TOXICOLOGY

HUMAN HEALTH THREATS

TOXICOLOGY | ENDOCRINE DISRUPTION | MAY 25, 2023

New Viewpoint on the Historic Link between Endocrine Disrupting Chemicals and Cancer Discussed

A review of the scientific literature published in the *Journal of Endocrinological Investigation* demonstrates exposure to past and current-use endocrine-disrupting chemicals (EDCs), like many pesticides, have a long history of severe adverse human health effects. Endocrine disruptors are xenobiotics (i.e., chemical substances like toxic pesticides foreign to an organism or ecosystem) present in nearly all organisms and ecosystems. The World Health Organization (WHO), European Union (EU), and endocrine disruptor expert (deceased) Theo Colborn, PhD, classify over 55 to 177 chemical compounds as endocrine disruptors, including various household products like detergents, disinfectants, plastics, and pesticides. Endocrine disruption can lead to several health problems, including hormone-related cancer development (e.g., thyroid, breast, ovarian, prostate, testicular), reproductive dysfunction, and diabetes/obesity that can span generations.Additionally, studies related to pesticides and endocrine disruption help scientists understand the underlying mechanisms that indirectly or directly cause infertility, early puberty, and other reproductive disorders, cardiovascular disease, attention deficit hyperactivity disorder (ADHD), Parkinson's, Alzheimer's, and childhood and adult cancers, among other health issues. The review notes, "New evidence supports the role of other EDCs as possibly carcinogenic and pregnant women should avoid risk area and exposure. The relationship between EDCs and cancer supports the need for effective prevention policies increasing public awareness."

The review examines the relationship between EDCs and various hormone-mediated effects (i.e., breast, prostate, testicle, ovary, and thyroid) to determine the carcinogenicity of the chemicals and their impact on public health. Researchers performed a literature review of meta-analyses and human studies between 1958 and 2022, searching for articles on "endocrine-disrupting chemicals," "EDCs," "phthalates," "TCDD," "dioxin," "polychlorinated biphenyls," "PCB," "bisphenol A," "BPA," "nitrate," "nitrite" and "breast cancer" or "prostate cancer" or "thyroid cancer" or "ovarian cancer" or "testicular cancer" on PubMed. Although the review finds many studies establishing a link between EDCs and cancers, there is a lack of current criteria to test new chemicals of endocrine disrupting potential and possible carcinogenic activity. The latent, adverse manifestation of cancers at varying ages makes it difficult to assess the full impact of human exposure to EDCs. For instance, evidence suggests that developing fetuses and neonates are most vulnerable to endocrine disruption, but cancer development manifestation needs more comprehensive research.

EDCs are chemicals that can, even at low exposure levels, disrupt normal

hormonal (endocrine) function. The endocrine system consists of glands (thyroid, gonads, adrenal, and pituitary) and the hormones they produce (thyroxine, estrogen, testosterone, and adrenaline). These glands and their respective hormones guide the development, growth, reproduction, and behavior of animals, including humans. Past research shows exposures to endocrine-disrupting chemicals can adversely impact human, animal—and thus environmental—health by altering the natural hormones responsible for conventional fertile, physical, and mental development. Research demonstrates that endocrine disruption is prevalent among many pesticide products like herbicides, fungicides, insecticides, and pesticide manufacturing byproducts like dioxin (e.g., TCDD). EDCs can enter the body and interfere with normal bodily function by mimicking the action of a naturally produced hormone, such as estrogen or testosterone, thereby setting off similar chemical reactions in the body, blocking hormone receptors in cells and preventing the action of natural hormones; or, affecting the synthesis, transport, metabolism, and excretion of hormones, thus altering the concentrations of natural hormones.

Endocrine disruption is an ever-present, growing issue that plagues the global population. The connection between cancers and EDCs has a historical record. However, this review highlights new perspectives on mechanisms involved in EDC-mediated cancers outside estrogen-receptor pathways, including mutation of damaged (unrepaired) DNA (genomic instability), and changes in the way genes work, which are influenced by behavior and the environment (epigenetic changes). The variations in EDC exposure levels and duration can make it difficult to investigate among humans.

The U.S. Environmental Protection Agency (EPA) fails to evaluate the depth and scope of chronic health and environmental concerns regarding exposure to EDCs. EDC chemicals can wreak havoc not only on humans but also on wildlife and their ecosystems. Hence, advocates maintain that policies stricter pesticide regulations and increase should enforce research on the long-term impacts of pesticide exposure.

Overall, endocrine disruption can negatively impact reproductive function, nervous system function, metabolic/immune function, hormone-related cancers, and fetal/body development. The International Agency for Research on Cancer (IARC) and the U.S. National Toxicology Program (NTP) classify many EDCs as possible carcinogens based on epidemiological studies identifying instances of kidney, ovarian, testicular, prostate, and thyroid cancer, as well as non-Hodgkin lymphoma and childhood leukemia. Considering that EDCs like organochlorines (e.g., DDT, lindane, chlordane, heptachlor, etc.) are structurally similar to fatty acids and may impair fatty acid metabolism and lipid synthesis in the liver, there may be an underestimation of the toxic effects on human, animal, and environmental health. Therefore, advocates say it is essential to avoid toxic chemical exposure to lessen potential acute and chronic health risks. The study concludes, "More studies are needed to clarify these associations, but, despite the uncertainties, the relationship between EDCs and cancer supports the need for effective prevention policies, paying attention to public awareness."

The ubiquity of pesticides in the environment and food supply is concerning, as current measures restricting pesticide use and exposure do not adequately detect and assess total environmental chemical contaminants. For instance, 90 percent of Americans have at least one pesticide biomarker (including parent compound and breakdown products) in their body. One way to reduce human and environmental contamination from pesticides is to buy, grow, and support organic. Numerous studies find that levels of pesticides in urine significantly drop when switching to an all-organic diet. Furthermore, given the wide availability of non-pesticidal alternative strategies, families, from rural to urban, can apply these methods to promote a safe and healthy environment, especially among chemically vulnerable individuals or those with health conditions. For more information on why organic is the right choice for consumers and the farmworkers that grow our food, see the Beyond Pesticides webpage, Health Benefits of Organic Agriculture.

SOURCE: R. Modica et al., A. Endocrine-disrupting chemicals (EDCs) and cancer: new perspectives on an old relationship. *J Endocrinol Invest* 46, 667–677 (2023). https://doi.org/10.1007/s40618-022-01983-4

TOXICOLOGY | ENDOCRINE DISRUPTION | JULY 13, 2023

Deadly Pesticide Poses an Increased Risk of Hormone-Associated Reproductive Cancers in Women

A study published in *Environmental Science and Pollution Research* finds exposure to *paradichlorobenzene*, a chlorophenol compound with uses as an insecticide, disinfectant, repellent, fumigant, fungicide, and deodorizer, can increase the risk of common endocrine (hormone)-mediated reproductive cancers (e.g., breast, uterine, and ovarian) in women. *p*-DCB has carcinogenic (cancer-causing) properties and the chemical has been

banned in the European Union (EU) since 2005 for air fresheners and 2008 for mothballs. Being a chlorinated aromatic hydrocarbon (with benzene) compound (chlorobenzene), in addition to its cancer-causing properties, *p*-DCB can cause acute illnesses like headaches, numbness, sleepiness, nausea and vomiting and chronic effects like nervous system disorders leading to depression, and impact on the brain, birth outcomes, reproductive system, liver, and kidneys.

Pesticides have a long history associated with endocrine-disrupting properties that induce various molecular changes, prompting disease development. Adding to the science, a similar review published in *Environmental Exposure, Biomonitoring, and Exposure Assessment* highlights how specific estrogen-mimicking pesticides increase the risk of disease, particularly hormone-related cancers among women (e.g., breast, ovarian, and endometrial cancer) and men (e.g., testicular, prostate cancer). *p*-DCB contains the carcinogenic benzene and is chlorine-based (a chlorinated aromatic hydrocarbon compound), which in December 2019 gained it the status of the U.S. Environmental Protection Agency's (EPA) "High-Priority Substance for Risk Evaluation" under the *Toxic Substances Control Act*. It is long-lasting in the environment. According to EPA, the chemical is mainly used as a fumigant for the control of moths, molds, and mildews, and as a space deodorant for toilets and refuse containers. Importantly, it is also used as an intermediate chemical in the production of other chemicals, including those for tree-boring insects, and in the control of mold in tobacco seeds. It shows up in ambient air testing, in drinking water, and in factories producing or processing the product.

The study "provides insights on the potential role of environmental exposures in the etiology of gynecological cancers. Further exploration of the epidemiological and pathophysiological interactions between *p*-DCB exposure and endocrine-related female cancers is warranted to expand upon these findings."

Exposure to *p*-DCB can disrupt metabolic and endocrine effects associated with endocrine-related female cancers (breast, ovarian, and uterine cancers). Using the U.S. National Health and Nutrition Examination Survey (NHANES) from 2003 to 2016, the study analyzes the urinary components of 4,459 women aged 20 years or older for concentrations of 2,5-dichlorophenol (2,5-DCP), the primary metabolite of *p*-DCB, to determine the association between *p*-DCB exposure and widespread endocrine-related cancers. Of the participants, 202 women have an endocrine-related reproductive cancer diagnosis with a significantly higher urinary concentration of 2,5-DCP than women without these cancers. Additionally, women experiencing moderate and high exposure to *p*-DCB have urinary concentrations of 2,5-DCP significant enough to increase the risk of endocrine-related reproductive cancers compared to low-exposure groups.

[See previous article for description of the endocrine system.]

This study adds to the sparse scientific literature concerning the probable link between *p*-DCB exposure and female reproductive cancers via endocrine disruption. Although endocrine-related cancers have genetic and behavioral components, the environmental components, like chemical exposure, are also essential to understand, especially since there is an incomplete understanding

of the role the endocrine system plays in the development of these cancers. As an endocrine disruptor, *p*-DCB causes a dose-dependent increase in estrogenic activities, directly affecting the size and function of reproductive organs. Additionally, the International Agency for Research on Cancer (IARC) categorizes *p*-DCB as a possible human carcinogen (Group 2B), warranting further investigations into the carcinogenic potential of this chemical to humans upon chronic exposure.

Studies directly link obesity with an increased risk of hormone-regulated endocrine cancers in women, finding an association between obesity/metabolic disorders and increased 2,5-DCP concentrations. This finding is unsurprising as *p*-DCB is a compound with lipophilic properties, accumulating in adipose (fatty) tissue. Like other EDCs and organochlorines, *p*-DCB may impair fatty acid metabolism and lipid synthesis in the liver, indicating a potential underestimation of toxicity effects on human, animal, and environmental health. Considering that products in the U.S. containing *p*-DCB are frequently used in households and workplaces, the potential risk to the metabolic and endocrine system among individuals is infinite.

See Inspector General Rips EPA for Failure to Test Pesticides for Endocrine Disruption. For a deeper dive into EPA's failure to meet its statutory responsibility to evaluate pesticides for endocrine disruption fully, see While France Bans a Common Endocrine Disrupting Pesticides, EPA Goes Silent: EPA ignores statutory mandate to review pesticides that cause deadly illnesses at minute doses, defying classical toxicology.

SOURCE: Young-Mi Go et al., Exposome epidemiology for suspect environmental chemical exposures during pregnancy linked to subsequent breast cancer diagnosis, *Environment International,* Volume 178, 2023, 108112, ISSN 0160-4120, https://doi.org/10.1016/j.envint.2023.108112.

MORE ON THIS SUBJECT **Erectile Dysfunction Among Younger Males Linked to Pesticide Exposures**— November 16, 2023

TOXICOLOGY | CANCER | AUGUST 11, 2023

Study Cites Multiple Chemical Characteristics, Strengthening Weed Killer Glyphosate Cancer Ranking

Reinforcing earlier findings, a systematic review published in *Chemosphere* finds the popular herbicide glyphosate and its formulations (glyphosate-based formulations-GBF) exhibit five out of the 10 key characteristics (KC) of carcinogens (cancer-causing chemicals). Specifically, glyphosate exhibits strong evidence of genotoxicity, epigenetic alterations (heritable changes in gene expression), oxidative stress, chronic inflammation, endocrine disruption, and disturbs gut microbiota implicated in lymphomagenesis (growth and development of lymphoma). Although organizations like the International Agency for Research on Cancer (IARC) designate glyphosate as a *probable human carcinogen*, and scientific literature supports the findings on these adverse effects associated with glyphosate, the chemical remains on the U.S. market in various formulations.

Glyphosate is the most commonly used active ingredient worldwide, appearing in many herbicide formulas, not just Bayer's (formerly Monsanto) Roundup®. The use of this chemical has been increasing since the inception of crops genetically modified to tolerate glyphosate over two decades ago. The toxic herbicide readily contaminates the ecosystem with residues pervasive in food and water commodities. In addition to this study, the scientific literature finds time and time again that glyphosate has an association with cancer development, as well as human, biotic, and ecosystem harm. Therefore, advocates point to the need for national policies to reassess hazards associated with disease development and diagnosis resulting from or exacerbated by exposure to chemical pollutants. The study highlights, "Our findings strengthen the mechanistic evidence that glyphosate is a probable human carcinogen and provide biological plausibility for previously reported cancer associations in humans, such as non-Hodgkin lymphoma."

Using *in vivo*, *ex vivo*, and *in vitro* human and mammalian mechanistic studies, researchers compare exposure to glyphosate/GBF with little to no exposure counterparts for evidence of the 10 KCs of carcinogens. All known human carcinogens have one or more of the ten KCs, and these mechanisms cause cancer through:

1. Electrophilic (an affinity towards electrons) or metabolic activation (KC1),
2. Genotoxicity (KC2),
3. Alterations in DNA repair, causing genome instability (KC3),
4. Inducing epigenetic changes (KC4),
5. Inducing oxidative stress (KC5),
6. Inducing chronic inflammation (KC6),
7. Immunosuppression (KC7),
8. Reducing receptor-mediated effects/endocrine disruption (KC8),
9. Immortalizing cancer cells (KC9), and
10. Alterations in cell proliferation, death, or nutrient supply (KC10).

Researchers screened all in vivo, ex vivo, and in vitro studies of glyphosate/GBF exposure in humans/mammals, reporting any KC-related outcome available in PubMed before August 2021. The researchers used the selected studies to construct a matrix, analyzing the matrix in program R to determine the strength of evidence and quality assessments. Although only 175 of the 2,537 articles met inclusion criteria, the researchers extracted over 50,000 data points related to the aforementioned KC outcomes.

The results of the analysis find strong evidence for KC2, KC4, KC5, KC6, and KC8, limited evidence for KC1 and KC3, and inadequate evidence for KC7, KC9, and KC10. Specifically, genotoxicity (KC2) and endocrine disruption (KC8) from GBF have the strongest association with carcinogenicity. The reviewed studies demonstrate that the evidence of genotoxicity is stronger among humans than in animal studies, with GBF having a greater impact on both study groups than just glyphosate alone. Additionally, the review indicates glyphosate can alter hormone (endocrine) levels and receptor activity, with the estrogen receptors being most sensitive to glyphosate and GBFs.

The chemical's ubiquity threatens 93 percent of all U.S. endangered species, resulting in biodiversity loss and ecosystem disruption.

Almost five decades of extensive glyphosate-based herbicide (GBH) use has put human, animal, and environmental health at risk. The chemical's ubiquity threatens 93 percent of all U.S. endangered species, resulting in biodiversity loss and ecosystem disruption (e.g., soil erosion and loss of services). Exposure to GBHs has implications for specific alterations in microbial gut composition and trophic cascades. Similar to this paper, past studies find a strong association between glyphosate exposure and the development of various health anomalies, including cancer, Parkinson's disease, and autism. Although the U.S. Environmental Protection Agency (EPA) classifies glyphosate herbicides as "not likely to be carcinogenic to humans," stark evidence demonstrates links to various cancers, including non-Hodgkin lymphoma. Thus, EPA's classification perpetuates environmental injustice among individuals disproportionately exposed to chemicals like farmworkers, especially in marginalized communities. Chemical companies have knowingly failed and continue to fail to warn farmers adequately about the dangers of glyphosate. Additionally, the manufacturer's (Bayer/Monsanto) discredited chemical review conclusions challenge the European Union research.

The territory for research on pesticides' potential carcinogenicity and other impacts on human health is exceedingly complicated. Yet there is some convergence across research that exposure to certain pesticides increases the risk of developing some cancers. The association that has been in the blinding spotlight for the past few years is between exposures to glyphosate and GBHs and the risk of developing cancer, particularly non-Hodgkin lymphoma (NHL). Beyond Pesticides has covered the mounting evidence of the dangers

of glyphosate, including a meta-study that suggests a compelling link between exposures to glyphosate-based herbicides and increased risk of NHL.

In addition, Beyond Pesticides has traced the developments in the science and regulatory arena, including:

- IARC's 2015 landmark designation of glyphosate as potentially carcinogenic,
- Evidence that EPA colluded with Monsanto (maker of Roundup, the most widely used glyphosate-based herbicide) to advantage industry and that Monsanto had ghostwritten research that countered scientific conclusions on the cancer associations of the compound,
- and California's 2017 listing of glyphosate under Proposition 65 as a probable carcinogen and a 2018 Appellate Court affirmation of its ability to do so.

Glyphosate has been the subject of public advocacy, regulatory attention, and the target of thousands of lawsuits. (Beyond Pesticides has covered the glyphosate exposure tragedy extensively; see its litigation archives for multiple articles on glyphosate lawsuits.) In June 2020, facing approximately 125,000 lawsuits for Roundup's role in cancer outcomes, Bayer announced a $10 billion settlement to resolve roughly 75 percent of current and potential future litigation. However, roughly 30,000 complainants ultimately did not sign on to the settlement, so the queue of possible lawsuits is still potentially enormous. Although Bayer tried for a second settlement (~$2 billion) to handle future claims, a U.S. District Court judge for the Northern District of California rejected Bayer's 2021 settlement proposal. The judge stated that the settlement was inadequate for future victims diagnosed with cancer after using the herbicide. Bayer has never acknowledged any harm caused by glyphosate, maintaining the chemical is safe for use. However, in July 2021, Bayer announced its plan to end sales of its glyphosate-based herbicides (including its flagship product, Roundup) in the domestic U.S. residential lawn and garden market in 2023. Under the plan, uses in food production will continue.

The results of the systemic review highlight an all too familiar issues. Despite these concerning data, evidence of widespread exposure to a carcinogen has failed to sway regulators at EPA, necessitating meaningful change by elected officials to reform pesticide law. Scientists identify epidemiologic evidence associating glyphosate with blood cancers like non-Hodgkin lymphoma and strong evidence of carcinogenicity in laboratory animal research brought on by genotoxicity (DNA damage) and oxidative stress.

In 2015, the IARC Working Group demonstrated glyphosate has strong evidence of genotoxicity (KC2) and oxidative stress (KC5). However, recent studies providing additional data supports evidence of KC2 and KC5, chronic inflammation (KC6), and endocrine disruption (KC8) regarding glyphosate and GBF. Thus, glyphosate presents evidence of five KCs of carcinogens. Although there is limited or inadequate evidence for the remaining KCs, the review encourages further examination of the effects of glyphosate and other chemicals through 10 KCs and its relation to lymphoid cancers.

The study concludes, "Overall, the mechanistic evidence for glyphosate and GBFs possessing multiple key characteristics of carcinogens has become stronger since IARC's evaluation in 2015 and implicates several pathways by which these substances could induce cancer, such as lymphoma, in humans. […][O]ur understanding of glyphosate's effects using the KCs paves the way for exploring the intricate mechanisms underlying its potential pathway to lymphoma."

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Cancer is one of the leading causes of death worldwide, with over eight million people succumbing to the disease every year. Notably, IARC predicts an increase in new cancer cases from 19.3 million to 30.2 million per year by 2040. Therefore, studies related to pesticides and cancer will aid in understanding the underlying mechanisms that cause the disease. Beyond Pesticides challenges the registration of chemicals like glyphosate in court due to their impacts on soil, air, water, and our health.

SOURCE: Iemaan Rana, et al., Mapping the key characteristics of carcinogens for glyphosate and its formulations: A systematic review, *Chemosphere,* Volume 339, 2023, 139572, ISSN 0045-6535, https://doi.org/10.1016/j.chemosphere.2023.139572.

MORE ON THIS SUBJECT

Glyphosate Induces Oxidative Stress, A Cancer Precursor, According to NIH Study— January 31, 2023

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TOXICOLOGY | CANCER | NOVEMBER 7, 2023

Pesticide-Intensive Agricultural Practices Lead to Elevated Childhood Cancer Rates in Brazil

Two decades after the introduction of genetically engineered, herbicide-tolerant crops and the consequential exponential growth in weed killers, Brazil is seeing an increase in childhood cancer. This is the conclusion reached in a comprehensive study spanning 15 years (2004–2019), "Agriculture Intensification and Childhood Cancer in Brazil," published in the *Proceedings of the National Academy of Sciences* (PNAS) in October. For the past 20 years, soybean herbicides have been killing and sickening children in the Cerrado and Amazon regions—where soybean cultivation is concentrated. The study reveals a link between an increase in soy cultivation and a spike in cases of acute lymphoblastic leukemia (ALL), the most common cancer affecting children, among indirectly exposed populations. Researchers identify pesticide-contaminated drinking water as the driving force behind the increased cancer rates occurring downstream from soybean sites.

In 2003, Brazil legalized its first official genetically modified (GM) crop, welcoming the era of GM soybeans and sparking a radical transformation in its agricultural landscape. The introduction of Monsanto's Roundup Ready soybean seed promised farmers an efficient and herbicide-tolerant alternative to traditional crops. A significant shift occurred in the areas dedicated to soy cultivation in the Cerrado region, tripling from five million hectares in 2000 to 15 million hectares in 2019. In the Amazon, the increase was even more staggering, experiencing a 20-fold surge from 0.25 million hectares to five million hectares. With this expansion came an intensive application of pesticides. Brazil's pesticide use per hectare soared to rates 2.3 times higher than the United States and three times higher than China.

The research findings identify that a 10-percentage-point increase in soy cultivation area is associated with an additional 0.40 deaths out of 10,000 due to ALL for children five years of age and lower and an additional 0.21 deaths of children 10 years of age and lower per 10,000 population. The study finds "a strong and persistent relationship between the arrival of high-intensity agriculture in a region and adverse human health outcomes," even after controlling for confounding factors.

