA Prioritization Report presumes were used in 2017 to the total potential use of neonics on California crop seeds in 2016 estimated in a recent report by Dr. Pierre Mineau (see Mineau 2020, Tables 6 and 7). In the first row, the PUR data—upon which OEHHA relies—largely does not include neonics used as seed treatments. In the second row, the total potential use of neonics applied as seed treatments in California is given, based on the possible total quantity of each neonic active ingredient that could be applied via treated seed use, assuming all seeds are treated if allowed.[3]

[2] Agency for Toxic Substances and Disease Registry (ATSDR). 2020. Toxicological profile for Glyphosate. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. https://www.atsdr.cdc.gov/toxprofiles/TP.asp?id=1488&tid=293

[3] Mineau P. 2020. Neonicotinoids in California: Their Use and Threats to the State's Aquatic Ecosystems and Pollinators, with a Focus on Neonic-Treated Seeds. Available at https://www.nrdc.org/resources/neonicotinoids-california-their-use-and-threats-states-aquatic-ecosystems-and-pollinators.

	Acetamiprid (lbs of a.i.)	Clothianidin (lbs of a.i.)	Imidacloprid (lbs of a.i.)	Thiamethoxam (lbs of a.i.)	TOTAL
Non-seed uses only (OEHHA)	61,000	26,000	346,400 (Mineau) [*587,000 OEHHA*]*	47,000	480,000
Total potential seed use in CA (Mineau 2020)	N/A	165,500	138,000	208,300	500,000
TOTAL	61,000	191,000	725,000	255,300	980,000

**Note: in this table I present the OEHHA report value for imidacloprid non-seed uses in square brackets, but disregard it in the tally of total pounds used, as I believe it may be misreported. In 2017, imidacloprid use across the whole U.S. was about 1.4 million lbs a.i. (see USGS pesticide use maps). That means the OEHHA value of 587,000 is almost half of the total U.S. use, which is not accurate*.[4] *All other values in the above table are in close agreement between the OEHHA report, the Mineau 2020 report, and the USGS pesticide use maps.*

If seed treatments were fully used on crops where they are allowed, the amount of neonics applied as seed treatments would equal roughly a half million pounds annually (Mineau 2020). This total is roughly equal to neonics applied by other means, thus doubling the estimate of the total amount of neonics applied in California. The Mineau 2020 report concludes that uses of neonics to coat seeds, "may account for one of the largest and most widespread insecticide uses in California, and one which likely contributes to the widespread pollution of state waters and causes substantial harm to pollinators and the state's ecosystems generally."

We suggest to DARTIC that it recommend that the uses of neonics on seed treatments be collected, publicly disclosed, and included in OEHHA's evaluation. California has an opportunity to close this loophole, given its already advanced pesticide tracking system, and its diverse agriculture industry. On September 23, 2020, NRDC and a coalition of environmental and health organizations petitioned CaDPR to do just that.[5]

Studies that fail to include metabolites may underpredict exposures

Studies that fail to measure metabolites will surely underestimate exposures. For example, the OEHHA Prioritization Report includes a summary of the human biomonitoring study that linked acetamiprid metabolites with an elevated risk of being small for gestational age (Ichikawa et al. 2019; OEHHA Prioritization Report, p. 80). The study demonstrates the importance of measuring metabolites in addition to the parent compound. The authors warn that, "The findings suggest a need to examine potential neurodevelopmental toxicity of neonicotinoids and metabolites in human fetuses" (Ichikawa et al. 2019).[6]

[4] USGS pesticide use maps for imidacloprid. https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2017&map=IMIDACLOPRID&hilo=L&disp=Imidacloprid.

[5] Daniel Raichel & Samuel Eisenberg, *Rulemaking Petition to Regulate Crop Seeds Treated with Neonicotinoids and Other Systemic Insecticides* (Sep. 23, 2020), https://on.nrdc.org/3lwTWOg.

[6] Ichikawa G, Kuribayashi R, Ikenaka Y, Ichise T, Nakayama SMM, Ishizuka M, Taira K, Fujioka K, Sairenchi T, Kobashi G, Bonmatin JM, Yoshihara S. LC-ESI/MS/MS analysis of neonicotinoids in urine of very low birth weight infants at birth. PLoS One. 2019 Jul 1;14(7):e0219208. doi: 10.1371/journal.pone.0219208.