The study observes that having a pediatric oncology center within a day's drive—defined as 100 km or less—dramatically lessens fatal outcomes. This is a glaring commentary on the vast inequality in health care access, particularly in countries still navigating the initial stages of agricultural development. These are often low-income and middle-income nations wrestling with instability, and the findings highlight

a concerning disparity and lack of urgency for action.

The apathy toward the absence of access to safe environments, decent working conditions, and health care is starkly visible in what some have referred to as the double standards prevalent in global pesticide laws. Pesticides, deemed too toxic for use in the European Union, are freely exported around the globe and find a ready market in many countries that do not disclose product ingredients and warnings or regulatory restrictions in place that might reduce hazards. Similarly, those harmed by pesticides may not have access to health care.

This discovery is highly relevant, especially for other emerging agrarian nations. Brazil has become a kind of prototype that agrochemical corporations, economists, and policymakers frequently reference.

Brazil's metamorphosis into a large agricultural force has garnered attention and praise from economists and policymakers alike. The country's economy witnessed a surge of over 40 percent between 2000 and 2010, largely attributed to the booming manufacturing sector. This transformation has been used to exemplify the potential of agrochemicals in boosting global food security.

Economists have highlighted the introduction of GM soy as a pivotal moment. It did not just boost agricultural productivity but also set off a chain reaction across the entire economy. Herbicide-tolerant seeds, it was argued, would help Brazil move from an agricultural to a more industrial economy with higher incomes and more spending. Farmers no longer would have to engage in tedious field tilling, allowing farm laborers to find work in other areas and contributing to urban growth.

However, while Brazil is often showcased as a model of success, the study offers a cautionary perspective. It notes, "The combination of restricted oversight, limited healthcare access, a rapidly evolving agricultural production system, and a new chemical technology provides a cautionary tale to regions in similar stages of agricultural intensification."

While many economists laude Brazil's growth, not only are the health consequences becoming increasingly evident, but so are the environmental effects of this rapid industrialization. The Amazon has been facing a series of catastrophic fires and deforestation incidents. The agricultural expansion that came with soybeans also resulted in forest clearing on an immense scale.

As agricultural intensification takes place, droughts are compounding the problem, leading to a noticeable drying of the Amazon River. The extended dry seasons over the past few decades have been taking a toll, making trees less resilient and severely affecting the region's biodiversity. This drying and deforestation have repercussions beyond habitat destruction. In tropical rainforests like the Amazon, the nutrient-rich biomass is crucial for maintaining ecological balance. When this biomass is removed, the tropical soil—poor in nutrients—is unable to sustain life, leading to irreversible damage.

So, while Brazil may be lauded for its economic leaps, the study prompts a critical reassessment. It emphasizes the need for careful consideration of development strategies, urging a nuanced approach that does not solely focus on economic gains, but also weighs the health and well-being of the population.

This story of Brazil is a call for a global rethinking of development models, urging a shift toward practices that are equitable, sustainable, and healthy. Any system that treats the lives of children as collateral is not one that should serve as a global archetype. As we rethink our approach to development models, the indiscriminate use of pesticides should be critically examined along with other discriminatory practice like double standards for banned pesticides.

SOURCE: Marin Elisabeth Skidmore, et al., Agricultural intensification and childhood cancer in Brazil, *PNAS*, Vol 120, No. 45, 2023, https://doi.org/10.1073/pnas.2306003120/

MORE ON THIS SUBJECT

Childhood Leukemia Linked to Pesticides Used in Vineyards—November 1, 2023

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TOXICOLOGY | CANCER | MARCH 30, 2023

Research Further Associates Widespread Atrazine Exposure to Breast Cancer

A study published in *Ecotoxicology and Environmental Safety* finds that the commonly used herbicide, atrazine, promotes breast cancer development through suppression of immune cell stimulation (and thus function) and upregulation (increase) of enzymes mediating tumor development. According to the Centers for Disease Control and Prevention (CDC), breast cancer is a disease that causes breast cells to grow out of control, with the type of breast cancer depending on the cells themselves. Several studies and reports, including U.S. Environmental Protection Agency (EPA) data, identify hundreds of chemicals as influential factors associated with breast cancer risk.

Breast cancer is the most common cancer among women, causing the second most cancer-related deaths in

the U.S. Past studies suggest genetic inheritance factors influence breast cancer occurrence. However, genetic factors only play a minor role in the incidence of breast cancer, while exposure to external environmental factors (i.e., chemical exposure) appears to play a more notable role. One in 120 women will receive a breast cancer diagnosis, and genetics can only account for five to ten percent of cases. There are grave concerns over exposure to endocrine (hormone) disrupting chemicals and pollutants that cause adverse health effects. Therefore, advocates point to the need for national policies to reassess hazards associated with disease development from exposure to chemical pollutants. The authors note, "This study demonstrated that atrazine accelerated the cell cycle and encouraged the proliferation and invasion of breast cancer tumor cells. Furthermore, atrazine can reduce anti-tumor immunity by decreasing lymphocyte infiltration and modulating cytokine production inside the tumor microenvironment, thereby promoting tumor immune escape and breast cancer progression. To fully understand the mechanism underlying atrazine's immunosuppression of breast cancers, further research is needed."

Beyond cancer, atrazine is a notoriously toxic herbicide known to cause different health issues, including skin and respiratory diseases, cancer, and cardiovasclar effects, kidney/liver damage. Therefore, it is essential to understand how external stimuli—like environmental pollution from pesticides—can drive breast cancer development.

The researchers examine how exposure to atrazine impacts 4T1 breast cancer cell development, facilitating tumor metastasis (spread from the primary site of origin into different parts of the body) and angiogenesis (the formation of new blood vessels to support tissue growth). Exposure to atrazine significantly increases breast cancer cell spread, tumor size, and the expression/upregulation of MMPs (matrix metalloproteinases) enzymes, mediating precursor tumors to breast cancer. The percentage of lymphocytes in the thymus and spleen responsible for coordinating the immune response by stimulating other immune cells (CD4 + and CD3) are lower in atrazine exposure cohorts, with the CD4/CD8 + immune cell ratio lower than control groups. The abundance of CD4 and CD8 lymphocytes that infiltrate tumors decreases, suggesting atrazine's suppression of the local and systemic immune function on tumors and upregulation of tumor growth promotes breast cancer development.

The connection between pesticides and associated cancer risks is nothing new. Several studies link pesticide use and residue to various cancers, from more prevalent forms like breast cancer to rare forms like nephroblastoma (Wilms' tumor), a form of kidney cancer. The link between agricultural practices and pesticide-related illnesses is stark, with over 63 percent of commonly used lawn pesticides and 70 percent of commonly used school pesticides showing links to cancer. Past research demonstrates the mechanism by which cancer can develop after pesticides enter the bloodstream. An experimental study shows that pesticide exposure produces reactive oxygen species (ROS), which are highly unstable and cause potential DNA and cell damage that propagates cancer development, cancer risk through alternate mechanisms, including genotoxicity (gene damage), epigenetics (gene expression), immunotoxicity, tumors, and endocrine (hormone) disruption.

EPA registers many agricultural uses of the pesticide as "restricted use," allowing only certified pesticide applicators to use the chemical because of its effects on health and ecology. However, the herbicide also is used on residential lawns, school grounds, and golf courses. Encountering pesticides can happen at any point during the pesticide's production, transportation, storage, application, or disposal. The general population mainly encounters atrazine through drinking water, as reports of atrazine contamination demonstrate the chemical's widespread contamination of waterways (e.g., rivers, streams, surface/groundwater). Furthermore, atrazine can volatilize into the atmosphere by up to 14 percent of the applied volume during treatments, resulting in inhalation exposure.

Hormone-related cancers have ties to endocrine disruption and immune disruption. The endocrine and immune systems transmit signals to one another as multiple immune processes are involved in endocrine diseases. Thus, hormones generated by the endocrine system greatly influence breast cancer and other hormonal cancer (e.g., prostate, thyroid, etc.) incidents among humans. Although most types of breast cancers are hormonally responsive and thus dependent on the synthesis of either estrogen, progesterone, or too much of the protein called HER2, G protein-coupled estrogen receptors (GPERs) regulate estrogen through non-genetic cellular pathways—forgoing attachment to standard molecular receptors and leading to triple-negative breast cancer (TNBC). Triple-negative breast cancer has a higher rate of recurrence and worse clinical outcomes than other breast cancers. Xenoestrogens (external estrogen and synthetic compounds sources) like atrazine, can stimulate GPER upregulation and activation in cancer cells. However, although the connection between pesticides and associated cancer risks is nothing new, this study demonstrates the upregulation of MMP enzymes in cancer cells (4T1-Luc) associated with breast cancer development. The researchers consider these cancer cells ideal models to study the immune mechanisms, especially for TNBC, as the cells in TNBC lack receptors for estrogen or progesterone hormones, and TNBC does not respond to hormonal therapy medicines or medicines that target the HER2 protein.

Cancer is a leading cause of death worldwide. Hence, studies concerning pesticides and cancer help future epidemiologic research understand the underlying mechanisms that cause cancer.

SOURCE: Mengqi Wang, et al., Atrazine promotes breast cancer development by suppressing immune function and upregulating MMP expression, *Ecotoxicology and Environmental Safety,*Volume 253, 2023, 114691, ISSN 0147-6513, https://doi.org/10.1016/j.ecoenv.2023.114691

MORE ON THIS SUBJECT **Breast Cancer Awareness Month: Study Finds New Chemicals Associated with Breast Cancer Risk**—October 12, 2023

TOXICOLOGY | PARKINSON'S DISEASE | JANUARY 12, 2023

Pesticides Not Only Linked to Parkinson's Disease Development, But Accelerating Disease Symptoms

Exposure to certain pesticides among individuals diagnosed with Parkinson's disease (PD) can increase the risk of symptom progression. According to a study published in *Science of the Total Environment,* nearly 20 percent of pesticides associated with the onset of PD also increase the risk of faster decline in motor and non-motor function. Several studies find exposure to chemical toxicants, like pesticides, has neurotoxic effects or exacerbates preexisting chemical damage to the nervous system. Past studies suggest neurological damage from oxidative stress, cell dysfunction, and synapse impairment, among others, can increase the incidence of PD following pesticide exposure. Despite the association between PD onset via pesticide exposure patterns, few epidemiologic studies examine the influence pesticides have on worsening motor and non-motor symptoms in PD.

Parkinson's disease is the second most common neurodegenerative disease, with at least one million Americans living with PD and about 50,000 new diagnoses annually. The disease affects 50 percent more men than women, and individuals with PD have a variety of symptoms, including loss of muscle control and trembling, anxiety and depression, constipation and urinary difficulties, dementia, and sleep disturbances. Over time, symptoms intensify, but there is no current cure for this fatal disease. Only 10 to 15 percent of PD cases are genetic, PD is quickly becoming the world's fastest-growing brain disease. Therefore, research like this highlights the need to examine how chemical exposure accelerates disease progression, especially among severe, incurable, and fatal illnesses. The study notes, "Pesticides are not applied in isolation, and people are not singly exposed to one agent over a lifetime. Both scientists and regulators need to consider co- and sequential application hazards and human exposures."

Using a geographic information system (GIS) tool to gather information on ambient exposure to pesticides in

residences and workplaces via California Pesticide Use Report records and land use records, the researchers examine the association between 53 pesticides with links to PD onset to determine PD symptom progression for five years and 2.7 years (respectively) for two patients. Measurements of PD symptom progression include movement disorder specialist-administered Unified Parkinson's Disease Rating Scale part III (UPDRS), Mini-Mental State Examination (MMSE), and Geriatric Depression Scale (GDS). Of the pesticides with links to PD onset, 10 or ~18.8 percent (e.g., copper sulfate [pentahydrate], 2-methyl-4-chlorophenoxyacetic acid [MCPA] dimethylamine salt, tribufos, sodium cacodylate, methamidophos, ethephon, propargite, bromoxynil octanoate, monosodium methanearsonate [MSMA], and dicamba) have associations with faster symptom progression. The study identifies a progressive decline among three endpoints: motor skills, cognitive function, and mental health regarding depression. Individuals living near residential areas or working in occupations with higher exposure to copper sulfate and MCPA experience a rapid decline in all endpoints.

Parkinson's disease occurs when there is damage to dopaminergic nerve cells (i.e., those activated by or sensitive to dopamine) in the brain responsible for dopamine production, one of the primary neurotransmitters mediating motor function. Although the cause of dopaminergic cell damage remains unknown, evidence suggests that pesticide exposure, especially chronic exposure, may be the culprit. Occupational exposure poses a unique risk, as pesticide exposure is direct via handling and application. A 2017 study finds that occupational use of pesticides (i.e., fungicides, herbicides, or insecticides) increases PD risk by 110 to 211 percent. Even more concerning, some personal protective equipment (PPE) may not adequately protect workers from chemical exposure during application. However, indirect nonoccupational (residential) exposure to pesticides, such as proximity to pesticide-treated areas, can also increase the risk of PD. A Louisiana State University study finds that residents living adjacent to pesticide-treated pasture and forests in the agriculture and timber industry have higher rates of PD incidence. Furthermore, pesticide residues in waterways and on produce present an alternate route for residential pesticide exposure to increase the risk for PD via ingestion. Pesticide contamination in waterways is historically commonplace and widespread in U.S. rivers and streams, with over 90 percent of water samples containing at least five or more pesticides. Pesticide exposure can cause severe health problems even at low residue levels, including endocrine disruption, cancers, reproductive dysfunction, respiratory problems (e.g., asthma, bronchitis), and neurological impacts (e.g., developmental effects and Parkinson's), among others. Nevertheless, direct occupational and indirect nonoccupational exposure to pesticides can increase the risk of PD.

This study is one of the few, possibly the first, to identify that pesticides can contribute to the progression of Parkinson's disease. The study identifies 53 pesticides associated with PD onset, with ten directly accelerating declines in motor and non-motor function and mental health from amplified disease progression. However, worsening disease risk following pesticide exposure is not an unfamiliar phenomenon for either physical or psychiatric health. For instance, pesticide exposure can cause

injury to cells responsible for safeguarding against viral infections, inducing more severe disease progression. Since the start of the COVID-19 pandemic, studies evaluating disease outcomes acknowledge excessive and improper use of pesticides, like disinfectants, as a culprit of immunocompromising the respiratory system of COVID-19 patients. COVID-19 is a systemic (general) disease that adversely impacts the respiratory system of many patients. The respiratory system is essential to human survival, regulating gas exchange (oxygen-carbon dioxide) in the body to balance acid and base tissue cells for normal function. Damage to the respiratory system can cause many issues—from asthma and bronchitis to oxidative stress that triggers the development of extra-respiratory, systemic manifestations like rheumatoid arthritis and cardiovascular disease. However, just as the respiratory system is far from the only bodily system affected by the virus, pesticides' adverse effects can span multiple bodily systems, even co-concurrently. Furthermore, underlying medical conditions (e.g., heart/kidney disease, diabetes, cancer, high blood pressure, obesity, etc.) heighten risks associated with severe illness from disease. Additionally, this study is not the first to identify an association between multiple disease risks and proximity to areas with regular pesticide applications. Studies can match disease risk to zip code, with individuals in low-income, indigenous, and people of color communities at the greatest risk of developing pesticide and other environmentally induced diseases.

Over 300 environmental contaminants and their byproducts, including pesticides, are chemicals commonly present in human blood and urine samples and can increase neurotoxicity risk. For instance, 90 percent of Americans have at least one pesticide compound in their body, primarily from dietary exposure, like food and drinking water. These compounds have a global distribution, with evaporation and precipitation facilitating long-range atmospheric transport, deposition, and bioaccumulation of hazardous chemicals in the environment. Thus, exposure to these toxicants can cause several adverse environmental and biological health effects. With the increasing ubiquity of pesticides, current measures safeguarding against pesticide use must adequately detect and assess total chemical contaminants.

The study concludes, "Identifying modifiable risk factors for disease progression may help identify new targets for research, perhaps leading to mechanistic insights important for medication development, and importantly help revise public health policy, aiming to reduce exposure to disease-modifying agents. Our study has implicated individual pesticides in Parkinson's disease progression in several domains. For some, previous epidemiologic or experimental data are supportive of our findings. Further investigation should target both these individual pesticides and the cumulative risk of their mixtures to tease out potential synergistic effects."

SOURCE: Shiwen Li, Beate, et al., Proximity to residential and workplace pesticides application and the risk of progression of Parkinson's diseases in Central California, *Science of The Total Environment,* Volume 864, 2023, 160851, https://doi.org/10.1016/j.scitotenv.2022.160851.

MORE ON THIS SUBJECT

New Study Spotlights Ten Pesticides Implicated in Development of Parkinson's—May 23, 2023

High Frequency of Household Pesticide Exposure Can Double the Risk of Parkinson's Disease Among the General Population—July 11, 2023

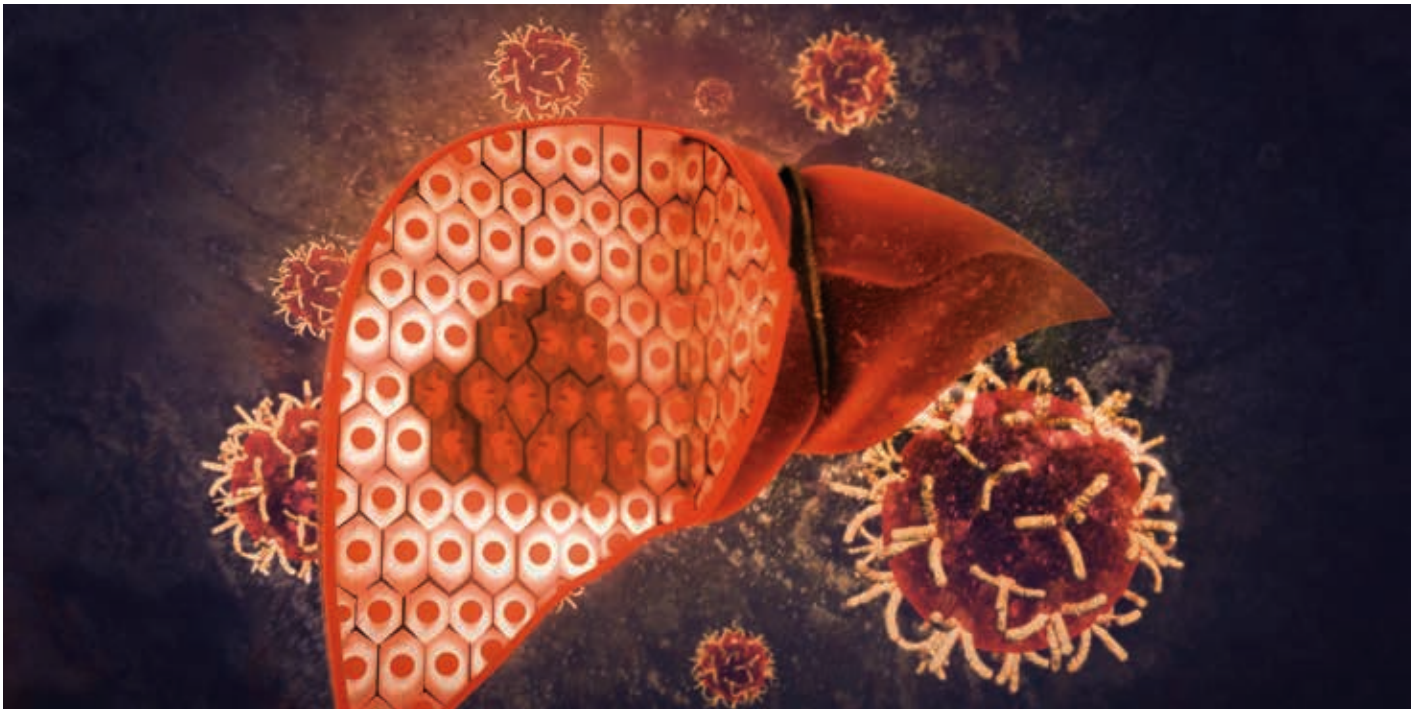
TOXICOLOGY | LIVER DAMAGE/FATTY LIVER DISEASE | JANUARY 11, 2023

Study Connects Neonicotinoids to Liver Damage Ignored by EPA

Neonicotinoid insecticides can have detrimental effects on liver health, according to research published in the Journal of Hazardous Materials. While this is the first study to investigate how these chemicals harm the liver, there is increasing evidence that neonicotinoids, notorious for their effects on pollinators and aquatic life, can cause direct harm to human health. As the U.S. Environmental Protection Agency (EPA) continues to protect the pesticide industry from any measure of meaningful regulation around these hazardous products, the job falls to advocates to place pressure on elected officials to make the changes necessary to safeguard long-term health and well-being.

Scientists postulated that neonicotinoids are neither metabolized by the liver nor excreted by urine. To test that hypothesis, 201 individuals from a hospital in China were enrolled into a study. Of the enrolled, 81 were cancer patients, and 120 were not. These individuals underwent a procedure called endoscopic retrograde cholangiopancreatography, whereby samples of their bile, a fluid produced in the liver, were retrieved and analyzed. Researchers also performed a series of blood tests, measuring a range of biomarkers, including cholesterol, bilirubin, bile acids, white blood cells, platelets, and others. Lastly, scientists determined the amount of eight neonicotinoids in bile samples, including acetamiprid, clothianidin, dinotefuran, imidacloprid, imidaclothiz, nitenpyram, thiacloprid, and thiamethoxam.

Researchers found their hypothesis to be correct. Of all samples taken, at least one neonicotinoid was detected in 99 percent of individuals tested. However, different neonicotinoids



were found to act in different ways. While the detection of acetamiprid was low (1 percent of samples), 97 percent contained nitenpyram. The widely used insecticide dinotefuran was detected in 86 percent of bile. Detections did not appear to differ between participants of different health backgrounds.

The results led scientists to believe that neonicotinoids found in bile will eventually be absorbed again by the intestines, make their way into blood, and eventually one's liver. Biomarkers tested, such as cholesterol, bilirubin, and bile acids, were found to correlate with higher concentrations of certain neonicotinoids. Of the various neonicotinoids, dinotefuran, thiamethoxam, and clothianidin were found to pose the greatest risk to liver health.

In this context, it may be interesting for readers to see how far EPA got in making a determination on liver health and neonicotinoids. Using dinotefuran as an example, here is a link to the Human Health Draft Risk Assessment the agency produced in 2017. As part of tests on the absorption, distribution, metabolism, and elimination studies on dinotefuran, EPA requires one single "special study" on neonatal rat metabolism to determine how the chemical absorbs once in the body. The results (EPA does not provide methodology, only results in its review documents) indicate that in 12-day old rats "absorption was high (absorption could not be adequately determined, but may have approached 80%) and the radiolabel was widely distributed within the body." Furthermore, the results indicate that, "The test material was essentially not metabolized, the parent compound accounting for >97% of the radiolabel in the excreta, plasma, kidneys, and stomach, and nearly 61-83% in intestines (and contents), and liver."

Thus, EPA has enough evidence to show that dinotefuran barely metabolizes at all in one's body. Yet, this result did not tip off EPA in any way. No further testing was conducted to understand or characterize the hepatotoxic (injurious to liver) nature of the insecticide, and it does not appear as though the results influenced any changes in the agency's determination around use patterns. In other words, EPA has enough data to investigate this issue and make even minor protective changes. Instead, after decades of this chemical being on the market, it has taken an independent, peer reviewed study to extrapolate and further investigate the critical details of how a near complete lack of dinotefuran adsorption in the body affects the liver.

This is not the only neonicotinoid health impact that the agency has failed to address. EPA is now being sued for long-term failure to screen and regulate pesticides that have the potential to disrupt the endocrine (hormone) system. In the context of neonicotinoids, there is growing evidence that exposure to these chemicals can result in hormone-dependent breast cancer. A 2019 study found that imidacloprid and thiacloprid can increase expression of a gene linked to breast cancer, and a 2022 study also found associations between neonicotinoid exposure and breast cancer.

In addition to the direct effects of cancer and liver toxicity, the latest evidence also shows these chemicals are indirectly killing hundreds of thousands of people around the world each year as a result of their detrimental impact to pollinator populations relied on for healthy, nutrient-dense food.

SOURCE: Yuanchen Chen, et al., First evidence of neonicotinoid insecticides in human bile and associated hepatotoxicity risk, *Journal of Hazardous Materials*, Volume 446, 2023, 130715, https://doi.org/10.1016/j.jhazmat.2022.130715.

TOXICOLOGY | LIVER DAMAGE/FATTY LIVER DISEASE | MARCH 7, 2023

Glyphosate Exposure Associated with Liver and Metabolic Disorders in Children, Young Adults

Exposure to glyphosate (Roundup) and its breakdown products is associated with an increased risk of liver and metabolic disorders in children and young adults, according to research published in Environmental Health Perspectives. While glyphosate has developed a science-based reputation as a carcinogen, research is finding that cancer is one of a myriad of chronic diseases associated with the notorious chemical. As this body of literature grows, growing awareness by the public is increasing pressure on the U.S. Environmental Protection Agency (EPA) to cancel its allowed uses.

Researchers began their investigation concerned about the rise of liver disorders and metabolic syndrome among young people. This trend has been pronounced among populations of color. The worrying increase has led many to consider synthetic chemical exposure as a contributing factor, as lack of diet and exercise is unlikely to account for the entirety of the increase.

To better understand these impacts, researchers enrolled existing participants in the CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) study, a long running cohort of mothers and their children born between the years 2000 and 2002 in the Salinas Valley of California. Enrolled participants consist mostly of farmworker families who were studied (including assessment of body measurements, contaminants in blood and urine, diet, interview questionnaires) at delivery and followed at one to two year intervals. For the present study, 480 participants who completed the 18-year-old follow up visit were enrolled in a nested case-control study. Out of this, 60 cases were selected based on blood tests for liver damage, while 91 controls without liver damage were used as a comparison.

Scientists reviewed urine samples stored from pregnancy, and at ages 5, 14 and 18 years old. These data were considered against an analysis of the amount of agricultural-use glyphosate occurring in and around each enrolled family's residence. The results confirm there is cause for concern among young people's exposure to glyphosate. At age five, urinary levels of glyphosate's primary breakdown product aminomethylphosphonic acid (AMPA) were associated with an increase in transaminases, liver enzymes that can cause harm at high levels in the body, as well as a nearly 2x increased risk of metabolic syndrome. This trend associating glyphosate exposure with adverse effects held throughout early adulthood. Glyphosate and AMPA exposure significantly increased risk of metabolic syndrome in 14-year-olds. When paired with data on the amount of agricultural use of glyphosate in a given area, having lived near a site where glyphosate was applied from birth until five years of

age was associated with contracting metabolic syndrome at age 18.

This is not the first study linking glyphosate to liver damage. A 2015 study determined that chronic exposure to even ultra-low doses of the chemical in drinking water could result in harm to the kidney and liver. A study in 2017 connected the chemical to the development of non-alcoholic fatty liver disease (NAFLD), and a 2019 study built on those findings, showing higher levels of glyphosate in the urine of individuals diagnosed with NAFLD. A 2022 study likewise found that glyphosate exposure before and after birth induces liver damage, posing a significant risk to pregnant women, infants, and children.

NAFLD and other liver disorders can increase the risk of metabolic syndrome. And a growing body of literature has implicated pesticide exposure and the rise of metabolic disorders and obesity, separate from concerns over diet and fitness.

SOURCE: Brenda Eskenazi et al., Association of Lifetime Exposure to Glyphosate and Aminomethylpyhosphonic Acid (AMPA) with Liver Inflammation and Metabolic Syndrome at Young Adulthood: Findings from CHAMACOS Study, *Environmental Health Perspectives*, Volume 131, Issue 3: 037001, https://doi.org/10.1289/EHP11721

MORE ON THIS SUBJECT

Pollution-Associated Liver Disease with Sex-Specific Effects Linked to Persistent Legacy Insecticide, Chlordane— October 4, 2023

Low-Dose Chronic Glyphosate Exposure Increases Diet-Induced Non-Alcoholic Fatty Liver Disease— December 21, 2023

TOXICOLOGY | CHRONIC KIDNEY DISEASE | AUGUST 8, 2023

Chronic Kidney Disease of Unknown Origins Linked to Indoor Pesticide Use, Disproportionally Affecting Women

A study published in *PLOS ONE* finds a positive association between chronic kidney disease (CKD) of unknown origins (CKDu) and the use of indoor pesticides. Longer exposure times have an especially detrimental impact on kidney function, even among individuals without underlying diseases like diabetes mellitus (diseases associated with blood sugar) and hypertension. The innovation of this study's purpose highlights the lack of exposure-related studies on kidney health outcomes associated with indoor pesticide use.

Although CKD risk increases with age and is associated with other health factors like smoking, heart disease, and diabetes, cases without clear causes are increasingly common, indicating that environmental factors are likely playing a role. Over six million people in the U.S. have kidney disease (e.g., nephritis [kidney inflammation], nephrotic syndrome [improper protein filtration], and

nephrosis). Although many studies find an association between exposure to outdoor environmental contaminants like pesticides and CKD, the association between CKDu and indoor pesticides—whose uses are more commonly concentrated in homes—remains unclear. Therefore, studies like this highlight the need for comprehensive information regarding co-occurring exposure patterns and disease prevalence that can have global implications.

The study notes, "Previous research has highlighted the potential harm of pesticides on kidney function, particularly in outdoor uses. Our findings raise concerns about the impact of indoor pesticide use on kidney function in individuals without common risk factors for CKD. Further, longitudinal studies are needed to evaluate the effects of indoor pesticide use on kidney health outcomes and to determine safe dosage levels for these substances."

The growing epidemic of CKDu globally, especially among residents of agricultural communities, has scientists questioning the cause of CKDu and if pesticide use plays a role in disease prognosis. Researchers at the Prospective Epidemiological Research Studies in Iran, using a population-based study, tested individuals to estimate a glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2 to indicate CKDu. Researchers obtained data on indoor pesticide use and duration of exposure through a questionnaire. After excluding subjects with diabetes mellitus and/or hypertension, estimated glomerular filtration rate (eGFR) between 60–89 ml/min/1.73 m^2, and unavailable creatinine measurement, 1079 subjects remained in the study.

The results find that the prevalence of CKD in females was 2.6 times higher than in male subjects. The duration of exposure to indoor use of pesticides is significantly higher in subjects in the CKDu group. Additionally, single women participating in low physical activity, with triglyceride (TG) levels of more than 150 mg/dl, a body mass index (BMI) of more than 25 kg/m^2, non-smoker, and high pesticide exposure time for indoor pesticide use have a greater association with CKDu. The most significant factors in the multivariable analysis are age, sex, TG levels of more than 150 mg/dl, pesticide use, and high pesticide exposure time.

Individuals may encounter malathion through consuming food produced in chemical-dependent agriculture or drinking water or as a result of drift from pesticide application and public use.

Many studies document pesticides' impacts on kidney function, finding a range of chemicals linked to kidney damage. Among the 40 most commonly used lawn care pesticides, 80 percent have associations with kidney or liver damage. These chemicals include widely used herbicides like glyphosate and organophosphate insecticides like malathion. Glyphosate was initially created as a chelating agent (bonding ions and molecules to metal ions) to form strong chemical bonds with metals.

In 2013, the Center for Public Integrity highlighted that glyphosate bonds with toxic heavy metals in the environment, such as cadmium and arsenic, forming stable compounds. These compounds are present in food and water for consumption and do not break down until they reach the kidneys. Thus, farmworkers exposed to glyphosate are likely to have these toxic metals in their kidneys. In 2019, researchers Sararath Guanatilake, MD, and Channa Jayasumana, PhD, were awarded the Freedom and Responsibility Award from the American Association of the Advancement of Science for their work uncovering the link between glyphosate and chronic kidney disease.

Another pesticide, malathion, has recently been cited for its close link to kidney damage. Individuals may encounter malathion through consuming food produced in chemical-dependent agriculture or drinking water or as a result of drift from pesticide application and public use. A study published in October 2021 found significant associations with malathion exposure, low kidney function, and increased risk of CKD. A 2022 study found that 68 percent of well water sampled in Sri Lanka (South Asia) contains at least one pesticide above the global drinking water guidelines, including the organophosphate insecticide diazinon. Individuals reporting drinking well water during their lifetime have significantly (6.7 times) lower kidney health on average than those who never drank well water. With researchers now finding evidence that pesticide-contaminated well water may be a source of kidney dysfunction, it is evident that pesticide mitigation measures must protect those in intensive agricultural areas from pesticide exposure. While there is a desire to neatly separate bad from good actors in environmental "mysteries," including chronic kidney disease and the ongoing decline of pollinators, it is evident that in a world awash in chemicals, it is a combination of these factors that is likely at play. Therefore, protection from pesticide exposure is critical for those working and living in chemical-intensive agricultural areas.

The study finds longer exposure to indoor pesticides is more frequent among patients with CKDu, with a history of indoor pesticide use having 1.36 times higher odds of CKDu. Although previous studies report the prevalence of CKDu is 1.7 times higher among women than men, this study highlights a greater prevalence of CKDu (2.6 times higher) among female patients, demonstrating a possible uptick in CKDu odds. In fact, the study used multivariable models, including indoor use of pesticides (model 1) and duration of exposure to indoor pesticides (model 2), to determine the odds of having CKDu, with the disease odds increasing 7.5 and 8.6 times among the respective models. The study suggests the disproportionate risk of CKDu to women may be because women spend more time

at home in pesticide-treated areas, increasing the risk of pesticide exposure. Moreover, patients who experience the highest quartile of pesticide exposure duration in the study have a 1.64 times higher risk of developing CKDu compared to individuals who never used indoor pesticides.

Thus, the study concludes, "This finding emphasizes the role of cumulative exposure dose at a specific time on kidney function. Although we cannot comment on safe threshold dose of house use of pesticides, as this was not in our study scope, but finding the safe use threshold of these materials could be of great interest that could be evaluated in longitudinal studies."

The kidneys are one of the most important organs for filtering waste out of the human body. However, kidneys are often the main target of pesticide toxicity mediated through oxidative stress.

SOURCE: Saba Alvand, et al., Association of indoor use of pesticides and CKD of unknown origin, *PLOS ONE*, 2023, https://doi.org/10.1371/journal.pone.0277151.

TOXICOLOGY | DIABETES AND OBESITY | SEPTEMBER 27, 2023

Metabolic Diseases, Including Diabetes and Obesity, Driven by Pesticide Exposure

A study published in *Pesticide Biochemistry and Physiology* finds organophosphate (OP), organochlorine (OC), and pyrethroid (PYR) pesticides have links to insulin resistance (IR) associated with metabolic disorders like diabetes, obesity, chronic kidney disease (CKD), and hypertension. Metabolic disorders are among the leading causes of morbidity and mortality, with over 11 percent (>37 million) of individuals in the U.S. having diabetes, and cases are growing by millions annually. Additionally, there is a rise in metabolic disorders among young people. Studies even find low levels of pesticide exposure during pregnancy or childhood cause adverse health effects, including metabolic disorders tied to gut microbiome disruption (dysbiosis). With increasing rates of diabetes and obesity, the two most prominent metabolic diseases in the study, cases among the global population highlight the importance of evaluating how chemical contaminants deregulate normal bodily function through metabolic changes.

To investigate the association between pesticide exposure and insulin-related metabolic disorders in humans, researchers searched the PubMed database for articles, performing a systematic review. The study notes, "IR is defined as a pathological state in which a higher-than-normal level of insulin is required to produce the optimal response in cells." The search generated 4,051 articles related to the topic.

Although general overeating and underexercising are attributed to obesity, researchers find the current obesity epidemic has alternative factors contributing to development. Besides genetics, exposure to obesogenic compounds, like pesticides, can promote obesity development.

However, after excluding duplicates and irrelevant studies, 75 epidemiologic studies linked human exposure to pesticides and IR-related metabolic diseases remained. In total, 30 articles find an association with diabetes, 20 with obesity, seven with hypertension (associated with cardiac issues), seven with chronic kidney disease (CKD), six with metabolic syndrome (i.e., high blood pressure, sugar and serum triglycerides), and three with polycystic ovarian syndrome (POS). The review highlights specific mechanisms of pesticide exposure associated with IR-related metabolic disorders, including liver enzymes and lipid profile alterations, weakening of intracellular insulin signaling from xenobiotic (a foreign chemical in the body) effects, oxidative stress, and inflammation response to chemical exposure.

There are many pesticides linked with the growing global metabolic disorder incidence rates over the past few decades. The World Health Organization (WHO), European Union (EU), and endocrine disruptor expert (deceased) Theo Colborn, PhD, classify over 55 to 177 chemical compounds (e.g., detergents, disinfectants, plastics, and pesticides, etc.) as endocrine disruptors associated with notorious metabolic disorders like diabetes/obesity that can span generations. The obesity rate is increasing and has been over the last five decades. Although general overeating and underexercising are attributed to obesity, researchers find the current obesity epidemic has alternative factors contributing to development. Besides genetics, exposure to obesogenic compounds, like pesticides, can promote obesity development. These compounds routinely cause reproductive, cardiovascular, and endocrine (hormone) issues among exposed individuals, especially farmers.

Obesogenic (obesity-causing) compounds affect the general population and future generational health. For instance, studies demonstrate that legacy DDT exposure increases the risk of breast cancer and cardiometabolic disorder—promoting an epigenetic inheritance of obesity—up to three successive generations. Although the U.S. banned DDT five decades ago, the insecticide (technically, its hazardous metabolite DDE) is still environmentally persistent in all ecosystems and is still used in some countries. Like DDT, exposure to other persistent organic pollutants (POPs), like per- and polyfluoroalkyl substances (PFAS), during pregnancy can increase cardiometabolic disorders, like obesity, diabetes, and cardiovascular diseases, among offspring. Since DDT/DDE residues, current-use pesticides, and other chemical pollutants contaminate the environment, exposure to these chemical mixtures can synergize to increase toxicity and disease effects.

The study is a comparative analysis. This systematic review adds to the growing research indicating pesticides' role in metabolic disorders. Pesticides have long been linked to higher rates of diabetes, as a 2008 study on pesticide applicators in two U.S. states found that every pesticide investigated increased diabetes risk by over 50 percent. A 2017 study zeroed in on one particular class of insecticides, carbamates, finding a propensity to adversely affect human melatonin receptors that regulate sleep, insulin secretion, and glucose homeostasis, increasing the risk of diabetes. A 2017 report commissioned by Gallup-Sharecare found that farmers recorded the second-highest rate of diabetes among all professions. Additionally, a 2019 study from the University of California, Davis, found that South Asian immigrants exposed to higher rates of DDT also displayed higher rates of type 2 diabetes. Regarding obesity, many pesticides are obesogenic compounds that directly impact hormone and receptor function and include pesticides like organochlorines, organophosphates, carbamates, and pyrethroids, as mentioned in this study. These chemicals can negatively affect reproductive function, nervous system function, metabolic/immune function, hormone-related cancers, and fetal/body development.

The study concludes, "Taken together, the link of pesticides with IR-related metabolic diseases can be a wide area of research from different aspects, including epidemiological evidences [of] cellular mechanisms weakening insulin signaling and preventing approaches. However, […] there is a need for studies to evaluate specific mechanisms by which different chemical groups of pesticides can develop IR-related metabolic diseases, especially those with increasing prevalence in the future."

Pesticides have long been linked to higher rates of diabetes, as a 2008 study on pesticide applicators in two U.S. states found that every pesticide investigated increased diabetes risk by over 50 percent.

Pesticides themselves can possess the ability to disrupt metabolic function, especially for chronically exposed individuals (e.g., farmworkers) or during critical windows of vulnerability and development (e.g., childhood, pregnancy). Health officials identify diabetes as one of the most common chronic diseases.

SOURCE: Ali Arab and Sara Mostafalou, Pesticides and insulin resistance-related metabolic diseases: Evidences and mechanisms, *Pesticide Biochemistry and Physiology,* Volume 195, 2023, 105521, https://doi.org/10.1016/j.pestbp.2023.105521.

TOXIOCOLOGY | SHINGLES | NOVEMBER 29, 2023

Study Finds Novel Relationship Between Shingles and Pesticide Exposure

A study published in *Environment International* finds high pesticide exposure incidence associated with shingles, a varicella-zoster virus (the same highly contagious virus that causes chicken pox) that reactivates in the body after having chicken pox. Shingles is a painful condition with a blistering rash that can lead to vision and hearing loss, brain and lung inflammation, and even death if not treated. Since shingles manifest decades after initial exposure, and the association is strongest among individuals already hospitalized for pesticide-related illnesses, researchers find the long-term/chronic effects most concerning. Although dermal pesticide exposure can cause a range of adverse reactions, including dermatitis, allergic sensitization, and cancer, any route of exposure can exacerbate dermal manifestations through immune system response, causing virus-based skin reactions like shingles.

People encounter toxic chemicals daily. However, frequent use of chemicals, including the use of everyday products like cleaning supplies, personal care products, agricultural chemicals, fabrics, non-stick cookware, and general airborne pollution, exacerbates pesticide exposure risks. Dermal exposure is the most common pesticide exposure route, composing 95 percent of all pesticide exposure incidents, and is a significant concern for occupational health.

The study notes, "[The] findings of elevated shingles risk associated with acute, clinically relevant pesticide exposures also highlights potential long-term costs of unintentional high-level pesticide exposures, especially those contributing to poisoning, which is a global problem in agricultural settings."

Using 22,753 licensed private pesticide applicators of 66 years and older with more than 12 consecutive months of Medicare hospital and outpatient coverage between 1999 and 2016, researchers identified patients who experience at least one shingles incident. Additionally, researchers gathered information on whether patients received medical care for pesticide-related illnesses or they encountered high pesticide exposure events (HPEE) and poisoning. The results find that 2,396 pesticide applicators were diagnosed with shingles during the 1996 to 2016 timeframe, with higher shingles rates among patients hospitalized for pesticide-related illness, pesticide poisoning, and HPEE. Thus, these initial findings suggest acute, high-level, and medically significant effects of pesticide exposure can increase shingles risk in individuals years to decades following exposure.

The skin responds to numerous external stimuli that can change its morphological (shape/structure), physiological (function), and histological (tissue) properties. Some responses to external stimuli are typical, including skin exposure to sunlight (UV-light), for tanning, or water wrinkling. However, exposure to excessive stimuli, including environmental contaminants,

can produce adverse permanent changes to the skin. Just as excessive exposure to UV rays can cause skin discoloration and cancer, prolonged dermal contact with disinfectants can cause many adverse reactions, including skin discoloration and cancer. One of the most predominant routes of pesticide exposure is dermal, and most disinfectants are potential skin irritants and sensitizers, suggesting that direct skin contact with these toxic chemicals and the adoption of proper application protocol is critical.

Most pesticides cause some form of acute skin irritation. Although certain pesticides are less harmful through dermal contact than others, many chemicals cause irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD is a nonimmune response that manifests into localized skin inflammation by directly damaging the skin following toxic agent exposure. ACD is an immune response to skin contact with a dermal allergen that an individual is already sensitized to, causing non-localized skin inflammation and systemic bodily response. However, chronic, cumulative exposure to more mild chemical irritants can elicit a skin reaction. As skin cancer has increased significantly over the past 50 years, many appropriately point to the link between sun exposure and the development of the disease. However, this research indicates that contact exposure to herbicides may be affecting risk. The authors point to studies finding links between dermal exposure of pesticides and exposure to UV radiation, as well as research that finds sunscreen itself may facilitate skin uptake of pesticide residue.

This study is the first to demonstrate the occurrence of shingles associated with pesticide exposure. However, this study is not the first to establish pesticides' relationship with immune system disorders related to the skin. A Dutch tudy found that infants exposed to dioxins (a pesticide byproduct) and PCBs have a higher incidence of recurrent chicken pox, which, as mentioned, is linked to shingles.

Although this study notes that the mechanism involved in shingles incidence is not well understood, studies, including this one, suggest immune system suppression is the main culprit. The immune system offers the best defense against viral infection, as the virus stimulates an innate and adaptive immune response to expel viral particles from the body. Innate immune responses are the first line of defense against viral infections, activating myeloid immunocytes (cells that mediate immune responses against pathogens). These mediating cells create antibodies that the complement system (a network of proteins that eliminate pathogens) enhances. Therefore, review researchers speculate that immunocytes and the complement system can restrict viral infections. However, coronavirus infections can suppress/delay interferon (INF) protein synthesis responsible for defending against viral infections, causing a lapse in the innate defense system. Similarly, an adaptive immune response involves various immune cells and antibodies essential to protect against coronavirus infections. Still, injury to cells responsible for safeguarding against viral infections can induce more severe disease progression. The global rate of shingles over recent decades is increasing despite vaccine availability. Therefore, there is an urgent need to evaluate the effect pesticide exposure and use have on disease health outcomes.