The importance of including metabolites in exposure studies was highlighted in a 2019 report by researchers from USGS and the University of Iowa, measuring imidacloprid in drinking water, that is not included in OEHHA's report.[7] The researchers made two relevant findings: first, that metabolites were present at lower concentrations than the parent compound, but exhibited much higher toxicity (desnitro-imidacloprid is about 319 times more toxic to mammals than imidacloprid); second, while both the parent compound and metabolites could be transformed by water treatment to form novel chlorinated products, the metabolites did it at a much faster rate. Had they only tracked the parent compound, the researchers would have missed most of the toxicity and potential for human health harm posed by imidacloprid residues in drinking water. These concerns have important implications for DARTIC's work on reproductive and developmental effects.

We suggest that DARTIC recommend incorporating relevant studies that monitor neonic metabolites in biota, including water, soil, and in human biomonitoring. Failure to consider metabolites is likely to cause DARTIC to overlook relevant evidence of toxicity, and underestimate reproductive and development risks.

Industry-sponsored guideline studies may underestimate risk – "no effect" results should be interpreted with caution

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), pesticide registrants are required to provide hazard information from laboratory rodent or other studies to support the regulatory approval of pesticides. These studies are required to follow pre-described guidelines, and are thus often called, 'guideline studies' (see 40 CFR Part 158 – Data Requirements for Pesticides). Guideline studies are generally insensitive to effects at low-doses, endocrine or hormonal effects, and subtle but significant neurobehavioral impacts. These health endpoints are relevant to tasks of DARTIC, to evaluate the development and reproductive effects of glyphosate and the neonic pesticides. This is because guideline studies are most often designed to identify major toxic effects (apical effects) like cancer, major organ weight changes, body weight changes, skeletal malformations, loss of fur, tremors and convulsions, diarrhea, and obvious signs of lethargy. However, by the time these major (apical) endpoints are observed, significant toxicity has already occurred. Because guideline studies must follow methods that are established over years of negotiations between regulatory agencies and the regulated community, almost by design, they simply cannot reflect modern methods for evaluating chemicals. In contrast, university or other non-industry research is often cutting edge and exploratory, using novel methods to advance scientific knowledge.

The OEHHA Prioritization Report lists a number of industry-sponsored guideline studies but fails to identify them as such. For example, on p. 81 of the OEHHA Prioritization Report, under the heading, 'Animal Studies' there are four guideline studies listed. Within the short summary, the report notes that they are conducted according to FIFRA guidelines, but then lists the authors as EPA, when, in fact, only the study summary is by EPA. The OEHHA Prioritization Report should clearly identify the study sponsor.

In short, the OEHHA report should include the study sponsor and a complete reference to help the public find the full study, especially where it is unpublished.

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[7] Klarich Wong KL, Webb DT, Nagorzanski MR, Kolpin DW, Hladik ML, Cwiertny DM, LeFevre GH. Chlorinated Byproducts of Neonicotinoids and Their Metabolites: An Unrecognized Human Exposure Potential? Environ. Sci. Technol. Lett. 2019, 6, 2, 98–105. https://doi.org/10.1021/acs.estlett.8b00706.

We recommend that DARTIC interpret 'no effect' results from industry-sponsored studies with caution, given the built-in bias in these studies to underestimate risks in these studies, particularly for subtle, complex, and systemic effects like developmental and reproductive outcomes.

SPECIFIC COMMENTS

Acetamiprid, industry guideline study uses insensitive statistics, disregards adverse effects-

In the acetamiprid rat developmental neurotoxicity (DNT) study summarized in the OEHHA Prioritization Report (p. 81), the report fails to identify the sponsor, listing the author only as 'Sheets et al., 2016. The acetamiprid rat developmental neurotoxicity study was published by Larry Sheets (Bayer CropScience) with co-authors from Exponent, Syngenta, Landis International, and Valent Corporation.[8] Sheets et al. 2016 concludes that, "Findings at high doses were associated with evidence of systemic toxicity, which indicates that these insecticides do not selectively affect the developing nervous system." In other words, the only significant adverse effects were at high doses, where the pregnant rat also showed toxicity, so effects on offspring were presumed to be the result of toxicity to the mother, and not treatment-related.