SOURCE: Christine Parks, et al., High pesticide exposures events, pesticide poisoning, and shingles: A medicare-linked study of pesticide applicators in the agricultural health study, *Environment International,* Volume 181, 2023, 108251, https://doi.org/10.1016/j.envint.2023.108251.

TOXICOLOGY | REPRODUCTIVE EFFECTS | DECEMBER 1, 2023

Study Confirms Connection Between Exposure to Pesticides and Male Reproductive Problems

Even though researchers have noted since the 1970s that human fertility appears to be declining globally, doubt is still circulating that it is really happening and that pesticides could have anything to do with it. Recently published studies, however, make it clear that, even without exact elucidation of the mechanisms by which pesticides damage male fertility, there is an unmistakable association with pesticides and many aspects of male reproductive health.

One of the recent studies, a meta-analysis of 25 studies on the connection between pesticides and male reproductive problems, finds that men exposed to organophosphate (such as malathion) and carbamate (such as carbaryl and methiocarb) pesticides have lower sperm concentrations than the general population. This is especially true of men exposed in work settings. The senior author of the study, Melissa J. Perry, ScD of the George Mason University College of Public Health, told HealthNews, "The evidence available has reached a point that we must take regulatory action to reduce insecticide exposure."

Human infertility is defined as "the failure to achieve pregnancy after 12 months or more of regular unprotected

sexual intercourse." Most public attention regarding infertility focuses on women's difficulties in getting pregnant, causing couples to resort to *in vitro* fertilization (IVF) and surrogates. But about a third to half the time, a couple's infertility results from problems with the male contribution. Men's reproductive health is measured by total sperm count, sperm's ability to move, the incidence of malformed sperm or reproductive organ structure, testosterone levels, and other criteria.

The relationships between aspects of male reproductive health, such as sperm count, fertility and testicular cancer, are not perfectly understood, but they are known to be interrelated. Low sperm counts can not only indicate decreased fertility, but also correlate with other markers of declining male reproductive health, including testicular tumors and testosterone levels. In 2017, Shanna Swan, PhD of the Icahn School of Medicine at Mount Sinai and colleagues published a major review of changes in sperm count between 1973 and 2011. They found that sperm counts declined by 52.4 percent over their study period.

Dr. Swan et al. also noted that reduced sperm count is a strong predictor of overall disease and death risk. In other words, sperm count reflects influences on health that go far beyond reproduction, and also that reproductive health is created by proper hormone balance, which many pesticides are well known to disturb.

Dr. Swan and colleagues wrote that chemical exposures, including pesticides (especially the endocrine disrupters) are plausible bad actors in the sperm count decline, but also said "lifestyle factors" such as diet and smoking are likely factors. High body mass index (BMI) and obesity have also been associated with low sperm counts.

Obesity is often cited as a "lifestyle choice" causing reproductive problems, unrelated to factors like pesticide exposures. This is misleading, however, because obesity itself can be an outcome of such exposures. For example, a 2022 review found that two carbamate insecticides and eight organophosphate insecticides were "significantly associated with higher obesity prevalence," suggesting that obesity and low sperm count may have a common cause rather than a direct cause-and-effect relationship.

Pesticides present an especially vexing problem in that they affect organisms through many different pathways, often simultaneously. For example, organophosphates notoriously damage neurotransmitters, but they have also been associated with poor semen quality in exposed factory workers. Similarly, carbamates interfere with neurotransmitters and are known for disrupting thyroid and steroid hormones and increasing the risk of both non-Hodgkin lymphoma and dementia, but they have also been associated with chromosome damage in sperm. Far less scientific attention has been devoted to these chemicals' effects on male reproduction than on their neurological ones, but the reproductive consequences may be even greater. For one thing, many pesticides, including organophosphates, can cross the placental barrier if the mother is exposed during pregnancy. Fetal exposures to organophosphates affect childhood cognition and coordination and predispose the child to develop cancer in later life.

But it gets worse. A father's environmental exposures can alter not only his direct fertility but also his epigenetic patterns, and these can be passed from parent to child. Epigenetics are a suite of cell processes in which gene expression is controlled by molecules that block or open access to genes in the double

DNA helix. In every cell of the body, this process continually operates to orchestrate the cell's biochemistry and its relation to other cells and organs, but it does not change genes themselves. Epigenetic patterns are a kind of template or history of the habits and exposures of the parent, including smoking history, diet, pesticide exposures, alcohol and drug consumption, and social stress. Sperm are major contributors of epigenetic information passed from one generation to the next, and pesticides affect that information.

"It is becoming clear that epigenetic information can function as molecular memory of past environmental exposures and be passed from one generation to another via the germline," according to the authors of a 2022 review by a pair of Georgetown University Medical Center and Lombardi Comprehensive Cancer Center scholars. Descendants of an exposed male may have no direct exposure themselves but be paying for the inadvertent "sins" of their fathers—"sins" such as agricultural or factory work.

A 2023 update of the 2017 review of temporal trends in sperm count, also coauthored by Dr. Swan, expanded the geographical range of the study by including data on men in 53 countries on six continents to get a global picture rather than one focused on industrialized countries where data are more plentiful. They found "strong evidence" that sperm counts have declined globally. Disturbingly, the authors show that the downward trend in sperm counts has become steeper since 2000, accelerating beyond the already worrisome rate seen in the 2017 meta-analysis. From 1972 to 1999, sperm count dropped by about one percent a year; since 2000, the rate has been about 2.6 percent.

The evidence has continued to mount that pesticides affect both male and female reproductive health, yet most of these chemicals remain on the market, contributing to the prospect of agricultural collapse and declining human population worldwide.

View Dr. Swan's talk, Modern Life and the Threat to the Future, at Beyond Pesticides 2021 National Pesticides Forum, Cultivating Healthy Communities.

SOURCE: Lauren B. Ellis, et al., Adult Organophosphate and Carbamate Insecticide Exposure and Sperm Concentration: A systematic Review and Meta-Analysis of the Epidemiological Evidence, *Environmental Health Perspectives,* 2023-11, 10.1289/EHP12678.

TOXICOLOGY | REPRODUCTIVE EFFECTS | JULY 26, 2023

Another Study Adds to Science Indicating Mothers' Exposure to Pesticides During Pregnancy Increases Adverse Birth Outcomes

An exploratory study published in *Environment International* adds to the many studies demonstrating residential prenatal pesticide exposure can result in adverse birth outcomes. Residential exposure to five active pesticide ingredients (AIs) fluroxypyr-meptyl, glufosinate-ammonium, linuron, vinclozolin, and picoxystrobin has adverse effects on gestational age (GA), birth weight (BW), mortality after birth, child's sex, premature development, low birth weight (LBW), including small for gestational age (SGA), and large for gestational age (LGA). Pesticides' presence in the body has implications for human health, especially during vulnerable life stages like childhood, puberty, pregnancy, and old age.

Pesticide exposure during pregnancy is of specific concern as health effects for all life stages can be long-lasting. Birth and reproductive complications are increasingly common among individuals exposed to environmental toxicants like pesticides. The Centers for Disease Control and Prevention (CDC) reports birth defects are the leading cause of infant mortality, with one in every 33 infants born with an abnormality that results in death. Therefore, studies like this can help government and health officials safeguard human health by assessing adverse effects following prevalent chemical exposure.

Pesticide exposure during pregnancy is of specific concern as health effects for all life stages can be long-lasting. Birth and reproductive complications are increasingly common among individuals exposed to environmental toxicants like pesticides.

Using a Dutch birth registry from 2009 to 2013, the researchers selected pregnant mothers over 16 years who were living in non-urban areas (who have never moved addresses or only moved once) as participants. Researchers estimated how many kg of the 139 active ingredients are used within 50, 100, 250, and 500 meters of the mother's home during pregnancy. To determine the association between evidence of reproductive toxicity and gestational age, birth weight, perinatal mortality, child's sex, prematurity, low birth weight, small for gestational age and large for gestational age among select active ingredients, the study employed generalized linear models, adjusting for individual and area-level confounders.

The results demonstrate maternal residential exposure to fluroxypyr-meptyl and vinclozolin has associations with longer GA, exposure to glufosinate-ammonium increases the risk of LBW, and linuron exposure has an association with higher BW and higher probabilities of LGA. Additionally, picoxystrobin has associations with a higher likelihood of LGA.

Environmental contaminants like pesticides are ubiquitous in the environment, with 90 percent of Americans having at least one pesticide compound in their body. Numerous studies indicate chemical exposure mainly stems from dietary exposure, like food and drinking water, and researchers caution that there are hundreds to thousands of chemicals that humans are likely to encounter. Just as nutrients are transferable between mother and fetus, so are chemical contaminants. Studies find pesticide compounds in the mother's blood can transfer to the fetus via the umbilical cord. A 2021 study finds pregnant women already have over 100 detectable chemicals in blood and umbilical cord samples, including banned chemicals. However, 89 percent of these chemical contaminants are from unidentified sources, lack adequate information, or were not previously detectable in humans. Considering that the first few weeks of pregnancy are the most vulnerable periods of fetal development, exposure to toxicants can have much more severe implications. A 2020 study finds prenatal pesticide exposure can increase the risk of the rare fetal disorder holoprosencephaly. This disorder prevents the embryonic forebrain from developing into two separate hemispheres. Moreover, women living near agricultural areas experience higher pesticide exposure rates, increasing the risk of birthing a baby with abnormalities. These birth abnormalities can include acute lymphoblastic leukemia and Attention-Deficit/Hyperactivity Disorder (ADHD). Even common household pesticide use during pregnancy can increase nephroblastoma (kidney cancer) and brain tumor risk in children. Therefore, prenatal and early-life exposure to environmental toxicants like pesticides increases susceptibility to disease for both mother and child's health.

Environmental contaminants like pesticides are ubiquitous in the environment, with 90 percent of Americans having at least one pesticide compound in their body.

The rates of preterm births, miscarriages/stillbirths, and birth malformations are increasing. Additionally, many current-use pesticides and metabolites (or breakdown products) of many long-banned pesticides still impart negative effects on human health that can continue into childhood and adulthood and may have multigenerational consequences. Thus, pesticide exposure poses a risk to mothers, their subsequent offspring, and future generations. Researchers at Drexel University report that higher levels of some organochlorine compounds, like DDT, during pregnancy are associated with autism spectrum disorder (ASD) and intellectual disability (ID). Although the U.S. has banned many organochlorine compounds, the ongoing poisoning and contamination underscore the pervasiveness and persistence of these chemicals, with their continued adverse impact on human health.

This study amplifies the growing body of scientific research evaluating

pesticides' effects on newborns. Exposure to specific pesticides can increase the risk of higher BW, LGA, and longer GA, which other studies have shown to be linked with increased risk of obesity and cardiovascular diseases later in life. Although fluroxypyr-meptyl is one of the only pesticides in the study still approved for use in the European Union (EU), imported products can contain contamination from the remaining active ingredients via countries where currently used. Moreover, some current-use pesticides share similar modes of action with the active ingredients in this study, suggesting future research on the effects of maternal pesticide exposure can use these findings as models. The study concludes, "The underlying mechanism driving these effects are unclear, but the findings warrant more research into the effects of (nonoccupational) exposure to these pesticides on human health, especially in the vulnerable population of pregnant women and their babies. [Active ingredients] that were correlated or that share the same modes of action with the identified in this study may also be considered as leads for further research."

SOURCE: M. Simões, et al., Exploring associations between residential exposure to pesticides and birth outcomes using the Dutch birth registry. *Environ Int.* 2023 Aug; 178:108085. 10.1016/j.envint.2023.108085. Epub 2023 Jul 4. PMID: 37421898.

MORE ON THIS SUBJECT

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TOXICOLOGY | EFFECTS ON CHILDREN/DEVELOPMENTAL EFFECTS | MARCH 9, 2023

Prenatal Pesticide Exposure Threatens Children's Language Development at 18 Months after Birth, Study Finds

A study published in *Environmental Research* finds exposure to organophosphate (OP) compounds during pregnancy, or prenatal OP exposure can cause shortfalls in language development abilities at 18 months, stifling preschool-age language expression. Additionally, a timely and co-occurring study published in *Environmental International* finds similar results, highlighting that the insecticide chlorpyrifos (an organophosphate, widely used in agriculture) impedes neurological and psychological development, including language communication and all motor skills of offspring at 12 and 18 months old. Prenatal development is one of the most vulnerable periods of

exposure, as the fetus is most susceptible to the harmful effects of chemical contaminants. Many studies indicate that prenatal and early-life exposure to environmental toxicants increases susceptibility to diseases, from learning and developmental disabilities to cancer. Given research links to pesticide exposure and neurological and cognitive development, studies like this can help government and health officials identify how pesticides' impact on the brain elevates health concerns. The *Environmental Research* authors note, "The etiology [cause] of language development is complex, and this work further highlights the importance of the prenatal environment as a mechanism of influence that are associated with deficits in early language acquisition and ability, which could signal increased behavioral problems and academic difficulties in later childhood that extend into adolescence."

Pesticide use is widespread and direct exposure from applications or indirect exposure from residues threatens human health. Children are more vulnerable to the impact of pesticides as their bodies are still developing and their intake is higher relative to body weight.

The study in *Environmental Research* includes 299 mother-child groups from Norway. Researchers examine chemical exposure in pregnant mothers during gestation week 17 and assessed the related language skills of children at 18 months of age and pre-school age (~4–6 years old). Parents and teachers report the child's language ability and apply it to structural equation models. Prenatal exposure to OP pesticides has a negative correlation with language ability in both 18 months and preschool-aged children. The results published in *Environmental International* mirror those of the Norwegian study as researchers assessing neuropsychological development in 12-month and 18-month-old children find the stages of communication and motor skills among children are underdeveloped relative to age.

Pesticide use is widespread, and direct exposure from applications or indirect exposure from residues threatens human health. Children are more vulnerable to the impact of pesticides as their bodies are still developing and their intake is higher relative to body weight. Many studies indicate prenatal and early-life exposure to environmental toxicants increases susceptibility to disease. A 2020 study finds the first few weeks of pregnancy are the most vulnerable periods during which prenatal pesticide exposure can increase disease risk. A pregnant mother's exposure to environmental toxicants can increase the likelihood of developmental disabilities, as most developmental disabilities begin before birth. Many studies link childhood pesticide exposure to lower IQ, but prenatal pesticide exposure even more so. Moreover, women living near areas of high toxic chemical use have an increased risk of birthing a baby with impaired cognitive function, like Attention-Deficit/Hyperactivity Disorder (ADHD). Many long-banned pesticides still cause adverse effects to human health. Researchers at Drexel University report that higher levels of some organochlorine compounds, like DDT, during pregnancy are associated with autism spectrum disorder (ASD) and intellectual disability (ID).

Both studies add to the growing evidence of the impacts that chemical exposure during pregnancy has on offspring health, specifically neurological development. Additionally, these studies highlight that early childhood developmental pathways are significant for future health. The findings on OP exposure and delayed communication skills are not new. Research underscores one of the mechanisms that allows chemical contamination in a mother's body to affect the fetus. In blood and umbilical cord samples, pregnant women already have over 100 detectable chemicals, and studies find pesticide compounds present in the mother's blood can transfer to the fetus via the umbilical cord. Like these studies, other studies demonstrate that exposure to pesticides, such as organophosphate insecticides like chlorpyrifos, have endocrine disruption properties that induce neurotoxicity via acetylcholinesterase (AChE) inhibition. The number of children with neurodevelopmental disabilities is increasing in the U.S., and many children in rural areas—where pesticide use is most prevalent—have a higher rate of neurological disabilities. Therefore, it is essential to effectively monitor and assess pesticide exposure for the sake of human health.

SOURCES: Amanda M. Ramos, et al., The association of prenatal phthalates, organophosphorous pesticides, and organophosphate esters with early child language ability in Norway, Environmental Research, Volume 225, 2023, 115508, https://doi.org/10.101 j.envres.2023.115508

Hongcheng Wei, Prenatal exposure to pesticides and domain-specific neurodevelopment at age 12 and 18 months in Nanjing, China, *Environment International*, Volume 173, 2023, 107814, https://doi.org/10.1016/j.envint.2023.107814

MORE ON THIS SUBJECT

Father's Exposure to Toxic Chemicals in the Workplace Increases Risk of Heart Disease in Infants—February 23, 2023

Glyphosate Exposure Associated with Liver and Metabolic Disorders in Children, Young Adults—March 7, 2023

The number of children with neurodevelopmental disabilities is increasing in the U.S., and many children in rural areas . . . have a higher rate of neurological disabilities. Therefore, it is essential to effectively monitor and assess pesticide exposure for the sake of human health.

TOXICOLOGY | NEUROTOXICITY | JANUARY 19, 2023

Neonicotinoid Insecticides Adversely Affect Nervous System Health, According to Study

Research published in *Environmental Health Perspectives* finds the presence of nine neonicotinoid (neonic) insecticides and six neonic metabolites within human cerebrospinal fluid (CSF). CSF is essential to the central nervous system (CNS), especially for CNS development. Specific chemical biomarkers (measurable indicators of biological state), like pesticides, found in CSF are useful for diagnosing and evaluating numerous neurological diseases.

The nervous system is an integral part of the human body and includes the brain, spinal cord, a vast network of nerves and neurons, all of which are responsible for many bodily functions—from sensing to movement. However, mounting evidence over the past years shows that chronic exposure to sublethal (nonfatal) levels of pesticides can cause neurotoxic effects or exacerbate pre-existing chemical damage to the nervous system. The impacts of pesticides on the nervous system, including the brain, are hazardous, especially for chronically exposed individuals (e.g., farmworkers) or during critical windows of vulnerability and development (e.g., childhood, pregnancy). Researchers identify the role agricultural chemicals play in CNS impacts causing neurological diseases, like amyotrophic lateral sclerosis (ALS) and Parkinson's disease, dementia-like diseases such as Alzheimer's, and other effects on cognitive function.

The study explores whether the presence of neonics and their metabolites in CSF is an indicator of adverse CNS effects. From April 2019 to January 2021, researchers gathered 314 CSF samples from patients aged one month to 89 years in the First Affiliated Hospital of Shantou University, Shantou, China using a clinical lumbar puncture. Researchers collected CSF samples from patients experiencing similar symptoms with a different disease/clinical diagnosis (e.g., "mostly viral encephalitis, encephalitis other than viral encephalitis, leukemia, cerebral hemorrhage, cerebral laceration, urinary tract infection, respiratory failure, pulmonary tuberculosis, and posterior circulation ischemia"). To analyze the presence of neonics and their metabolites in CSF, researchers used acidification, solid phase extraction, and high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Ninety-nine percent of the 314 CSF samples contain at least one neonic. Of the 314 CSF samples, nine percent (28) have a single neonic compound, 84 percent (265) have between 2 and 6, and six percent (19) have between 7 and 10 neonic compounds. Nine of these neonics in CSF samples are nitenpyram (NIT), thiamethoxam, imidacloprid, acetamiprid (ACE), thiacloprid, clothianidin, flonicamid, imidaclothiz, and sulfoxaflor. Additionally, six neonic metabolites are present in CSF: N-desmethyl-thiamethoxam, olefin-imidacloprid, 5-hydroxy-imidacloprid,

N-desmethyl-acetamiprid (N-dm-ACE), thiacloprid-amide, and 6-chloronicotinic acid.

Over the past 20 years, neonicotinoids have served as an alternative for four major chemical classes of insecticides in the global market (organophosphates, carbamates, phenyl-pyrazoles, and pyrethroids). These systemic agricultural pesticides are highly toxic, resembling nicotine, and affect the central nervous system of insects, resulting in paralysis and death, even at low doses. Like other pesticides, neonics readily contaminate water and food resources as traditional water waste treatments typically fail to remove the chemical from tap water, and the systemic nature of neonics allows the chemical to accumulate within plant products. According to the Centers for Disease Control and Prevention (CDC), nearly half the U.S. population encounters at least one type of neonic daily, with children ages three to five having the highest exposure risk. Health impacts of exposure to neonics can include neurotoxicity, reproductive anomalies, hepatic and renal damage, and an increase in gene expression linked to hormone-dependent breast cancer. Additionally, researchers identified that some neonicotinoids play a role in enzyme (aromatase) production that stimulates excess estrogen production, a known event in hormone-dependent cancer development.

Beyond its link to human health effects, neonicotinoids are infamous for their well-documented role in driving mass pollinator declines. However, pollinators are far from the only victims of ubiquitous neonicotinoid contamination. In a recent avian risk assessment, EPA scientists found that neonicotinoids levels in treated seeds exceed the agency's threshold of concern for certain birds by as much as 200-fold. A 2017 study by researchers at the University of Saskatchewan confirmed that tiny amounts of neonicotinoids—the equivalent of just four treated canola seeds, for example—are enough to cause migrating songbirds to lose their sense of direction and become emaciated. Recent research uncovered the endocrine-disrupting health impacts of imidacloprid on white-tailed deer, adding to the concern of the same effect in humans.

This study adds to the growing research on pesticides and neurotoxic consequences. Although past studies on neonic toxicity focus on neurotoxicity among insects and aquatic invertebrates, emerging evidence demonstrates these compounds also adversely impact the nervous system of animals, including humans as well. Not only does research find that exposure to sublethal doses of chemicals affects hormone receptors (endocrine disruption), but neural receptors, such as connections between nerves, the brain, enzymes, and DNA, are affected as well. In addition to this research, several studies demonstrate autism, mood disorders (e.g., depression), and degenerative neurological conditions among aquatic and terrestrial animals, including humans, exposed to pesticides. Pesticides themselves, mixtures of chemicals such as the defoliant Agent Orange (2,4-D and 2,4,5-T) and its dioxin contaminants and therapeutic hormones in pharmaceutical products, possess the ability to disrupt neurological function.

Furthermore, studies suggest that pesticide formulants (adjuvants) such as POEA (polyoxyethylene tallow amine) have both neurological and endocrine-disrupting activity. POEA is present in some glyphosate-based herbicides, like Roundup, and has higher nervous system toxicity than the active ingredient (glyphosate). Although the biological function and mechanism of neurotoxicity related to pesticide exposure is unclear, scientists note synchronized communication within and between cells that have a mechanism of action of "spamming" communication signals. The study concludes, "For continued global use of NEOs [neonics], mechanisms of toxicity, especially to the CNS in humans, need to be more rigorously investigated."