In fact, it seems that USEPA Agency staff felt that there were treatment-related effects: "the DNT Workgroup determined that the effect at the mid dose was biologically significant and treatment related" (USEPA memo p. 41).[9] Agency experts from EPA Chemistry and Exposure Branch (CEB) wrote a memo that provided a corrected statistical analysis, "using a more appropriate model for data structure and appropriate statistical methods" that concluded the auditory startle reflex in male rats was statistically significant at both the mid (10 mg/kg) and high dose (45 mg/kg) compared with control animals (p-value=0.0015) (EPA memo, p. 46) .[10] The memo was sent to the Co-Chairs of the DNT Workgroup, Jess Rowland and Louis Scarano.

In their corrected statistical analysis, the CEB experts summarized several concerns with the industry submission: "In general, CEB had concerns with the incorrect reporting of the results of some of the significance tests, as well as the selected model used to analyze the data which did not allow the statistical power of the DNT study design to be optimized. Additionally, CEB provided a statistical

[8] Sheets LP, Li AA, Minnema DJ, Collier RH, Creek MR, Peffer RC. A critical review of neonicotinoid insecticides for developmental neurotoxicity. Crit Rev Toxicol. 2016 Feb;46(2):153-90. doi: 10.3109/10408444.2015.1090948. Epub 2015 Oct 29. PMID: 26513508; PMCID: PMC4732412.

[9] Memorandum from James Nguyen, Mathematical Statistician, Chemistry and Exposure Branch, Health Effects Division, through David Miller to Jess Rowland. July 24, 2007. See Appendix 1, p. 41. Data Evaluation Record, Acetamiprid, Developmental Neurotoxicity Study- Rat. MRID 46255619. See: csr_PC-099050_28-Feb-08_a Acetamiprid MRID 46255619 Available at https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-099050_28-Feb-08_a.pdf

[10] Memorandum from James Nguyen, Mathematical Statistician, Chemistry and Exposure Branch, Health Effects Division, through David Miller to Jess Rowland. July 24, 2007. See Appendix 1, p. 46. Data Evaluation Record, Acetamiprid, Developmental Neurotoxicity Study- Rat. MRID 46255619. See: csr_PC-099050_28-Feb-08_a Acetamiprid MRID 46255619 Available at https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-099050_28-Feb-08_a.pdf

analysis which utilized a more appropriate model given the structure of the data and also increased the power of the statistical tests to detect significant differences and trends." (USEPA memo, p. 41). [11]

Additionally, EPA identified study deficiencies to include an "inadequate assessment of motor activity and learning and memory" (USEPA memo, p. 38). [12] Thus, failure to detect adverse effects in this study is more likely due to the failure to properly assess them. Absence of evidence should not be taken as evidence of absence, when evaluating adverse effects in this study.

OEHHA should amend its report on p. 81 to note the significant adverse effects at the mid-dose.

Acetamiprid, imidacloprid male reproductive effects–

There are several rat studies that report adverse effects of acetamiprid on sperm, including a study published in Nature reporting on dose-dependent decreased sperm concentration and testosterone levels associated with a 90-day exposure (Arican et al 2020), increases in abnormal sperm and low sperm count (Mosbah et al 2018), and a guinea pig study with similar results (Guiekep et al 2019).[13] These are discussed in the OEHHA Prioritization Report (p. 82).

Similarly, rat studies with imidacloprid also report effects on male reproductive system, including decreased sperm count, sperm motility, and live sperm, and decreased testosterone (p. 95-96) (Lonare et al 2016; Bal et al 2012a, 2012b; Najafi et al 2010).[14] Additional studies reported on increased sperm

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[11] USEPA Data Evaluation Record, Acetamiprid, Developmental Neurotoxicity Study- Rat. MRID 46255619. P. 41. See: csr_PC-099050_28-Feb-08_a Acetamiprid MRID 46255619 Available at https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-099050_28-Feb-08_a.pdf

[12] USEPA Data Evaluation Record, Acetamiprid, Developmental Neurotoxicity Study- Rat. MRID 46255619. P. 38. See: csr_PC-099050_28-Feb-08_a Acetamiprid MRID 46255619 Available at https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-099050_28-Feb-08_a.pdf

[13] Arıcan, E.Y., Gökçeoğlu Kayalı, D., Ulus Karaca, B. et al. Reproductive effects of subchronic exposure to acetamiprid in male rats. Sci Rep 10, 8985 (2020). https://doi.org/10.1038/s41598-020-65887-0

Guiekep AJN, Kenfack A, Ngoula F, Vemo BN, Nguemmeugne KS, Tedonkeng EP. 2019. Attenuating effects of mangifera indica leaves ethanolic extract against acetamiprid induced reproductive toxicity in male guinea pigs. Vet Res Forum 10:187-192

Mosbah R, Djerrou Z, Mantovani A. 2018. Protective effect of nigella sativa oil against acetamiprid induced reproductive toxicity in male rats. Drug Chem Toxicol 41:206-212

[14] Bal R, Naziroğlu M, Türk G, Yilmaz Ö, Kuloğlu T, Etem E, Eht al Eht al Eht al Eht al . 2012a. Insecticide imidacloprid induces morphological and DNA damage through oxidative toxicity on the reproductive organs of developing male rats. Cell Biochem Funct 30:492-499.

Bal R, Türk G, Tuzcu M, Yilmaz O, Kuloglu T, Gundogdu R, Eht al Eht al Eht al 2012b. Assessment of imidacloprid toxicity on reproductive organ system of adult male rats. J Environ Sci Health B 47:434-444.

Lonare M, Kumar M, Raut S, More A, Doltade S, Badgujar P, et al 2016. Evaluation of ameliorative effect of curcumin on imidacloprid-induced male reproductive toxicity in Wistar rats. Environ Toxicol 31:1250-1263

Najafi G, Mazdak Razi, Aref Hoshyar, Simineh Shahmohamadloo, Feyzi S. 2010. The effect of chronic exposure with imidaclopridinsecticide on fertility in mature male rats International Journal of Fertility and Sterility 4:9-16.

abnormalities in rats (Hafez et al 2016) and mice (Bagri et al 2015).[15] A chronic exposure study in beagles reported observing testicular degeneration (CDPR 2006).[16]

This is relevant to humans, given that roughly one-third of all infertility is due to the male, with the most common cause being deficiencies in sperm quality and sperm count.[17] Whether neonic exposures may contribute to male infertility or other male reproductive problems will be of great interest to the public.

Acetamiprid, clothianidin, thiamethoxam, imidacloprid - altered auditory startle response-

Rat guideline studies report a decreased auditory startle response in offspring treated during development with acetamiprid, clothianidin (p. 87), thiamethoxam (p. 102), and imidacloprid (not reported by OEHHA).

For acetamiprid, as discussed above, a corrected statistical analysis from EPA Chemistry and Exposure Branch concluded that the auditory startle reflex in male rats was statistically significantly altered in rodents of both the mid (10 mg/kg) and high dose (45 mg/kg) grroups compared with control animals (p-value=0.0015) (see Acetamiprid DNT Study at 46).[18]

The clothianidin guideline developmental neurotoxicity study also reports a decrease in the auditory response reflex of exposed rats (p. 87).

For thiamethoxam, although the OEHHA Prioritization Report states that the rat guideline DNT study did not observe effects on offspring at any dose (p. 102), this is a summary of the conclusions of EPA and the industry (Syngenta) author (see US EPA 2005; CDPR 2008; Sheets et al 2016).[19] It fact, in the thiamethoxam rat guideline DNT study, the offspring demonstrated several adverse effects at the low (4.3 mg/kg) and mid-doses (34.5 mg/kg) at which the adult mother did not show effects; these included a thinner brain cortex, altered auditory startle reflexes, delayed reproductive development (delayed preputial separation) in males, and an increase in stillbirths.[20] These effects in offspring were statistically

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[15] Bagri P, Kumar V, Sikka AK. 2015. An in vivo assay of the mutagenic potential of imidacloprid using sperm head abnormality test and dominant lethal test. Drug Chem Toxicol 38:342-348

Hafez EM, Sahar YI, Maha KA-M, Karem TI, Safaa MAR. 2016. The neonicotinoid insecticide imidacloprid: A male reproductive system toxicity inducer-human and experimental study. Toxicology: Open Access 2:1-8

[16] CaDPR. 2006. Imidacloprid. Risk Characterization Document (RCD) Dietary and Drinking Water Exposure.

[17] NIH 2016. How common is male fertility, and what are its causes? https://www.nichd.nih.gov/health/topics/menshealth/conditioninfo/infertility

[18] U.S. EPA, HIARC Meeting on Acetamiprid, Briefing Package (Sept. 20, 2001).