SOURCE: Jing Li, et al., Detection of Neonicotinoid Insecticides and Their Metabolites in Human Cerebrospinal Fluid, *Environmental Health Perspectives*, Volume 130, Issue 12, 127702, https://doi.org/10.1289/EHP1137

TOXICOLOGY | NEUROTOXICITY | MAY 5, 2023

New Study Links Synthetic Pyrethroids to Neurodevelopmental Problems

Low level exposure to pyrethroid insecticides found in common pesticide brands like RAID and ORTHO result in neurodevelopmental damage to laboratory animals, reinforcing evidence of harm found in epidemiologic studies on human exposure to these chemicals, according to research published in PNAS Nexus. In the study, mice exposed to the pyrethroid deltamethrin displayed atypical behavior similar to humans with developmental disorders. "We are not saying these mice have autism or that they have ADHD. That's not the goal here," said James Burkett, PhD, study coauthor and assistant professor of neuroscience in the UToledo College of Medicine. "What we are saying is that something in their brain has been altered by this exposure and it is resulting in the same kinds of behaviors that we see in children with autism."

Scientists arrived at this determination by exposing a group of mouse mothers to consistent low levels of deltamethrin in their food during preconception, pregnancy, and lactation. The study notes that the amount of pesticide provided was "well below the benchmark dose for regulatory guidance."

A separate control group was given no pesticide in its food. Offspring from the female mice were then put through behavioral tests on social behavior, restrictive or repetitive behaviors, cognition and communication.

Results find that mouse pups whose mothers were exposed to deltamethrin increase their repetitive behaviors. In tests, they buried more marbles than control pups, and performed more self-grooming than the control group. Male pups exposed to deltamethrin also produced fewer vocalizations when being separated from their mothers. Pesticide exposure also impaired learning and memory; in a fear conditioning test, exposed mice were less likely to react to a fearful event they encountered previously.

In addition to behavior, scientists observed physiological changes in pups whose mothers were pyrethroid-exposed. These mice exhibited significant changes in dopamine levels and transport around the body. For "autistic" individuals, the metabolite homovanillic acid (HVA) is considered the earliest biomarker for the condition, and exposed mice pups displayed increased levels of the substance. "These are all similar to symptoms human patients with neurodevelopmental disorders might have," Dr. Burkett said.

Synthetic pyrethroids are hazardous pesticides that have flown below radar of those concerned about pesticides for far too long, not receiving nearly as much attention as other dangerous and commonly used pesticides like the weed killer glyphosate.

"If you have someone who comes and sprays in your house, this is likely what they're spraying. It's used in landscaping, it's what they fog in the streets for mosquitoes. It's everywhere," said Dr. Burkett. "Our study, however, adds to the evidence that these chemicals might not be as safe for children and pregnant women as we once believed." In fact, Beyond Pesticides has never believed these chemicals to be safe for children or pregnant women. The depth of historical reporting on these chemicals in the *Daily News* bears this out. As far back as 2008, Beyond Pesticides was reporting on the risk these chemicals pose to children's development.

The research on this class of chemicals has sounded a consistent drumbeat of developmental harm to children. In 2011, research determined that children exposed to higher levels of synthetic pyrethroids are three times as likely to have mental delay compared to less exposed children. A 2014 study associated proximity to pesticide-treated agricultural fields in pregnancy to increased risk of autism to children of exposed mothers. Research published in 2015 finds that deltamethrin increases risk of ADHD in children, with one study finding impacts specifically to boys. Studies published two years later determined that synthetic pyrethroid exposure increases risk of premature puberty in boys, and another associated the chemicals with externalizing and internalizing disorders. Another study found that aerial mosquito spraying, which is most frequently conducted with synthetic pyrethroids, is linked to elevated autism rates.

The impacts seen are not all developmental. A 2012 study associates pyrethroid exposure before, during, and after pregnancy with increased risk of infant leukemia. And a recent study published earlier this year finds that synthetic pyrethroid exposure during mosquito control operations increases risk of respiratory disease and certain allergies.

Rather than rein in use of these chemicals, EPA in 2019 stripped away protections that reduced children's exposure to pyrethroids. In making its decision, the agency allowed a letter from the pesticide industry trade group Croplife America to dictate its approach to protecting children from hazardous, neurotoxic pyrethroids. The model proposed by Croplife eliminated safety factors for children. In a rare instance, EPA conducted an outside literature review to buttress its argument, but instead ignored that research and prioritized the unprotective model proposed by the pesticide industry.

After reducing protection for children's health, the agency then took directions from a group referring to themselves as the Pyrethroid Working Group (PWG), comprised of major pesticide manufacturers Bayer, FMC, Syngenta, BASF, AMVAC, and Valent. At the request of this working group, EPA reduced a proposal from EPA staff scientists to implement 66-foot buffer zones between agricultural fields and water bodies down to 10–25 feet. The agency also agreed that wind speeds up to 15 miles per hour were acceptable for pyrethroid applications, despite previous proposals setting the cut-off at 10 mph.

While further study is warranted, safety advocates urge that it be conducted while this class of chemicals is suspended. Rather than place the burden of proof on scientists to show harm, they say that chemical manufacturers should be required to provide evidence that these chemicals will not harm children's health.

"We have reduced our exposures to many classes of dangerous pesticides over the past few decades through restrictions and regulations," said study coauthor Gary Miller, PhD, vice dean for research strategy and innovation at Columbia University Mailman School of Public Health. "This study adds to a growing body of literature that the widely used pyrethroids are not without adverse effects and should be further evaluated for their safety."

While further study is warranted, safety advocates urge that it be conducted while this class of chemicals is suspended from public use. Rather than place the burden of proof on scientists to show harm, they say that chemical manufacturers should be required to provide evidence that these chemicals will not harm children's health.

SOURCE: Melissa A Curtis, et al., Developmental pyrethroid exposure causes a neurodevelopmental disorder phenotype in mice, *PNAS Nexus*, Volume 2, Issue 4, April 2023, pgad085, https://doi.org/10.1093/pnasnexus/pgad085

MORE ON THIS SUBJECT

Study Finds Glyphosate Exposure Among the General Population Poses a Risk to Neurological Health—August 31, 2023

Popular Pyrethroid Insecticides, Already Linked to Rheumatoid Arthritis, Associated with Osteoarthritis—September 20, 2023

All Pesticide Classes Increase the Risk of Central Nervous System Tumors in Children—September 21, 2023

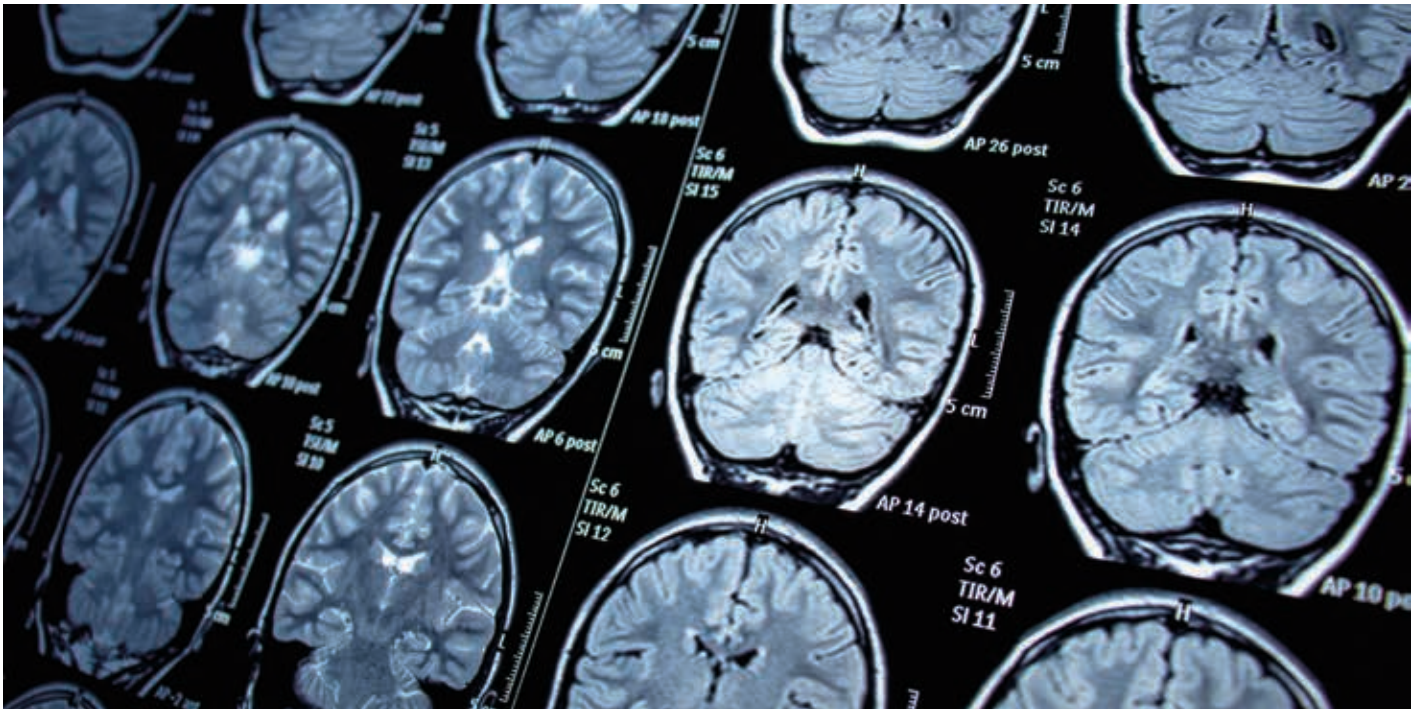
TOXICOLOGY | SEIZURE DISORDERS—EPILEPSY | MAY 11, 2023

Pesticide Exposure Increases the Risk of All Seizure Disorders, Especially Epilepsy

A study published in *NeuroToxicology* finds occupational, chronic exposure to pesticides increases risk factors of epilepsy, a neurological disorder causing unprovoked, reoccurring seizures. Mounting evidence over the past years shows that chronic exposure to sublethal (nonfatal) levels of pesticides can cause neurotoxic effects or exacerbate preexisting chemical damage to the nervous system. Although the mechanism by which pesticides induce disease development remains unclear, this study suggests environmental pesticide exposure increases seizure risk through mechanisms at molecular or subcellular levels.

Approximately 3.4 million individuals in the U.S. live with epilepsy, and mortality from this disorder is rising nationwide. Over 300 environmental contaminants and their byproducts, including pesticides, are chemicals commonly present in human blood and urine samples and can increase neurotoxicity risk when crossing the brain barrier. Considering that half of all epilepsy etiologies (causes) are of idiopathic (unknown) origins, studies like this highlight the importance of understanding how consistent chemical exposure can impact long-term health and disease prognosis. The study notes that their approach of using real-world exposure over extended time and space can be combined with simulations proposed by other authors to give "a better understanding of the real-life risk associated with long-term exposure to multiple pesticides."

To determine work-related risk factors associated with epilepsy among farmers



and pesticide applicators, researchers performed a case-control study on 19,704 individuals from 2000 to 2016 (17 years) to observe epilepsy cases. Researchers gathered data from Almería (South-Eastern Spain) hospital records and the Centre for Prevention of Occupational Risks. Of the 19,704 individuals, 5,091 have a record of epilepsy. The researchers attribute an increase in epilepsy risk among those working in chemical-intensive, enclosed (indoor) agriculture (high-yield greenhouse crops) compared to chemical-intensive, open-air (outdoor) agriculture (open-air crops). However, this study supports previous findings on the association between epilepsy and pesticide exposure in the general population. Epilepsy risk is greatest among individuals living in rural areas with high pesticide use (e.g., farming regions) and individuals without proper personal protective equipment (PPE), including gloves and masks.

Epilepsy is a common neurological disorder that affects a person's brain and central nervous system (CNS). These conditions can disrupt nerve cell communication in the brain and lead to prolonged seizures (*status epilepticus*) due to abnormal electrical activity in the brain. Although the most common cause of seizures is epilepsy, not every person who has a seizure has epilepsy. Although medical treatments can manage epilepsy, typical anti-seizure medication for epilepsy is ineffective in the treatment `of non- epileptic seizures.

Sublethal levels of pesticides can cause neurotoxic effects or exacerbate preexisting chemical damage to the nervous system.

Certain chemicals, including pesticides, can be seizurogenic chemicals or toxic agents that cause seizures by different mechanisms and molecular pathways. The most-known mechanisms include hyperstimulation of nicotinic and muscarinic acetylcholine receptors (neurotransmitters), blockage of voltage-gated sodium channels, altered function of GABAergic neurons, glutamatergic hyperactivity, neuronal excitotoxicity, intracellular calcium overload, oxidative stress, and increased neuro-inflammatory responses, among others. Pesticides with neurotoxic properties include organophosphates, carbamates, neonicotinoids, pyrethroids, and organochlorines.

Despite many studies linking acute pesticide poisonings to seizures, this study is one of the few to address concerns about those chronically exposed to pesticides. A 2016 study in the same region of Spain demonstrates that workers who applied pesticides were more likely to have neurological symptoms lasting more than two days, such as cramps, tremors, muscle fatigue, loss of consciousness, and convulsions. Many pesticides used in the past and present can contribute to the formation of a single seizure or epilepsy due to chronic poisoning. Thus, the study highlights at the very least the importance of PPE as a preventive measure critical to reducing the risk of developing pesticide-related symptoms and diseases. Farmers without gloves and masks have two and three times higher risks of epilepsy, respectively. The Agricultural Health Study (AHS), used to estimate pesticide exposure intensity, finds that farmers experience a 90 percent reduction in pesticide exposure when using proper PPE. However, PPE alone is not

enough to prevent pesticide exposure, especially for everyday exposure from disinfectants, residues on food, and contamination of the ecosystem. The study concludes, "[T]his study supports previous findings suggesting a higher risk of epilepsy in the general population associated [with] pesticide exposure and extends the presumed increased risk to farmers occupationally exposed to pesticides, particularly those with lack of or improper use of PPE."

The impacts of pesticides on the nervous system are hazardous, especially for chronically exposed individuals (e.g., farmworkers) or during critical windows of vulnerability and development (e.g., childhood, pregnancy). Researchers identify the role agricultural chemicals play in CNS impacts causing neurological diseases like amyotrophic lateral sclerosis (ALS) and Parkinson's disease, dementia-like diseases, such as Alzheimer's, and other effects on cognitive function. Therefore, studies related to pesticides and neurological disorders can help scientists understand the underlying mechanisms that cause neurodegenerative diseases.

SOURCE: Raquel Alarcón, et al., Occupational exposure to pesticides as a potential risk factor for epilepsy, *NeuroToxicology,* Volume 96, 2023, Pages 166-173, https://doi.org/10.1016/j.neuro.2023.04.012.

TOXICOLOGY | GUT MICROBIOME HEALTH | JUNE 27, 2023

Study Elevates the Connection Between Pesticides, the Gut-Brain Axis, and Disease

A review article by Irish and Dutch researchers in the *ISME Journal* adds to the emerging scientific literature examining how pesticides affect the relationship between the human gut and the human brain (the "gut-brain axis"). Often called the "second brain" because it houses nerve cells and produces neurotransmitters, the gut-brain axis may be the most important locus where microbes and pesticides meet. The human gut plays host to a variety of microorganisms, ranging from bacteria and archaea to fungi, viruses and yeasts. (see *Daily News*). In a healthy person, these microbes remain in balance and often cooperate both with each other and with human cells.

The gut and the brain are deeply integrated through the vagus nerve and the neuroendocrine system. The vagus nerve is a treelike bundle of fibers extending from the lower part of the brain to nearly every body organ, but particularly the heart, lungs, and digestive tract. The neuroendocrine system comprises specialized cells inhabiting nearly all the organs of the body that respond to signals from the brain and gut to produce hormones that regulate digestive enzymes, the pace of digestion, air and blood flow in the lungs, blood pressure, heart rate, blood glucose levels, and other functions.

Pesticides may exert influence over any or all of these processes. They may

also affect the immune system, and some, such as glyphosate, can cross the blood-brain barrier. Pesticides can affect the production of many chemicals by gut bacteria, including serotonin and gamma-aminobutyric acid (GABA), both important neurotransmitters. They are also notorious for disrupting the endocrine system, including reproductive hormones; a 2020 review by Spanish scientists proposed that xenobiotics such as pesticides should be termed "microbiota disrupting chemicals," as they can interfere with microbes' role in metabolizing steroid hormones such as estradiol, cortisol, and testosterone.

Beyond Pesticides has previously reported on numerous studies elucidating the deleterious effects of pesticides on disease risks involving the gut-brain axis. These include the close association between digestive disruption and Type 1 diabetes in children and Type 2 diabetes in adults, and the ability of azoxystrobin (AZO) fungicide to impair the function of the colonic barrier in nutrient absorption and protection from harmful substances. The digestive problems associated with Type I diabetes have been linked to exposure to antibiotics and some pesticides. Such exposures reduce the numbers of certain bacteria in the gut that can help protect against the inflammation triggered by these chemicals. The effects of pesticides on gut microbes have also been linked to autism spectrum disorder (ASD), as has digestive dysfunction.

Adult-onset neurological diseases also involve digestive disruption, which in turn may be related to disruption of the gut microbe balance. In 2022, Beyond Pesticides reported on a study showing that the gastrointestinal disruptions, including damage to enteric glial cells that lead to Parkinson's disease (the second most common neurodegenerative disease after Alzheimer's), are associated with exposure to the insecticides rotenone and chlorpyrifos, as well as the herbicides 2,4-D, glyphosate, and paraquat. The Irish and Dutch researchers also reviewed a study showing that glyphosate can enter the brain and raise inflammation levels, a process that has been linked to Alzheimer's. A 2022 study suggests that chronic exposure to dietary pesticides can affect gut microbes and trigger a cascade of changes leading to these neurodegenerative diseases.

Pesticides' effects on host-microbe processes are not confined to humans. Importantly, pesticides affect the microbes associated with plants and nontarget insects, often changing the proportions of various species. For example, French researchers in 2022 identified glyphosate's changes to honey bees' immune systems and gut microbiota, demonstrating a plausible mechanism for the bees' susceptibility to certain diseases. Sometimes pesticides have a seemingly perverse—but predictable—Darwinian effect: In 2018, Beyond Pesticides reported on research detailing how insect pests' gut microbiota contribute to the skyrocketing incidence of pesticide resistance. Microbes are nothing if not adaptable.

One common bacterial genus, *Lactobacillus,* which lives in the digestive tract and the female reproductive tract as well as in fermented foods such as yogurt and kefir, demonstrates abilities that could point toward protection from pesticides' damage to the gut-brain axis. *Lactobacillus* species are adversely affected by herbicides, fungicides, and insecticides, according to the authors of the current study. They are known to enhance mood and reduce anxiety and depression, and they also provide vital services in the gut, where they produce mucus that lines the intestinal walls and enhance signaling among different types of immune cells. Thus, their reduced presence in the gut caused by pesticides may contribute to many, if not all, diseases affecting the brain-gut axis.

They may also come to the rescue after pesticide exposure. Interestingly, *Lactobacillus* and other bacterial genera actually degrade pesticides in the foods they ferment. A combination of *L. acidophilus* and *Bifidus animalus* synergistically reduces levels of "up to 48.6% for heptachlor and 54.7% for pp'DDE in goat milk bio-yogurts after 14 days of cold storage when both cultures were used," according to a recent Bulgarian study.

A remarkable Chinese study, reported in the journal *Cell* in 2022, exposed human volunteers to high doses of organophosphorus and organochlorine compounds. These triggered inflammatory responses and increased numbers of pathogenic bacteria in the gut. The researchers then dosed a subset of the exposed group with a proprietary version of a lactobacillus strain called *Lactiplantibacillus plantarum.* Lactobacilli are already present in many probiotic supplements and are used to improve symptoms of eczema, high cholesterol, and bowel inflammation. In the Chinese study's probiotic group, microbial diversity was reestablished, inflammatory markers decreased—including two factors associated with kidney disease—and the bacteria promoted the breakdown of the pesticides and excretion of their metabolites.

Microbes are everywhere—even in the rocks deep below the seafloor. They are certainly everywhere in the human body, not only the gastrointestinal tract—one study found pesticides reduced the flora in the human mouth—and it appears that pesticides may affect microbes wherever they are. Estimates of the total number of microbial cells in a typical human—about 39 trillion—exceed the number of actual human cells—about 30 trillion. This has led many scientists to adopt pioneering microbiologist Lynn Margulis's (PhD) proposal that humans and most other multicellular organisms should be viewed as "holobonts," that is, a single organism comprising a host and one or more symbionts—generally microbes. It would encourage a paradigm shift away from the pesticide industry's assumption that its products' effects are siloed and target only specific agricultural pests. Not even a monoculture field is free of trillions of microbes on its plants, in its soil, and in its water. Many of these are beneficial and may have their own ability to control pests.

SOURCE: R. Matsuzaki, et al., Pesticide exposure and the microbiota-gut-brain axis. *ISME J* 17, 1153–1166 (2023). https://doi.org/10.1038/s41396-023-01450-9

TOXICOLOGY | GUT MICROBIOME HEALTH | NOVEMBER 15, 2023

Glyphosate Exposure Linked to Behavioral and Gut Health Concerns in New Studies

A study previously published in the Federation of American Societies for Experimental Biology (FASEB) is drawing renewed attention to the gut microbiome in the scientific community. The study, involving a team including Demetrio Sierra-Mercado, PhD, of the University of Puerto Rico School of Medicine, initially established a link between glyphosate exposure and increased anxiety and fear-related behavior in rats. Glyphosate, a widely-used herbicide, has been detected in trace amounts in fruits, vegetables, grains, and other food and beverages, according to the U.S. Environmental Protection Agency (EPA). Originally deemed safe for humans due to the way it interacts with the shikimic acid pathway—a metabolic route that is absent in humans—glyphosate's indirect effects on human health are now under scrutiny as the research linking it to anxiety-like behavior grows.

Dr. Sierra-Mercado's team is expanding on his previous research to take a closer look at the compound's potential disruption of the gut microbiome, which plays a pivotal role in regulating both physical and mental health. His upcoming study, anticipated in August 2024, aims to delve into the intricate relationship between glyphosate exposure and the gut-brain axis, with a focus on how this may influence neurological and emotional health in humans. This investigation is critical as it prompts the world to rethink the initial toxicity assessments of glyphosate, accounting for a broader scope on the internal systems that the pesticide affects.