[19] Sheets LP, Li AA, Minnema DJ, Collier RH, Creek MR, Peffer RC. 2016. A critical review of neonicotinoid insecticides for developmental neurotoxicity. Crit Rev Toxicol 46:153-190.

US EPA (US Environmental Protection Agency). 2005. Thiamethoxam - Developmental Neurotoxicity Study, Data Evaluation Record (DER). MRID 46028202

CDPR. 2008. Thiamethoxam California Department of Pesticide Regulation, Summary of Toxicology Data.

[20] EPA, Thiamethoxam. Review of Developmental Neurotoxicity Study including Brain Morphometry Data in Low- and Mid-Dose Groups, MRID 46028202 main study, 47034201 additional morphometry (March 9, 2007) ("Thiam.

significant in many of the low-and-mid-dose groups, and all the high-dose (298.7 mg/kg) groups. U.S. EPA disregarded these results, saying they were sporadic, did not show consistent dose-response relationships, and were not always significant when compared with historical controls (Thiam. DNT Review, p. 30).

For imidacloprid, the OEHHA Prioritization Report fails to note that the rat guideline DNT study reported that female offspring at the lowest dose (8 mg/kg-day) had a statistically significant elevated auditory startle reflex peak amplitude for all subjects at post-natal day 60.[21] EPA reviewers noted that peak amplitude was also increased for the mid-dose females (20 mg/kg-day), and high-dose females (55-58 mg/kg-day), but did not reach statistical significance.

Impairment of this outcome is thought to be a result of brainstem processing delays. It is particularly relevant that the cortex, thalamus, and cerebellum were heavily affected brain regions, given that they are all areas known to be heavily populated with nACh receptors that contain the α4β2 subunit that is the target of neonics. [22]

Before any industry-sponsored guideline studies be considered as evidence of 'no effect,' they should be thoroughly examined, including data from low-dose and mid-dose treatment groups. In particular, conclusions offered by the study sponsor should be met with skepticism. As the updated EPA Integrated Risk Information System (IRIS) Handbook states, "When there is evidence that a conflict of interest is may be present, a more careful assessment of the consistency of study results, publication and reporting bias may be merited for a health effect"[23] (EPA IRIS Handbook 2020, p. 9-14).

Imidacloprid, human birth defects –

The studies linking prenatal imidacloprid exposure with birth defects are well described in the OEHHA document (p. 91-92). Many of the effects were statistically significant. I provide a short summary here, with some additional details not included in the OEHHA summary, for DARTIC's consideration:

- In a study of 407 children in the United States with confirmed autism spectrum disorder (ASD), researchers found a statistically significant association between prenatal exposure to imidacloprid and ASD in study participants who self-identified as "frequent users" of flea and tick medicines containing imidacloprid (OR=2.0, 95% CrI: 1.0, 3.9).[24]

DNT Review"). NRDC obtained a version of the Thiam. DNT Review (Attachment A) received via a FOIA request to the agency, because the previous publicly available version was illegible in certain areas.

[21] US EPA Data Evaluation Record: Imidacloprid, Developmental Neurotoxicity Study – Rat, MRID 45537501 (Oct. 8, 2002), https://bit.ly/2KX7HEZ .*See* Table 10, p. 19-20.

[22] Posadas et al. (2013), doi: 10.2174/1570159X11311030005, https://bit.ly/35wTg47.

[23] U.S. EPA. ORD Staff Handbook for Developing IRIS Assessments (Public Comment Draft, Nov 2020). U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-20/137, 2020. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350086

[24] Keil A, Daniels J, Hertz-Picciotto I, Autism Spectrum Disorder, Flea and Tick Medication, and Adjustments for Exposure Misclassification: The CHARGE (Childhood Autism Risks from Genetics and Environment) Case-Control Study, 13 (1) Environ. Health 3 (2014), https://bit.ly/2yd5Fy4.