This research emerges as the impacts of glyphosate consumption become clearer with decades of accumulated studies. In recent years, numerous lawsuits have targeted Monsanto (now Bayer), producer of Roundup (which contains glyphosate), alleging that the herbicide contributes to the plaintiffs' cancers. Moreover, the International Agency for Research on Cancer classifies the chemical as a probable carcinogen. Concurrently, research links the chemical to increased rates of toxic body burden, noting adolescents have higher bodily concentrations of glyphosate than adults. An article by Beyond Pesticides on this research spotlights the study finding that over 90 percent of participants, including many child/parent pairs, had recent exposure to glyphosate, with children often showing up to four times the glyphosate levels of their parents. This corroborates evidence that children may be more vulnerable to the chemical's risks. Additionally, an extensive 15-year study associates high rates of childhood blood cancers with children living in Brazil's soy-growing areas—regions that rely on intensive glyphosate inputs. Comprehending the full spectrum of glyphosate's effects on human health,

from its carcinogenicity to its neurological and emotional ramifications, is crucial.

As part of Dr. Sierra-Mercado's revealing insights at the September 25 Keystone Science Lecture, part of the multi-day workshop and lecture series at the National Institute of Environmental Health Sciences (NIEHS), the extended research on glyphosate's impact on behavior has gained substantial depth. In his lecture, Dr. Sierra-Mercado presented findings from his team's rigorous investigation into the effects of prolonged oral exposure to glyphosate, a chemical with an EPA-deemed acceptable risk for humans at a daily exposure rate of 2.0 mg/kg over a lifetime. The team administered glyphosate-contaminated water at the EPA's accepted safe dose, with control rats receiving filtered drinking water. No initial behavioral changes were noted after four weeks of exposure, as determined by an open field test. However, the narrative changed with prolonged exposure. After 14 weeks, the rats displayed significant anxiety-like behaviors, with a pronounced decrease in time spent exploring novel objects and a marked increase in threat response to new stimuli, which could indicate heightened anxiety or negative anticipation. Additionally, Dr. Sierra-Mercado notes increased cellular activity in the bed nucleus of the stria terminalis (BNST), a brain region associated with anxiety—a physiological marker that demonstrates glyphosate's potential effect on neural pathways. Further highlighting the biological impact, a notable decrease in *Lactobacillus* in the feces was observed, pointing to glyphosate's disruption of gut bacteria. This is significant due to the role of *Lactobacillus* in serotonin production, often referred to as the body's "feel-good" hormone.

The research from Dr. Sierra-Mercado and his team demonstrates the intricate interplay between glyphosate consumption and the gut-brain axis, highlighting how even levels deemed safe can lead to anxiety-like behaviors and alter the delicate balance of gut microbiota. These disruptions may initiate a series of events culminating in emotional dysregulation, suggesting that if the research is applicable to all mammals, glyphosate's safety must be reassessed in light of its broader biological impacts.

This study is the first of its kind to understand the connections between glyphosate exposure and gut health. It, along with an ongoing surge of new research into the impacts of pesticide exposure, highlights the significant gaps in the global scientific community's understanding of these chemicals, particularly their long-term implications. The susceptibility of children to glyphosate, with their higher propensity for absorption and retention, is especially concerning. The possibility that even regulated levels of exposure cause unacknowledged dangers necessitates a more cautious approach to such chemicals.

Despite the mounting research and remaining uncertainties, EPA's stance on glyphosate remains firm. The agency continues to classify the chemical as "not likely to be carcinogenic to humans," authorizing its ongoing use. This stance is at odds with the advancing scientific conversation, indicating a concerning gap between science and regulation.

SOURCE: Mauricio Cáceres-Chacón et al., Glyphosate increases anxiety-like behavior and threat response to novel neutral stimuli, *FASEB Journal*, First published: 13 May 2022, https://doi.org/10.1096/fasebj.2022.36.S1.0R100

TOXICOLOGY | BEHAVIOR—MOOD—PSYCHIATRIC | JUNE 7, 2023

Pesticides and Neurotoxicity: The Link Between Mood Disorders and Pesticide Exposures

A systematic review of scientific literature published in *Environmental Research* on the development of mood disorders among pesticide applicators (farmers, landscapers, etc.) finds an increased risk of depression symptoms over the last decade. The evidence in the review highlights the presence of pesticide-specific biomarkers and biomarkers of depression that determine the positive association between pesticide exposure and the development of depressive symptoms. With more high-quality longitudinal studies to control sociocultural variables, researchers can directly pinpoint risks of developing depression, especially among agricultural workers and landscapers who use pesticides.

Research on pesticide-induced diseases commonly investigates pesticide exposure concerning the development of various physical illnesses. However, previous studies show that occupational (work-related) risks of developing depression are high in agriculture, where pesticide use is rampant. Acute exposure to chemicals, including organophosphate, organochlorine, triazine, and carbamate pesticides, tends to put farmers at greater risk of suicide than the general population. There is a lack of information connecting pesticide exposure to the subsequent psychological (psychiatric) effects on the general population. Additionally, household pesticide exposure varies from occupational exposure via exposure frequency, duration, intensity, and type.

According to the World Health Organization (WHO), depression affects 322 million people globally, with the number of diagnosed patients increasing by 18.4 percent from 2005 to 2015. Although the etiology of depression—

and many other psychiatric disorders—is often genetic, studies suggest that other etiological factors, like pesticide exposure, play a role in depression incidents. Poor mental health has a tangible influence on physical health (e.g., depression and cardiovascular disease); therefore, the combination of pesticide exposure and mental illness worsens the adverse effects on human health. If pesticide exposure exacerbates psychiatric disorder symptoms, it is important to evaluate how pesticide exposure affects mental health, in addition to physical health. This research highlights the significance of researching potential mental health effects resulting from pesticide exposure, especially as society tends to rank mental health risks second to physical health. The study notes, "Given the rise in pesticide use in agriculture, the low adherence of farmers to safety training, and the health risks associated with depression, it is recommended to implement stricter surveillance measures on agricultural companies and monitor the mental health of exposed workers. It is also important to actively involve the community in prevention and intervention efforts."

The review conducted a thorough scientific literature search on occupational pesticide exposure and depression symptom development in the *PubMed* and *Scopus* databases for the period 2011 to September 2022. Using guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Population, Exposure, Comparison, and Outcomes (PECO) strategy, researchers examined the association between occupational exposure to pesticides and symptoms of depression in agricultural workers. Among the reviewed articles, 78 percent indicate a link between exposure to pesticides and the prevalence of depression symptoms. The pesticides most associated with depressive symptoms include organophosphate insecticides, general herbicides, and pyrethroid insecticides.

For over two decades, research concerning pesticide exposure and psychiatric disorders, such as depression, focused on occupational hazards, especially for agricultural farmworkers. Exposure to agricultural pesticides puts farmers at a six times greater risk of exhibiting depressive symptoms, including chronic anxiety, irritability, restlessness, and sadness. Specifically, exposure to organochlorines and fumigants (gaseous pesticides) heighten an individual's risk of depression by 90 percent and 80 percent, respectively. Organochlorines are chemicals of concern as they can induce a myriad of health problems, including reproductive dysfunction, endocrine disruption, cancer, and fetal defects. Though the U.S. has banned the use of most organochlorines, because they are highly persistent, they still present an exposure hazard for people and the environment. Fumigants are a human health concern as many fumigants are gases that can cause acute toxicity upon inhalation and ingestion.

However, other pesticides also affect the nervous system and have psychiatric effects. Organophosphates are a family of insecticides derived from World War II nerve agents. They are cholinesterase inhibitors, meaning they bind irreversibly to the active site of an essential enzyme for normal nerve impulse transmission, acetylcholine esterase (AchE), inactivating the enzyme. Linear models reveal an association between lifelong pesticide poisoning episodes and the increased risk of developing mental disorders among tobacco farmers. Tobacco farmers using organophosphate pesticides have a higher prevalence of minor psychiatric disorders.

Individuals suffering from occupational pesticide exposure face a disproportionate risk of developing depression. However, pesticide exposure from nearby agricultural fields remains a threat to residential (nonoccupational) human health. Previous studies found that populations living near farms are more likely to have high depressive symptoms. Similarly, a 2019 study found that teens and adolescents living in agricultural areas, where organophosphate exposure is prevalent, are at higher risk of depression. Gender (female), physical health, and age (young adult) indicate likelihood of having depressive symptoms, with the most adverse effects in women, those in poor physical health, and children under 14.

Understanding the mental health implications of conventional pesticide exposure can help identify the various physiological mechanisms attributed to psychiatric disorders. Like this review, past research finds that organophosphates have significant associations with depressive symptom development, including disturbing normal nerve impulses. So, scientists can analyze information to determine if the lack of normal nerve impulses contributes to non-pesticide-induced depression.

Whether pesticide exposure is occupational or residential, the development of depression symptoms is of concern. Annually, only half of Americans with a depression diagnosis seek treatment for symptoms. Untreated symptoms of depression can increase the risk of suicide, a severe sign of depression. Commonalities between occupational and household pesticide exposure are suicidal thoughts and pesticide provocation as a suicide agent. A study published in the WHO Bulletin finds that people storing organophosphate pesticides in their homes are more likely to have suicidal thoughts as the exposure rate is higher. The study finds an association between suicidal thoughts and ease of household pesticide accessibility. Geographic areas with more frequent home storage of pesticides have higher rates of suicidal thoughts than the general population. WHO scientists recognize pesticide self-poisoning as one of the most significant global methods of suicide, as increases in pesticide toxicity make them potentially lethal substances. Robert Stewart, PhD, a researcher for the WHO Bulletin, stated that: "Organophosphate pesticides are widely used around the world. They are particularly lethal chemicals when taken in overdose and are a cause of many suicides worldwide." With that in mind, researchers say it is vital to recognize how pesticide exposure and accessibility can influence mental illnesses.

To address health issues regarding pesticide exposure and mental health incidents, health care providers must be sensitive to the signs and symptoms of chemical exposure. Farmers, landscapers, and other individuals encountering chemical exposure through ingestion, inhalation, and skin (dermal) contact are often unaware of the non-physical side effects. Considering that depression related to acute pesticide exposure may persist long after initial exposure, those working with toxic pesticides require adequate protective equipment to minimize exposure.

The study concludes "[…] that governments worldwide bear greater responsibility in addressing this matter, which could help control the various systemic sources of exposure to pesticides and other environmental pollutants and lessen the harm to the health of workers."

SOURCE: Javier Cancino et al., Occupational exposure to pesticides and symptoms of depression in agricultural workers. A systematic review, *Environmental Research*, Volume 231, Part 2, 2023, https://doi.org/10.1016/j.envres.2023.116190

MORE ON THIS SUBJECT

Prenatal Exposure to Organophosphate Pesticides Have Links to Behavior—July 6, 2023

Study Further Strengthens Link Between Common Insecticide Class and Psychiatric Disorders—October 25, 2023

TOXICOLOGY | ASTHMA—RESPIRATORY DISEASE | AUGUST 16, 2023

Pesticide Exposure with Disproportionate Effects Increases Risk of Asthma

A study published in *Environmental Science and Pollution Research* further supports the indication that exposure to organophosphate insecticides (OPs) increases the risk of asthma among the U.S. general population. According to the Asthma and Allergy Foundation of America, "The burden of asthma in the United States falls disproportionately on people with low-income, senior adults, and Black, Hispanic and American Indian/Alaska Native people," making these groups more susceptible to developing this chronic lung disease upon OP exposure.

Organophosphorus pesticides have a wide range of biological uses—from insecticides to flame retardants—that make these chemicals ubiquitous, significantly contributing to ecosystem contamination. Furthermore, while organophosphates have less bioaccumulation potential than organochlorines, residues are consistently present in human and animal blood, urine, tissues, and milk. Although research demonstrates that OPs are highly toxic, there remains an inadequate understanding of how OP exposure impacts body systems like the respiratory system.

The respiratory system is essential to human survival, regulating gas exchange (oxygen-carbon dioxide) in the body to balance acid and base tissue cells for normal function. However, damage to the respiratory system can cause several issues—from asthma and bronchitis to oxidative stress that triggers the development of extra-respiratory manifestations

like rheumatoid arthritis and cardiovascular disease. Therefore, the rise in respiratory illnesses and organophosphate use over the last three decades is highly concerning, especially as research fails to identify an exact cause for the increase in respiratory disease cases.

Focusing on noninstitutionalized U.S. adults, researchers gathered representative information on health and nutritional well-being from the Centers for Disease Control and Prevention's (CDC) National Health and Nutrition Examination Survey (NHANES). In total, 6,009 adults ranging from 20 to 85 years old represent the 313.5 million adults in the noninstitutionalized U.S. population. The study detected OP exposure using the urinary concentrations of six metabolites of dialkyl phosphates (DAPs), an indicator of OP concentration in the body. A survey-multivariable logistic regression (SMLR), a generalized weighted quantile sum (WQS) regression, and Bayesian kernel machine regression (BKMR) evaluated the link between OPs and asthma.

The study finds that of the 6,009 participants, 842 participants have asthma. Upon examining urine samples of the 842 patients, four out of the six DAPs are present—dimethyl phosphate (DMP), diethyl phosphate (DEP), dimethyl thiophosphate (DMTP), and dimethyl dithiophosphate (DMDTP)—demonstrating a positive association with asthma in adults. The strongest associations between asthma and OPs occur among females, non-Hispanic White populations, and individuals lacking physical activity. Thus, OP exposure can elevate asthma risk in the general population.

Working in close contact with pesticides throughout one's lifetime increases the risk of asthma, Chronic Obstructive Pulmonary Disease (COPD), and other respiratory issues. Thus, the connection between pesticides and associated respiratory risks is nothing new, as many studies link pesticide use and residue to various respiratory illnesses. Studies find pesticide exposure can trigger asthma attacks and also cause asthma, as exposure to insecticides before the age of five can increase the risk of an asthma diagnosis, with toddlers twice as likely to become asthmatic.

Chronic inhalation of agriculture-related dust (e.g., particulates from grains, feed, soils, and biological aerosols from plant and animal matter that may harbor synthetic pesticide and fertilizer residues) can increase airway inflammatory diseases, including asthma, chronic bronchitis, and COPD. The particulates in dust play a part in disease development, but so, too, do the various microbiota that may be part of a dusty agricultural environment. A disruption of the homeostasis of the human microbiome (known as dysbiosis) can increase the risk of asthma and other respiratory diseases. In addition, pesticide exposures can alter the gut microbiome, which mediates a significant portion of the human immune response.

Many researchers, including those on this study, suggest an increase in environmental pollutants like pesticides may be responsible for the increase in respiratory diseases. Regarding this study, OPs have a significant influence on respiratory pathology. This chemical class has a similar mode of action as cholinesterase inhibitors, which means they bind to receptor sites for the enzyme acetylcholinesterase (AChE), essential to normal nerve impulse transmission. In binding to these receptor sites, cholinesterase inhibitors inactivate AChE and prevent the clearing of acetylcholine. The buildup of acetylcholine can lead

to acute impacts, such as uncontrolled, rapid twitching of some muscles, paralyzed breathing, convulsions, and, in extreme cases, death. The compromise of neural transmission can have broad systemic impacts on the function of multiple body systems, including the respiratory system.

This study also adds to the growing body of research demonstrating disproportionate risk to certain population groups from chemical exposure. The stronger association between asthma, OPs, and women highlights sex-specific disparities characterized by chemical metabolization (breakdown) and elimination in the body. OPs exhibit endocrine-disrupting properties that may alter estrogen or testosterone activity and receptors, resulting in differences in the clearance rate and toxicity of OPs. For instance, a 2018 study finds female rats manifest airway hyperactivity—a characteristic asthma symptom—at lower OP doses than males. Additionally, CDC data establishes women as having a higher prevalence of asthma incidence compared to men. Low-income popula-tions, people of color, and children living in inner cities also experience disproportionately high morbidity and mortality due to asthma. For instance, African Americans are at least three times more likely than whites to die from asthma. Therefore, any time policies allow regulators to permit the use of pesticides with known asthma effects, a disproportionate impact is felt among these communities.

Despite the difference in methods, the study emphasizes that the data results remain consistent. "Though with different study designs, objectives, and populations, our study found plenty of evidence that is consistent with previous similar studies which explore the complicated associations of OPI [organophosphate insecticide] metabolites with asthma." The study concludes, "Our findings suggest that more urinary OPIs exposure may be associated with an increased risk of asthma in the general US adults. Meanwhile, further prospective studies are needed to confirm the causality between OPIs exposure and asthma and explore the potential harm of low-dose but chronic exposure to OPIs in the development of asthma." In the U.S., over 25 million people live with asthma. The increasing rate of respiratory pathology since the 1980s demonstrates a need for better environmental policies and protocols surrounding contaminants like pesticides. Since respiratory diseases represent a significant health issue for agricultural workers—who often experience pesticide exposure at higher rates due to their occupation—it is essential to understand the association between pesticide exposure and respiratory pathology. Furthermore, with a new report finding an association between air pollution and higher death rates (9 percent) related to SARS-CoV-2 (COVID-19), global leaders should eliminate excessive pesticide use to mitigate respiratory diseases' impacts on human health.

SOURCE: Liang JH et al., Biomarkers of organophosphate insecticides exposure and asthma in general US adults: findings from NHANES 1999-2018 data. *Environ Sci Pollut Res Int.* 2023 Aug;30(40): 92295-92305, Epub 2023 Jul 24. PMID: 37482592.

MORE ON THIS SUBJECT

Organophosphate Pesticides and the Link to Respiratory, Metabolic, and Heart Disease—October 18, 2023

Elevated Asthma Risk from Chlorpyrifos and Organophosphates Reported as Court Rolls Back Protections—November 8, 2023

TOXICOLOGY | IMMUNE SYSTEM EFFECTS | AUGUST 22, 2023

Illness Tied to Petrochemicals' Impact on Body's Essential Mast Cells (Immune System Regulators), Study Finds

A recently completed study (available in preprint before peer review) identifies the development of what the authors term "Toxicant-Induced Loss of Tolerance" (TILT), a constellation of symptoms associated with chemical exposures. The authors describe a two-part process. First, during initiation, a person is exposed at an acute level or repeated low-level doses to a toxicant, such as an organophosphate pesticide or a natural substance like mold, that triggers immune reactions from mast cells, which are crucial immune system regulators. Stage 2, or triggering, is when exposure to previously tolerated substances causes the mast cells to degranulate, or release many inflammatory molecules such as histamines and cytokines into the cellular environment. The work is spearheaded by Claudia B. Miller, M.D., immunology professor emeritus at the University of Texas Health Science Center at San Antonio, along with Nicholas Ashford, PhD, professor of technology at the Massachusetts Institute of Technology, and other researchers. Dr. Miller's talk on the subject is found at Beyond Pesticides 2022 National Forum site (go to 7:50 time stamp).

Western medicine, for all its spectacular successes, has tended to view the human body as separate from its environment. Further, it divides the body into various systems and zones, which, though understood to be interrelated, have their own sets of symptoms, derangements, and diseases. In addition, the discipline of toxicology—especially regulatory toxicology—until very recently has been unable to account for exposure

to multiple toxicants—pesticides, building materials, medical equipment, antibiotics, and molds—simultaneously or in series.

The last couple of decades, however, have begun to shed light on the consequences of exposure to many different chemicals that may affect different body systems and result in constellations of symptoms and disorders previously unconnected in the medical mind. Now people with what has been called Multiple Chemical Sensitivity (MCS) or Chemical Intolerance (CI) have a framework that begins to explain their problems. Some 15 percent to 36 percent of U.S. adults have reported symptoms of these disorders. Medical practitioners do not currently agree on the causes, development, or treatment of MCS/CI.

Dr. Miller finds that clinicians' "failure to ask patients about possible initiating events has caused confusion concerning the origins of other comorbid conditions such as ADHD, autism, asthma, irritable bowel syndrome, migraine headaches, depression, anxiety, brain fog, and other cognitive and mood difficulties." Moreover, Dr. Miller and colleagues note that in concurrent exposures to different toxicants, many symptoms are common to more than one, resulting in a "masking" effect. Once someone develops TILT, intolerances to structurally different chemicals may arise, ranging from pesticides and paints to anesthetics and hairdressing chemicals. Notably, women develop TILT more than men, possibly because women are more likely to use fragranced cosmetics, soaps, sprays, fragranced cleaning, and laundry products, usually in confined spaces. However, men are formally diagnosed with MCS more often, possibly reflecting medical gender bias.

In 2021, Beyond Pesticides reported on a study, "Toxicant-induced loss of tolerance for chemicals, foods, and drugs: assessing patterns of exposure behind a global phenomenon," in which the authors, including the authors on the TILT preprint study, investigated initiating events by studying eight groups with chemical intolerance who had known exposures to different toxicants: EPA workers in offices where new carpet was installed; Gulf War veterans; casino workers exposed to organophosphate pesticides; pilots and cabin crews breathing aircraft oil fumes; World Trade Center first responders and others in close proximity to the buildings; breast and other implant recipients; people exposed to mold at home; and tunnel workers breathing benzene. Among these groups, volatile organic compounds (VOCs), which were present in nearly all the toxicants studied, were the most common initiators.

Some of the most egregious exposures were suffered by military members during the Gulf War, who were required to swallow pyridostigmine bromide to help defend against possible chemical weapons. This compound's effects resemble those of organophosphate pesticides. Some 100,000 soldiers were directly exposed to sarin and cyclosarin when the U.S. blew up an Iraqi weapons depot. In addition, soldiers' uniforms were saturated with lindane, an organochlorine pesticide and member of the Stockholm Dirty Dozen now banned for U.S. agricultural use but still allowed as a second-line treatment for lice and scabies. Permethrin, a pyrethroid insecticide, which was also used on uniforms, and in combination with the insect repellent DEET (also given to soldiers), has neurotoxic effects.

In this previous study, the authors note that the post-World War II expansion of petrochemicals into pesticides, solvents, dyes, and fragrances mushroomed, and in the 1970s building construction became more airtight even as

Americans spent more and more of their time indoors—the latter proportion now at 90 percent. This has resulted in more people being exposed to a staggering array of synthetic chemicals (defined by the authors as compounds not found in nature) and molds, which release naturally-occurring VOCs.

The authors of the current study also take the medical profession and research scientists to task for two things. Many clinicians dismiss chemical sensitivities, which they label as "Medically Unexplained Symptoms" or psychosomatic issues, or "idiopathic environmental intolerance." Dr. Miller and colleagues are pushing to replace these terms with TILT. They provide two questionnaires, available on the University of Texas website, that individuals can complete and present the results to their medical caregivers. The advantage of TILT, they say, is that it provides both a suggested mechanism by which sensitivity is started and an explanation for how exposures to different toxicants result in common symptoms stemming from the activity of mast cells, which have broad influence over immune responses to many different challenges.