- In a study of 101 children in the United States with confirmed heart defects, researchers found a statistically significant association between residential proximity to agricultural use of imidacloprid and heart defects (tetralogy of Fallot) (AOR 2.4, 95% CI: 1.1, 5.4).[25]
- In a study of 73 babies born with anencephaly (absence of large portion of the brain, usually resulting in stillbirth), researchers reported a 'suggestive association' between residential proximity to agricultural use of imidacloprid and anencephaly (AOR 2.9, 95% CI: 1.0, 8.2).[26]

A systematic review of publicly available literature on unintentional human exposures to neonics, including the above-mentioned studies, reported a link between neonic exposures and malformations of the developing heart and brain, as well as a cluster of symptoms including memory loss and finger tremors.[27]

Under FIFRA Sec. 6(a)(2) reporting requirements, EPA identified roughly 1,630 incidents of imidacloprid poisoning over a 10-year period, about 160/year.[28] Some of the reported symptoms included skin rash, muscle tremor, difficulty breathing, vomiting, wheezing, lock jaw, memory loss, and renal failure. While not a direct indication of developmental harm, it is evidence of frequent exposures to consumers, including families, from home uses of imidacloprid at doses high enough to elicit acute poisoning symptoms.

Imidacloprid, neurodevelopmental effects –

The OEHHA report (p. 93) identifies a rat DNT guideline study that reported reduced motor activity and changes in brain structures that included a reduction in the thickness of the corpus callosum and decreased width of the caudate putamen in the high dose group. The OEHHA report correctly noted that information on these endpoints in the mid-dose and low-dose groups was not provided (CDPR 2013; Sheets et al 2016). It is a continuing frustration that complete data analysis is not provided to the regulatory agencies by the industry study sponsor (Bayer). [29]

Glyphosate transgenerational effects –

The developmental effects associated with glyphosate exposures are alarming given how many studies identify transgenerational effects in the F2 (grand-pups) and even F3 (great grand-pups) generations (p. 59-60).

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[25] Carmichael SL, Yang W, Roberts E, Kegley SE, Padula AM, English PB, Lammer EJ, Shaw GM, Residential Agricultural Pesticide Exposures and Risk of Selected Congenital Heart Defects Among Offspring in the San Joaquin Valley of California, 135 Environ. Res. 133-38 (Nov. 2014), https://bit.ly/35sYHkz.

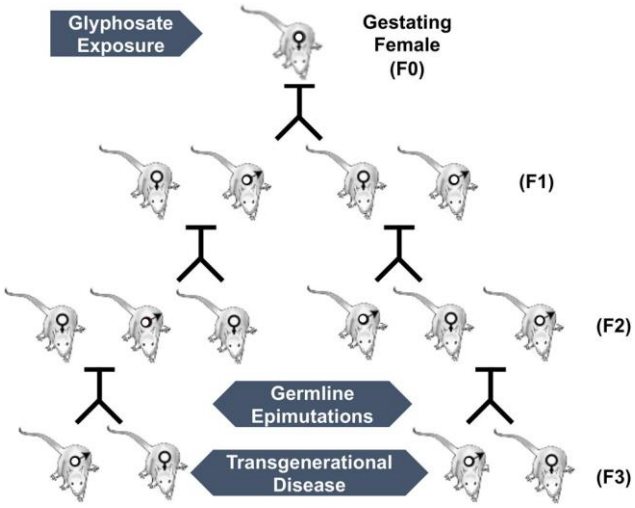
[26] Yang W, Carmichael SL, Roberts EM, Kegley SE, Padula AM, English PB, Shaw GM, Residential Agricultural Pesticide Exposures and Risk of Neural Tube Defects and Orofacial Clefts Among Offspring in the San Joaquin Valley of California, 179 (6) Am J Epidemiol. 740-48 (Mar. 15, 2014), https://bit.ly/2ypYoe2.

[27] Cimino AM, Boyles AL, Thayer KA, Perry MJ, Effects of Neonicotinoid Pesticide Exposure on Human Health: A Systematic Review, 125 (2) Env. Health Perspectives 155-62 (Feb. 2017), doi: 10.1289/EHP515, https://bit.ly/3dejHOz.

[28] EPA, Office of Pesticide Programs Incident Data System, Neonicotinoid incident reports for 01/01/2009 to 04/04/2019. Received by NRDC via Freedom of Information Act Request No. EPA-HQ-2019-004044.

[29] US EPA Data Evaluation Record: Imidacloprid, Developmental Neurotoxicity Study – Rat, MRID 45537501 (Oct. 8, 2002), https://bit.ly/2KX7HEZ .*See* Table 10, p. 19-20.