Scientific tunnel vision has affected the way medicine defines and diagnoses chemical intolerances. "Allergy and toxicology as currently practiced appear to have overlooked the two steps of TILT and the fact that toxic exposures can sensitize mast cells," according to the current preprint study. Mast cells are part of the innate immune system, which responds to acute or persistent infections or injuries. They signal other immune cells using the inflammatory biomarkers cytokines and chemokines. Dr. Miller and colleagues note that mast cells are present in large numbers in the gut, also home to trillions of microbes that are disrupted by antibiotics and pesticides. They add, "Future research should explore the mechanism by which exposures and/or alterations in the gut microbiome may compromise our ancient mast cells and innate cell-mediated tolerance."

The study is based on 10,981 responses to a 2020 Survey Monkey questionnaire that used the same questions as those available on the University of Texas Health Science Center website. These ask participants about medical diagnoses, exposures to chemicals, antibiotic use, and the timing of the onset of their condition. The survey also asked the participant to identify what they believed was the condition's cause.

A low-carbon civilization, relying on ecosystem-level biochemistry rather than a single protein, might both survive climate catastrophe and enjoy a drastic improvement in human health.

More than half of the respondents are women, most of them under 60. Two-thirds of respondents are unable to identify an initiating event. For respondents reporting more than one initial exposure, each additional event tripled the chance they would have TILT.

Overall, a fifth of respondents met the study criteria for TILT. The most frequent initiating exposure was reported as mold, with pesticides second, and in decreasing order, new construction or remodeling materials, medical procedures, fires, and implants. Antibiotics used for long periods to treat infections in several organs were also associated with the onset of TILT.

The researchers stress the need for "policies and practices that reduce initiating exposures as well as ubiquitous and often unavoidable triggers such as fragranced personal care, cleaning, and laundry products in multi-occupant housing, workplaces, medical settings, schools, places of worship, and all public buildings—literally anywhere air is shared."

The current study does have limitations. Although it does have a large number of participants, it is based on individual self-reporting and not a direct measurement of the physiological processes associated with TILT. The participants were not randomly selected, and there was no control group. Also, only around half of the participants could attribute their initial symptoms to a specific event. Despite these constraints, the cumulative evidence Dr. Miller has produced finds that people in large numbers are suffering the consequences of the "exponential increase in exposures to toxicants derived from fossil fuels and biological sources, coupled with reduced fresh air in buildings" and the authors conclude that "*TILT has become epidemic*." [Emphasis in original.]

Finally, Dr. Miller and colleagues emphasize that fossil fuels "are assaulting humans and other animal species both *from within* via mast cell sensitization and *from without* via climate change." [Emphasis in original.] A low-carbon civilization, relying on ecosystem-level biochemistry rather than a single protein, an insidious and harmful source of energy and materials, might both survive climate catastrophe and enjoy a drastic improvement in human health.

For more information:

- Take the questionnaires used in the studies.
- See a video from Beyond Pesticides' 2022 Virtual Seminar featuring a talk with Dr. Miller and Kaipo Kekona, an indigenous Hawaiian working to restore traditional farming techniques.
- Read a transcript of a talk given by Doris Rapp, MD published in *Pesticides and You*.
- Visit the University of Texas, San Antonio website for the Hoffman TILT program
- View a presentation by Dr. Miller at the Hoffman TILT program.

SOURCES: Claudia Miller et al., What Initiates Chemical Intolerance? Findings from a Large Population-Based Survey of U.S. Adults, *Research Square*, June 15, 2023, https://doi.org/10.21203/rs.3.rs-3064297/v1.

S. Masri,, C. Miller, et al. Toxicant-induced loss of tolerance for chemicals, foods, and drugs: assessing patterns of exposure behind a global phenomenon. *Environ Sci Eur* 33, 65 (2021). https://doi.org/10.1186/s12302-021-00504-z

TOXICOLOGY | POISONING | MARCH 23, 2023

Death Tied to 1,3-D (Telone) Fumigant Highlights Sensitivity of the Brain to Pesticide Exposure

A case report article published in *Frontiers in Public Health* confirms one of the first reported deaths from inhalation of the fumigant 1,3-dichloropropene (1,3-D or Telone) during work, resulting from acute renal (kidney) failure, hyperkalemia (high potassium levels in the blood), and brain edema (swelling). 1,3-D is a highly toxic fumigant used on a variety of crops, but primarily on potatoes, tobacco, strawberries, peanuts, and tomatoes to manage unwanted nematodes in soils. The chlorine-containing compound used in a greenhouse space entered the body of a 50-year-old man in China, being absorbed through the respiratory tract. Despite dilution from his wife, the compound was still strong enough to cause harm to human health. Without proper ventilation and personal protective equipment, he wore only a surgical mask which did not adequately defend against exposure to 1,3-D.

This case represents the broader issue of how toxic chemical compounds can enter the body, causing physiological damage. Specifically, pesticides can increase the permeability of the blood-brain barrier that filters various molecules entering the brain from the circulatory system. The permeation of pesticide molecules elevates the expression and accumulation of soluble proteins in the brain involved in neuroinflammation, which plays a critical role in neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's diseases (PD), and Huntington's diseases (HD). Therefore, cases like this highlight the importance of understanding how chemicals interact with the body to induce long-term health and disease prognosis.

A 50-year-old man, who worked in the family greenhouse, inspected the greenhouse between the hour of 10 pm to 3 am without proper ventilation, without wearing respiratory protection, and bare-chested. Before these five hours, the man's wife diluted 1,3-D with water at a 1:50 ratio and irrigated the enclosed greenhouse using the diluted 1,3-D on the floor surface at the door and a trench in the field. After application, the man entered the greenhouse alone for inspection. Upon returning home, the man began to experience headaches, dizziness, and other discomforts for three days before other symptoms arose, including blurred vision, unclear speech, and worsened dizziness. By the end of the third day, the man presented to the emergency department of a local hospital with dizziness, nonchalance (out of it), confusion, as well as newly developed irritability symptoms. Despite a cranial CT scan, the brain displayed no abnormalities on the third and fourth days. However, doctors shortly transferred the man to the ICU. By the fifth day, CT examinations showed unclear portions of the brain (sulci and cisternae), suggesting atrophic changes (wasting

or thinning of tissue) in the brain, and on day six, a craniocerebral magnetic resonance examination showed widespread enlargement of the brainstem, uneven nerve signal, and a narrowed fourth ventricle (a series of interconnected hollows within the brain that contain cerebrospinal fluid [CSF]). The brain tissue exhibited widespread swelling, the downward shifting of the cerebellar tonsil, and indistinguishable sulci (brain furrows) and cisternae (brain pouches). Additionally, the three paired main arteries that supply blood to the brain (bilateral anterior, middle, and posterior cerebral arteries) were nearly invisible.

The case determined that: "Walking in the damp climate, high temperature, and poorly ventilated greenhouses, when exposed to 1,3-dichloropropene for a short time, the patient inhaled 1, 3-dichloropropene and quickly experienced dizziness, fatigue, nausea, unconsciousness, breathing difficulties, and other symptoms. Combined with the results of the serological test and brain magnetic resonance imaging, the symptomatic presentation was consistent with the manifestation of acute 1, 3-dichloropropene poisoning."

Exposure to chemical toxicants like pesticides can cause neurotoxic effects or exacerbate preexisting chemical damage to the nervous system. The impacts of pesticides on the nervous system, including the brain, are hazardous, especially for chronically exposed individuals (e.g., farmworkers) or during critical windows of vulnerability and development (e.g., childhood, pregnancy). Mounting evidence over the past years shows that chronic exposure to sublethal (nonfatal) levels of pesticides adversely affects the central nervous system (CNS) and neural receptors, such as connections between nerves, the brain, enzymes, and DNA. Specifically, researchers identify agricultural chemical exposure as a cause of many adverse CNS impacts and neurological diseases, including Alzheimer's, amyotrophic lateral sclerosis (ALS), and Parkinson's disease. Therefore, advocates say it is essential to avoid toxic chemical exposure to lessen potential acute and chronic health risks.

Whether 1,3-D exposure is short-term or long-term, certain concentrations are harmful to the human body in a closed environment, like the greenhouse in this case. Absorption through the respiratory tract may allow the compound to cross the blood-brain barrier, depose in the brain tissue, then inhibit the central nervous system and cause diffuse brain tissue edema, leading to acute damage to the heart (including the vascular system), lung (respiratory), and kidney (renal) function, eventually resulting in death. EPA first classified 1,3-D as "likely to be carcinogenic to humans" in 1985 until the primary manufacturer, Dow Chemical Company, requested EPA conduct the current cancer reevaluation, resulting in 1,3-D downgrading from "likely" to "suggestive evidence of carcinogenicity."

For those who may consider this issue outside of their concern, note that a recent study focusing on the Western United States determined fumigant pesticides have close links to county-level cancer rates. Not only does this compound cause respiratory stimulation response and central nervous system inhibition after inhalation, but the volatile organic compound also contributes to the formation of ground-level ozone and poor air quality.

There is a lack of complete understanding of the etiology of pesticide-induced diseases, including predictable lag time between chemical exposure, health impacts, and epidemiologic data. Pesticides themselves can possess the ability to disrupt neurological function. Pesticides' impact on the nervous system, including the brain, are hazardous, especially for chronically exposed individuals or during critical windows of vulnerability and development.

SOURCE: Zhiqiang Ahou et al., Case report, Death caused by 1,3-dichloropropene, a novel fumigant used in China, *Front. Public Health,* Sec. Occupational Health and Safety, Volume 11, 15 February 2023 https://doi.org/10.3389/fpubh.2023.1088296.

MORE ON THIS SUBJECT **Pittsburgh-Area Pesticide Poisoning: InTown Suites Residents Return After Rat Poison Incident**—October 5, 2023

TOXICOLOGY | PETS | JULY 20, 2023

Despite Nearly 1,700 Pet Deaths from Seresto Pet Collars, Pesticide Product Remains on Market

Despite evidence of toxicity to pets from Seresto pet collars (manufactured with the neurotoxic insecticide flumethrin, as well as the neonicotinoid insecticide imidacloprid), the U.S. Environmental Protection Agency's (EPA) has announced that the popular flea and tick collars will remain on the market, but with new mitigation measures. However, safety advocates say that these measures will do little to protect people and pets from chemical exposure using these collars. The agency will require Elanco—the manufacturer of Seresto—to conduct enhanced reporting for various factors, including adverse symptoms, veterinary community outreach, and place warnings on the product's label. Seresto, developed by Bayer and sold by Elanco, has been linked to nearly 1,700 pet deaths, injuries to tens of thousands of animals, and harm to hundreds of people. There are nontoxic ways to protect pets from fleas and

other pests while protecting human family members.

Children Ignored by the Agency. EPA has a history of ignoring the exposure patterns to children who come into close contact with pets and their flea collars and the potential adverse health threats, opting for warnings instead of regulatory action. In 2017, EPA issued a warning for tetrachlorvinphos (TCVP) flea collars that advised: "not allowing children to play with [the] pet collars; keeping [the] spray and power products out of reach of children; and, washing hands thoroughly with soap and water after handling." Safety advocates point to the unrealistic nature of the precautions being advised, given that children come into contact with collars and other toxicants sprayed on pets when they play and sleep with their pets and through hand-to-mouth contact (ingestion). With TCVP pet collars (not pump/trigger liquid sprays), EPA announced a Notice of Intent to Cancel in October 2022 pending additional manufacturer data. In the case of Seresto collars and the synthetic pyrethoid ingredient, EPA is ignoring a plethora of studies in the independent scientific literature on adverse effects to children, including a 2022 study on prenatal and infant daily exposure effects.

EPA Opts for Warnings and More Information and Monitoring, Not Regulatory Action. EPA's multi-year scientific review of Seresto-related incidents analyzes all reports of death and injury associated with these collars from 2016 to 2020. Although EPA highlights the two percent of Seresto-related incidents that resulted in death, death-related incidents are missing critical details that prevent EPA from determining the cause. Sublethal exposure to chemicals in these pet collars can cause severe adverse effects—from pruritus (itchy skin) and dermal lesions and changes in fur to lethargy, anorexia, and neurological symptoms. Since the removal of the collar can alleviate moderate to severe clinical signs of adverse health incidence, and reapplication of the collar results in a reoccurrence of clinal symptoms, EPA will require the registrant of Seresto to implement the following measures:

Safety advocates point to the unrealistic nature of the precautions being advised, given that children come into contact with collars and other toxicants sprayed on pets when they play and sleep with their pets and through hand-to-mouth contact (ingestion).

"To alert veterinarians and consumers of potential risks, the terms of continued registration require Elanco to include label warnings on Seresto products that describe common adverse effects that have been reported, along with instructions to remove the collar if those effects occur and instructions on how to report the incident. Elanco also must develop an outreach program to more effectively communicate with veterinarians and the public on the risks of using the product and other similar pesticides on pets.

- To improve the quality of data reported when receiving reported incidents from consumers, Elanco must pursue

additional information to the greatest extent possible to ensure that complete details of each event are captured. This information includes whether the pet had any preexisting conditions or previous history of the reported condition. The Seresto pet collar registration has also been split into two registrations, one for cats and one for dogs, to make comparison of incident data across products easier in the future. Elanco must report incident and sales data to EPA on an annual basis.

- To reduce the risk of strangulation, Elanco must evaluate potential changes to the emergency release mechanism of Seresto pet collars to prevent death by strangulation or choking. The company must submit a report detailing the data and analysis collected and performed in pursuit of this effort within one year. Based on this evaluation, EPA may require a modified release mechanism for the Seresto collar.
- To allow for the continued evaluation of reported incidents, EPA has limited its current approval of Seresto collar registrations to five years. EPA will continue to evaluate Seresto incident data over that period."

Background. Seresto collars are plastic pet collars embedded with pesticides designed to kill fleas, ticks, and lice; they contain the active ingredients flumethrin and imidacloprid. Flumethrin, a chemical in the pyrethroid class of synthetic neurotoxic insecticides, has been linked repeatedly to neurological issues, such as seizures and learning disabilities in children, to gastrointestinal distress, and to damage to invertebrates, according to EPA's own analysis. However, this is not the first-time tick and flea pet products have garnered negative attention regarding pet health, as numerous flea and tick prevention products (e.g., collars, topical treatments, sprays, and dust) include pesticides such as TCVP (mentioned above), propoxur, synthetic pyrethroids, and fipronil are toxic, not just to pets and nontarget organisms, but to humans, as well.

Moreover, the agency fails to evaluate the synergistic effects of pesticides as these pest collars can contain more than one active ingredient that can work in tandem with another to exacerbate the adverse health symptoms. For instance, *USA Today* reports, "A 2012 Bayer study found [flumethrin and imidacloprid] have a 'synergistic effect,' meaning they are more toxic together on fleas…." However, a 2016 EPA bulletin concluded, "The risk of the combination of the two active ingredients, flumethrin, and imidacloprid, was not assessed because the two chemicals act in completely different ways." Therefore, the EPA does not adequately evaluate the risks and harms of exposure to multiple pesticide compounds and "inert" or "other" pesticide ingredients.

In 2021, internal emails at EPA show that career scientists at the agency expressed concern about pesticide-laced pet collars, such as the notorious Seresto flea and tick collars, but that EPA managers "instructed them to avoid documenting those worries in publicly accessible records."

EPA's review of these Seresto-related incidents highlights the agency's failure to thoroughly evaluate these products for animal safety with ongoing monitoring. In fact, in 2021, internal emails at EPA show that career scientists at the agency expressed concern about pesticide-laced pet collars, such as the notorious Seresto flea and tick collars, but that EPA managers "instructed them to avoid documenting those worries in publicly accessible records." Additionally, the 2021 internal email revelations are further and unfortunate evidence of the state of EPA's function in carrying out its fundamental mission "to protect human health and the environment." For EPA's Office of Pesticide Programs, this means protection from the broadly damaging impacts of synthetic pesticides. Beyond Pesticides has chronicled EPA's "capture" by industry influence and the corruption that has marked both agrichemical industry behavior and, occasionally, internal EPA actions, as well as specific instances of EPA failures, such as those (like the pesticide pet collars) that put children at risk, and those that continue to allow the devastation of critical species (such as pollinators), ecosystems, and fragile habitats.

Furthermore, the Center for Biological Diversity (CBD) notes that EPA has received more than 75,000 complaints about these pet collars, associating their use with problems ranging from skin irritation to death. Gizmodo puts the current count of complaints to the EPA about Seresto, since 2012, at more than 86,000—with 2,340 of those relating to pet deaths. CBD's environmental health director, Lori Ann Burd, commented that—given EPA's estimate of the ratio of pesticide incidents "in the real world" to complaints filed with EPA as roughly 5:1—a sensible extrapolation is that many more pets wearing Seresto collars have been hurt or have died than are represented by reports filed with the agency. Karen McCormack, a retired EPA scientist and communications officer, notes that these collars have generated the greatest number of incident reports of any pesticide product in her long experience. She says, "EPA appears to be turning a blind eye to this problem, and after seven years of an increasing number of incidents, they are telling the public that they are continuing to monitor the situation. But I think this is a significant problem that needs to be addressed sooner rather than later."

SOURCE: D. Stanneck et al., The synergistic action of imidacloprid and flumethrin and their release kinetics from collars applied for ectoparasite control in dogs and cats. *Parasites Vectors* 5, 73 (2012). https://doi.org/10.1186/1756-3305-5-73.

TOXICOLOGY | EXPOSURE | JANUARY 4, 2023

Neonicotinoid Insecticides Add to the Growing List of Chemicals that Transfer between Mother and Fetus

A study published in *Environmental Science and Technology* finds neonicotinoids (neonics) and their breakdown products (metabolites), like other chemical pesticide compounds, can readily transfer from mother to fetus. The National Health and Nutrition Examination Survey (NHANES) finds U.S. pregnant women experience frequent exposure to environmental pollutants that pose serious health risks to both mother and newborn. Many known pollutants (e.g., heavy metals, polychlorinated biphenyl, and pesticides) are chemicals that can move from the mother to the developing fetus at higher exposure rates. Hence, prenatal exposure to these chemicals may increase the prevalence of birth-related health consequences like natal abnormalities and learning/developmental disabilities. Children are particularly vulnerable to the impacts of pesticide exposure as their developing bodies cannot adequately combat exposure effects. Moreover, a mother's pesticide exposure can have a stronger association with health disorders than childhood exposure, and a newborn can still encounter pesticides. Therefore, it is essential to understand how pesticides impact the health and well-being of individuals during critical developmental periods.

Beyond Pesticides has covered a variety of pregnancy risks from pesticides and other toxic chemicals, including these in just the last three years: pesticides and children's sleep disorders; prenatal exposures to a multitude of chemicals; insecticides and childhood leukemia; insecticides and Attention Deficit/Hyperactivity Disorder.

The study evaluates the transplacental transfer rates (TTR) of neonics from mother to fetus via prenatal exposure. Researchers collected 95 paired samples from mothers' serum (MS) and accompanying (umbilical) cord serum (CS) to measure the levels of five neonics (acetamiprid, imidacloprid, clothianidin, thiacloprid, and thiamethoxam) and two metabolites of acetamiprid and imidacloprid. After calculating the transplacental transfer efficiencies (TTEs) of each neonic and metabolite, researchers focus on three chemical mechanisms: passive diffusion, active transport, and pinocytosis. Lastly, a multilinear regression analysis explores the association between blood biomarkers for neonics in mothers and related birth outcomes among fetuses.

The most abundant neonic in MS and CS samples is imidacloprid, whereas acetamiprid's metabolite is the most abundant in CS and MS. Both parent and metabolite neonics have a high TTE, with imidacloprid having the highest transfer rate (1.61). Even the neonic with the lowest TTE of 0.81, thiamethoxam, is within the high TTE range, indicating proficient placental transfer of

these chemicals from mother to fetus. Researchers identify that transplacental transfer of these chemicals mainly occurs through passive mechanisms depending on chemical structure. Therefore, neonics like acetamiprid and thiacloprid (known as cyanoamidines) have higher TTE values than neonics like clothianidin and thiamethoxam (known as nitroguanidines). Lastly, multilinear regression demonstrates that most neonics in MS samples have associations with blood biomarkers related to hepatotoxicity (liver toxicity) and renal (kidney) toxicity.

Studies find pesticide compounds in the mother's blood can transfer to the fetus via the umbilical cord. A 2021 study finds pregnant women already have over 100 chemicals in blood and umbilical cord samples, including banned persistent organic pollutants. However, 89 percent of these chemical contaminants are from unidentified sources, lack adequate information, or were not previously detectable in humans. Since the first few weeks of pregnancy are the most vulnerable periods of fetal development, exposure to toxicants can have much more severe implications. A 2020 study finds prenatal pesticide exposure can increase the risk of the rare fetal disorder holoprosencephaly. This disorder prevents the embryonic forebrain from developing into two separate hemispheres. Moreover, women living near agricultural areas experience higher exposure rates increasing the risk of neonatal abnormalities like acute lymphoblastic leukemia and Attention-Deficit/Hyperactivity Disorder (ADHD).

Over the past 20 years, neonicotinoids have replaced four major chemical classes of insecticides in the global market (organophosphates, carbamates, phenyl-pyrazoles, and pyrethroids). These highly toxic systemic agricultural pesticides resemble nicotine and affect the central nervous system of insects, resulting in paralysis and death, even at low doses. Like other pesticides, neonics readily contaminate water and food resources as traditional wastewater treatments typically fail to remove the chemical from tap water, and the systemic nature of neonics allows the chemical to accumulate within treated plants. According to the Centers for Disease Control and Prevention (CDC), nearly half the U.S. population encounters at least one type of neonic daily, with children ages three to five having the highest exposure risk. Health impacts of exposure to neonics include neurotoxicity, reproductive disorders, liver/kidney damage, and an increase in gene expression and enzyme production linked to hormone-dependent breast cancer.

Studies find pesticide compounds in the mother's blood can transfer to the fetus via the umbilical cord. A 2021 study finds pregnant women already have over 100 chemicals in blood and umbilical cord samples, including banned POPs. However, 89 percent of these chemical contaminants are from unidentified sources, lack adequate information, or were not previously detectable in humans.