For example, OEHAA reports on a 3-generation study published in Nature (Kubsad et al 2019), where female Sprague-Dawley rats, the F0 generation, were treated with 25 mg/kg/day of glyphosate technical during gestational days 8-14, resulting in, "dramatic increases in pathologies in the F2 generation grand-offspring, and F3 transgenerational great-grand-offspring." The statistically significant generational pathologies observed include, "prostate disease, obesity, kidney disease, ovarian disease, and parturition (birth) abnormalities. Epigenetic analysis of the F1, F2 and F3 generation sperm identified differential DNA methylation regions (DMRs)" (p. 60). In this study, almost a third of F2 generation females (7/20) died during late gestation or experienced litter mortality, whereas neither of these abnormalities were observed in the 16 controls. The authors note that a number of the regions of DNA where genes were methylated were previously shown to be involved in pathologies. The authors conclude by proposing that, " glyphosate can induce the transgenerational inheritance of disease and germline (e.g., sperm) epimutations. Observations suggest the generational toxicology of glyphosate needs to be considered in the disease etiology of future generations."[30] (Figure from Kubsad et al. 2019)



In another rat study that OEHHA reported, pregnant F0 Wistar dams were fed a glyphosate-based herbicide from gestation day 9 to lactation day 21. The F1 female offspring from the lower exposure group (3.7 mg/kg-day) gave birth to offspring (F2 generation) with a 2% decrease in fetal length, 6% decrease in body weight, and an increased risk of being small for gestational age (RR= 2.43, 91% CI: 1.66, 3.55) compared to controls. In the high-dose group (352 mg/kg-day), the F1 females gave birth to offspring (F2) with increased fetal anomalies (conjoined fetuses and abnormal limbs) compared to controls, as well as the fetal growth effects found in the lower exposure group (Milesi et al. 2018).

A 3-generation reproduction study of glyphosate in rats was submitted to EPA by the registrant in 1992. While I do not have the study, or EPA's review of it, the ATSDR 2020 glyphosate assessment notes that increased incidence of kidney tubular dilation was reported in the F3 male pups, but that it was dismissed as spurious by EPA (see ATSDR 2020, p. A-10).[31] It is unclear if OEHHA has obtained this study, and its Data Evaluation Record (DER), from EPA. The OEHHA report does note a rat study, cited as US EPA 1992e as cited by ATSDR 2020 (see p. 60), but this is not the 3-generational study, which is referenced in ATSDR 2020 as US EPA 1992g.[32] We suggest that DARTIC request this study, and the EPA

[30] Kubsad D, Nilsson EE, King SE, et al. 2019. Assessment of glyphosate induced epigenetic transgenerational inheritance of pathologies and sperm epimutations: Generational toxicology. Sci Rep 9(1):6372. https://doi.org/10.1038/s41598-019-42860-0.

[31] Agency for Toxic Substances and Disease Registry (ATSDR). 2020. Toxicological profile for Glyphosate. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. https://www.atsdr.cdc.gov/toxprofiles/TP.asp?id=1488&tid=293

[32] As cited in ATSDR (2020): EPA. 1992g. Data evaluation report. Test material: Glyphosate, technical; 98.7% purity; lot XHJ-64. A three-generation reproduction study with glyphosate in rats. MRID 00105995. In: July 22, 1992.

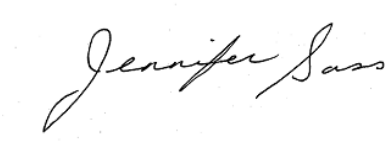
DER. We further note that this is yet another example where a registrant study either fails to find an effect, or fails to acknowledge an effect, that is reported in the non-industry sponsored published literature. As noted above, we recommend that DARTIC interpret 'no effect' results from industry-sponsored studies with caution, given the built-in bias in these studies to underestimate risks in these studies, particularly for subtle, complex, and systemic effects like developmental and reproductive outcomes.

CONCLUSION

In summary, the available scientific evidence all support the prioritization of glyphosate-based herbicides and the neonic insecticides for the further development of hazard identification materials, and we encourage the DART to prioritize these chemicals.

Thank you for the opportunity to comment on the list of priority chemicals.

Respectfully submitted,



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Senior Scientist, Natural Resources Defense Council

Memorandum. Glyphosate-List A chemical for reregistration-rereview of toxicology studies for acceptability. The 7-22-92 memorandum contains the Agency reviews for the following glyphosate studies: MRID numbers 0046362, 00046363, 00046364, 00067039, 00078619, 00078620, 00093879, 00098460, 00105995, 00132681, 00132683, 00132685 and 00132686 [Received via FOIA request]. HED pages 59-72. U.S. Environmental Protection Agency