Although previous studies demonstrate pesticide classes like pyrethroids, organophosphate, carbamates, and organochlorines readily transfer from mother to fetus, this study is among the first to document and identify the occurrence and distribution specific to neonics in MS and CS. This finding supports long-known concepts regarding the hazards of pesticides for children's health. Early life exposures during "critical windows of vulnerability" can predict the likelihood or otherwise increase the chances of an individual suffering a range of pernicious diseases. In addition to findings on learning and development, early life exposures have links to increased risks of cancer, asthma, birth disorders, among others. Thus, a parent's exposure to pesticides during these critical periods indicates an increased risk in childhood disease.

Pesticide exposure not only poses a risk to mothers and their subsequent offspring but also to future generations. Current-use pesticides and metabolites (or breakdown products) of many long-banned pesticides still cause adverse effects. These negative effects can continue into childhood and adulthood and may have multigenerational consequences. Researchers at Drexel University report that higher levels of some organochlorine compounds, like DDT (its breakdown product DDE), during pregnancy are associated with autism spectrum disorder (ASD) and intellectual disabilities. Although the U.S. bans many organochlorine compounds, the ongoing poisoning and contamination underscore the pervasiveness and persistence of these chemicals, as well as their continued adverse impact on human health. Moreover, these exposures have real, tangible effects on society. Environmental disease in children costs an estimated $76.8 billion annually. Exposure that harms learning and development also impacts future economic growth in the form of lost brain power, racking up a debt to society in the hundreds of billions of dollars.

The study concludes, "This is the first study to associate maternal hematological parameters with p-NEOs [parent neonics] or their metabolites in MS, and further studies with larger sample sizes are needed to confirm our findings. […]A recent study reported that urinary IMI [imidacloprid] and ACE [acetamiprid] concentrations in pregnant women (n = 296) were significantly negatively associated with neonatal HC. This finding implied the influence of NEOs on cognitive and neurologic development in neonates."

SOURCE: D. Stanneck et al., Neonicotinoid Insecticides and Their Metabolites Can Pass through the Human Placenta Unimpeded, *Environ. Sci. Technol.* 2022, 56, 23, 17143–17152, https://doi.org/10.1021/acs.est.2c06091

TOXICOLOGY | EXPOSURE | MAY 4, 2023

Report Adds to Evidence of Widespread PFAS Contamination; Calls for Removal of Products

One of the most widely used insecticides in California, Intrepid 2F, contains harmful levels of per- and polyfluoroalkyl substances (PFAS), or "forever chemicals," according to a report by the Center for Biological Diversity (CBD) and Public Employees for Environmental Responsibility (PEER). In fact, 40 percent of pesticide products in the report tested positive for high levels of PFAS. PFAS are common in nonstick cookware, cleaning/personal care products, food packaging, and other consumer products. However, these compounds are also in pesticide products. Despite evidence on the dangers of PFAS stretching as far back as the 1950s, federal agencies sat on the sidelines as the plastics industry continued adding the material to new products. From their widespread presence in farm fields and sewage sludge to contaminated water bodies throughout the U.S., PFAS have made its way into the environment and our bodies. PFAS are even present in remote environments like the Arctic, Antarctica, and Eastern European Tibetan Plateau. A study published in 2020 identified PFAS as common chemicals to which U.S. residents are exposed daily.

The U.S. Centers for Disease Control and Prevention (CDC) determined that 98 percent of U.S. residents have some level of PFAS in their bloodstream, with studies reporting that PFAS compounds are detectable in infants, children, and pregnant women. With health risks including developmental, metabolic, cardiovascular, and reproductive harm, cancer, damage to the liver, kidneys, and respiratory system, as well as the potential to increase the chance of disease infection and severity, PFAS presents a chronic danger to people that demands urgent regulatory action. CBD and PEER submitted the test results to EPA and the California Department of Pesticide Regulation (CDPR), advising the agencies to remove these pesticide products from the market until contaminants from supply lines can be removed.

Despite evidence on the dangers of PFAS stretching as far back as the 1950s, federal agencies sat on the sidelines as the plastics industry continued adding the material to new products.

CBD authorized independent, certified lab testing on seven agricultural pesticides with common uses in California to determine the parts per trillion (ppt) of PFAS in pesticide products. The insecticide product Malathion 5EC (active ingredient: malathion) contains 510 ppt perfluorooctanoic acid (PFOA) and 680 ppt perfluoroheptanesulfonic acid (PFHpS), with a PFOA level over 100,000 times higher than the level

EPA considers acceptable in drinking water (0.004 ppt). The insecticide Oberon 2SC (active ingredient: spiromesifin) contains 1,500 ppt perfluorobutanoic acid (PFBA), and Intrepid 2F (active ingredient: methoxyfenozide) contains 50 ppt of perfluorobutanesulfonic acid (PFBS).

PFAS are a group of nearly 10,000 human-made chemicals in various consumer products that people use daily. Although some PFAS compound manufacturing has ceased, these chemicals last forever in the environment as their chemical structure makes them resistant to breakdown. Thus, PFAS contamination is significantly underreported and much more pervasive than previously thought, polluting storage and transportation containers, food and water resources, and other chemical products. For instance, many reports address the high levels of PFAS contamination in the mosquito insecticide Anvil 10+10. Not only is the public exposed to such chemicals, but those who work in factories that create products that include PFAS, or workers who use them regularly, have higher cumulative exposures. Across multiple states, firefighters have begun to bring lawsuits against manufacturers of the foams, charging that the companies knowingly made and sold products with these forever chemicals that put the workers' health at risk. Others at greater-than-average exposure risk include pregnant or lactating people and young children.

Although EPA does not regulate PFAS in pesticide formulations, the agency lists these substances in the inert ingredient database, and product labels do not require disclosure of contaminants fundamental to pesticide products as a result of the manufacturing or packaging process. The ongoing detection of PFAS in various environments and soils also threatens the ability of growers, including organic growers, to produce food that does not harbor these compounds. PFAS do not break down in the environment and are detectable in more than 330 animal species globally, including species at extinction risk. PFAS chemical residues persist in food and drinking water, with over six million U.S. residents regularly encountering drinking water with PFAS levels above the EPA health advisory of 70 ng/L. Therefore, PFAS are detectable in almost all of the U.S. population—disproportionately afflicting people of color communities—and have implications for human health.

Ubiquitous environmental contaminants, like PFAS, have severe consequences, especially on the health of vulnerable individuals. Various pesticide products act similarly to PFAS.

Nathan Donley, PhD, environmental health science director at CBD, states, "I can't imagine anything that could make these products any more dangerous than they already are, but apparently, my imagination isn't big enough. […] The EPA has to take control of this situation and remove pesticide products that are contaminated with these extremely dangerous, persistent chemicals."

Although EPA considers that the primary source of PFAS contamination in pesticides is PFBS and PFHpS leaching from fluorinated containers, they are not known to leach. Thus, this report indicates that PFAS contamination of agricultural pesticide products comes from additional unknown sources. For instance, PFAS in rainwater, surface water, and soil exceeds the planetary boundary for chemical pollution, contaminating above EPA's proposed guideline levels, and exceeding safe limits for humanity.

Despite reductions in the global emissions for PFAS compounds the environmental persistence and hydrological cycling of these toxic chemicals make them an ever-present source of contamination, especially as PFAS compounds do not break down in the environment. Studies from the past year highlight:

1. "Levels of PFOA and PFOS in rainwater often greatly exceed US Environmental Protection Agency (EPA) Lifetime Drinking Water Health Advisory levels, and the sum of the aforementioned four PFAAs (Σ4 PFAS) in rainwater is often above Danish drinking water limit values also based on Σ4 PFAS;
2. Levels of PFOS in rainwater are often above Environmental Quality Standard for Inland European Union Surface Water; and
3. Atmospheric deposition also leads to global soils being ubiquitously contaminated, and to be often above proposed Dutch guideline values."

PEER's science policy director Kyla Bennett, PhD cautions, "While communities around the country are struggling to remove PFAS from their drinking-water supplies, we are spraying millions of acres of our land with the same toxic chemicals. […] It's nonsensical; we can't protect our drinking water unless and until we get PFAS out of all pesticides."

Ubiquitous environmental contaminants, like PFAS, have severe consequences, especially on the health of vulnerable individuals. Various pesticide products act similarly to PFAS. Individuals can encounter these substances simultaneously, resulting in more severe health outcomes. Therefore, advocates urge that policies enforce stricter pesticide regulations and increase research on the long-term impacts of pesticide exposure. Many states are issuing regulatory limits on various PFAS in drinking water, groundwater, and soil. However, safety advocates urge EPA to require complete product testing and disclosure of ingredients for proper PFAS regulation and identify the unreasonableness of exposure to toxic pesticides by citing the productivity and profitability of organic and ecological pest management practices.

SOURCE: Eurofins Lancaster Laboratories Environment Testing, LLC, *Analytical Report: PFAS Pesticide Testing*, 3-28-2023, PFAS Pesticide Testing (biologicaldiversity.org)

TOXICOLOGY | EXPOSURE | OCTOBER 31, 2023

Hidden Volatile Organic Compounds (VOCs) in Indoor Air Cause Adverse Effects

With cooler weather setting in and people heading indoors and closing windows, the issue of COVID-19 transmission escalates, as do concerns about toxic chemicals filling the indoor ambient air. As a recent segment of *60 Minutes* (October 29, 2023) stresses, COVID-19 transmissions elevated public concern and understanding about the importance of ventilation, filtration, and air exchange to indoor air quality. Unfortunately, the concerns about indoor air are not limited to COVID-19 as volatile organic compounds (VOCs) invade most spaces where people live and work. These invisible toxic substances can be found in common household products, furniture, mattresses, and more, including pesticides in and around the house. Recognizing the risks associated with VOCs and the potentially hazardous off-gassing process is crucial for protecting public health.

VOC ingredients in pesticide products are typically withheld from product labels, hidden under the general category of "inerts" or "other" in the ingredients panel. However, the undisclosed pesticide ingredients may cause adverse biological or chemical activity.

VOCs are a group of chemicals that can easily vaporize into the air at room temperature. These compounds are found in many everyday items, including furniture, cleaning products, pesticides, cosmetics, and even air fresheners. Some household products, particularly pesticides, can introduce their own set of risks in addition to the risks they pose due to their VOC content. VOCs can range from harmless to harmful, and their presence can have a significant impact on indoor air quality. VOCs encompass a wide range of chemicals, including formaldehyde, polyurethane foam, phthalates, acetone, and benzene.

VOC ingredients in pesticide products are typically withheld from product labels, hidden under the general category of "inerts" or "other" in the ingredients panel. Manufacturers claim the ingredients to be proprietary and are not required to be disclosed to the consumer under federal pesticide law because the companies argue that they are not in the product formulation to attack the target pest. However, the undisclosed pesticide ingredients may cause adverse biological or chemical activity. This issue has sparked controversy, as environmental and health advocates have unsuccessfully attempted to

change U.S. Environmental Protection Agency (EPA) policy under the *Federal Insecticide, Fungicide, and Rodenticide Act*, which regulates pesticides in the U.S.

While VOC exposure is not a new issue, there is a renewed sense of urgency to improve indoor air quality following notable studies by Joe Allen, PhD, of Harvard University, and Linsey Marr, PhD, of Virginia Polytechnic Institute, which have highlighted the pivotal role of subpar indoor air ventilation systems in increasing the spread of COVID-19. Namely, the studies finds that the aerosolized particles containing the virus were able to spread throughout indoor rooms and increase infection rates without proper air exchange rates. In a demonstration by Dr. Marr, she visualizes how exhaled breath traveled in all directions in a room with stagnant air flow, leading to the increased airborne transmission of COVID and other airborne illnesses. Then, she shows how exhaled breath travels upwards in a uniform path inside a properly ventilated room, showing how the risk of spread decreases significantly under these conditions.

These findings are significant in the context of harmful VOCs in indoor spaces. As most indoor spaces meet bare minimum requirements of air circulation and refresh rates, places like living spaces and school classrooms are especially susceptible to locking in and spreading harmful VOCs and illnesses alike.

Poor ventilation indoors can exacerbate symptoms of VOC exposure. Short-term exposure symptoms include headaches, dizziness, nausea, and irritation of the eyes, nose, and throat. Prolonged exposure to harmful VOCs can result in more severe health problems, including damage to the kidney, liver, and central nervous system. Some VOCs are classified as carcinogens, increasing the risk of conditions like lung cancer.

These effects are exacerbated by a process called off-gassing, which is of critical concern when it comes to VOCs and furniture. It refers to the process by which materials containing VOCs release these chemicals into the air over time. Off-gassing is particularly prevalent in new furniture, as the VOCs have not yet been released, leading to higher emission rates.

The primary sources of off-gassing in homes are plywood and particle board furniture (which often contain formaldehyde), electronic devices, mattresses, carpets, couches, paint, and construction materials found in newly built homes. Plywood and wood furniture are especially significant contributors to off-gassing because they are highly porous, absorbing substantial amounts of VOCs. This high porosity results in a prolonged release of these harmful compounds into the indoor environment, making them notable culprits in diminishing indoor air quality.

The off-gassing process is especially concerning, given that EPA has expressed concerns about VOCs due to their potential health impacts. According to information on the EPA's website, a study called the "Total Exposure Assessment Methodology (TEAM) Study," which was completed in 1985, discovered that approximately a dozen common organic pollutants were two to five times more concentrated inside homes compared to outdoor environments. This held true regardless of whether the homes were situated in rural or highly industrial areas. The TEAM studies also reveal that when people use products containing organic chemicals, they can expose themselves and others to high levels of pollutants. Even after the activity is finished, these elevated concentrations can persist in the air. The New York State Department of Health also addresses this issue in its publication titled "Volatile Organic Compounds (VOCs) in Commonly Used Products."

The widespread presence of these harmful chemicals in furniture and other household goods can be traced back to California's old flame retardant regulations. In 1975, California implemented a regulation requiring all upholstered furniture in the state to contain flame-retardant chemicals. As California was a substantial market, manufacturers opted to adopt these standards for furniture sold nationwide, which led to the pervasive use of these toxic chemicals.

The chemicals used in flame retardants have been linked to cancer, endocrine disruption, neurobehavioral function issues, and adverse effects on fetal development. Eventually, this regulation was revised under the California flammability standard. SB 1019, which passed in 2014, allows furniture manufacturers to cease using harmful flame retardant chemicals in polyurethane foam, offering a safer option for consumers. Furniture manufactured after January 1, 2015 is less likely to contain these harmful flame retardants, while products purchased between 1975 and 2014 may expose families to these toxic chemicals.

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However, other harmful VOCs are still present in furniture and other household items. Newborns and infants are especially vulnerable to the effects of the resulting off-gassing, as their developing bodies are more sensitive to environmental toxins. Mattresses and baby items can emit harmful VOCs, potentially affecting the health and well-being of children. Parents should exercise caution when choosing products for their nurseries and opt for those labeled with Greenguard certifications, which indicate low or no levels of hazardous VOCs.

Despite the well-documented adverse effects of certain VOCs that permeate

household products, EPA refrains from implementing regulations concerning these chemicals within the home. This is in stark contrast to their oversight of outdoor air quality, where VOCs are regulated. EPA maintains that its jurisdiction does not extend to indoor air quality and it regulates only under section 183(e) of the *Clean Air Act* (Act), while states have plans approved by the agency.

EPA explicitly notes that "[E]ven if we had the authority to regulate indoor air quality, it would be difficult to regulate household (or other) products because we have no authority to collect information on the chemical content of products in the marketplace (nor does any Federal Agency)."

In fact, EPA has a history of approving harmful aerosol air sanitizer pesticides for use against COVID-19 and other bacteria and viruses. In October 2022, EPA approved 32 varieties of a new pesticide for air sanitizers. The formulation contained 14 percent dipropylene glycol, with the other 86 percent of the formulation not specified. This action, while intended to decrease pathogens in indoor air, fails to do so by not taking into account that disinfectants and sanitizers emit VOCs and negatively affect the immune system, thus reducing resistance to disease. Instead of exercising jurisdiction over improving indoor air ventilation, EPA turned to harmful pesticides once again, putting people with preexisting conditions, the elderly, and children at elevated risk from exposure.

Therefore, given the lack of protective action from government agencies, it is crucial to make informed choices and protect families. Consider these steps when shopping for furniture and household items:

1. Check Labels: With pressed-wood products, look for furniture items that meet ultra-low emitting formaldehyde (ULEF) or no added formaldehyde (NAF) standards. Products labeled as "Zero VOC" and "Low VOC" are also safer choices.
2. Look for organic furniture and mattresses that are certified free from VOCs and flame retardants. With mattresses, check whether materials meet the Global Organic Textile Standard.
3. Increase Ventilation: Proper ventilation can help reduce indoor air pollution. Ensure your living space is well-ventilated, particularly when introducing new furniture or items.
4. Filter Your Air: Air purifiers with activated carbon filters can help remove VOCs from the air, improving indoor air quality.
5. Choose Safer Alternatives: When possible, opt for solid wood furniture, used furniture that has had time to air out, and electronic devices with low VOC emissions.

Products containing harmful VOCs or flame retardants can be disposed of responsibly, such as disposing of them at hazardous waste facilities or contacting manufacturers. Some manufacturers offer take-back programs for their products, which can be an environmentally responsible way to dispose of old items.

SOURCE: Jon LaPook, Indoor air systems crucial to curbing spread of viruses, aerosol researchers say, 60 minutes, CBS News, 10-29-2023, Indoor air systems crucial to curbing spread of viruses, aerosol researchers say—CBS News

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Train Tragedy Highlights Law's Failure to End Use of Needless Toxic Pesticides and Co-formulants

The February 3 derailment of a Norfolk Southern train in Ohio has been huge news. Less well known perhaps is that 20 of the 50 cars involved were carrying hazardous materials, defined by the National Transportation Safety Board as "cargo that could pose any kind of danger 'including flammables, combustibles, or environmental risks.'" The incident resulted in a huge fire, evacuations, and worries about explosions and discharge of toxic chemical gases; on February 6, officials conducted "controlled releases" of some of the chemicals. Some of the toxic chemicals involved are precursors to production of synthetic pesticides.

[Eds. Note: We are deeply concerned for the victims of this terrible crisis who are asking legitimate questions about contaminated drinking water and the effects of both the initial acute exposure after the derailment, resulting in the release of toxic chemicals, and long-term exposure to low levels of toxic residues in homes and the environment.]

Among the compounds on board those 20 cars were "inert" pesticide ingredients (vinyl chloride, ethylhexyl acrylate, and isobutylene), an antimicrobial compound (ethylene glycol monobutyl ether [EGBE]), benzene (a carcinogenic solvent), and butyl acrylate. This event brings into high relief the cradle-to-grave issues that travel with pesticide (and broad chemical) dependency, including disasters such as this one, and subsequent threats to health and the environment—which are never part of the U.S. Environmental Protection Agency's (EPA) calculus in registering pesticides. The Ohio derailment also adds to the case for getting off the toxic pesticide treadmill, which would reduce transport of such compounds.

Air quality readings within a mile of the site began soon after the event.

Evacuation orders were lifted on February 8 because officials indicated that air quality was safe enough for people to return to their homes. *The Washington Post* reports that environmental officials, as of February 14, were saying that ongoing "air monitoring done for the railroad and by government agencies—including testing inside nearly 400 homes—hasn't detected dangerous levels in the area since residents were allowed to return. The U.S. Environmental Protection Agency has shared air monitoring results online."

Nevertheless, some residents continue to have concerns not only about contaminated air, but about potential contamination of their drinking water; Ohio Environmental Protection Agency officials insist the water has been protected and is safe. Yet, others, including Ohio Governor Mike DeWine, delivered a different message, leading to heightened confusion and frustration among residents. As *The New York Times* (*NYT*) reported, "State officials have continued to recommend that some residents drink bottled water as testing continues in private wells, municipal water, and streams, and fears have percolated over the possible dangers of long-term exposure to the chemicals."

Understandably, area residents are worried about toxic chemicals in their air or water or soils. And as with many concerning public events, social media has spread both sound information and some that is decidedly not. In speaking to *The Washington Post*, one resident summed up what many people are feeling and thinking: "For a small town, we have to trust them [i.e., officials], because what else do we have to do? We have to trust that they are not lying to us." The paper quoted Peter DeCarlo, an environmental health professor at Johns Hopkins University: "The biggest question remaining is what, if anything, is still being released from the site, first and foremost. If there are still residual chemical emissions, then that still presents a danger for people in the area."

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Indeed, just prior to publication of this *Daily News* article, the *NYT* reported that hundreds of residents gathered in a school gym on the evening of February 15 for what had been billed as a "town hall" meeting about the disastrous event. But Norfolk Southern officials failed to show up, and the format was changed to one of state, county, and local agency officials sitting at separate tables around the room and fielding individual questions so that the whole group was not privy to the questions or answers. None of this went over well with the crowd, which was animated in demanding answers to their concerns and angry at railroad officials' absence; the mayor ultimately switched back to a town hall format.

The *NYT* elaborated: "We have become increasingly concerned about the growing physical threat to our employees and members of the community around this event stemming from the increasing likelihood of the participation of outside parties, a spokesman for the railroad company

said, though the nature or origin of the threats was unclear. The spokesman added: 'We are not going anywhere. We are committed to East Palestine and will continue to respond to community concerns.' On Wednesday, that was clearly not enough to satisfy the throngs of people gathered in the gym, who shouted demands to know where the company was. Citing the statement from the company, one man stood up and declared, 'We're scared, too.'"

Possibly caused by an overheated wheel bearing, the derailment in East Palestine, Ohio (near the Pennsylvania border) has been described by some experts as a potentially huge, unfolding environmental disaster, with much about the health and environmental impacts still to be determined via ongoing investigations. The incident looms as even more alarming, given that at least one train derails every day in the U.S. Although most trains carry multiple kinds of cargo—the Norfolk Southern had frozen vegetables, autos, and medical cotton balls on board—they also typically have one or more hazardous materials in tow. According to *The Guardian*, "About 4.5m tons of toxic chemicals are shipped by rail each year and an average of 12,000 rail cars carrying hazardous materials pass through cities and towns each day, according to the U.S. Department of Transportation." In 2022, train accidents resulted in releases of hazardous chemicals 11 times, down from 20 times in 2018 and 2020.

Perhaps the most memorable recent rail disaster was the 2013 explosion and fire from 72 rail tankers of petroleum crude oil that erupted in Lac-Megantic, Quebec (near the western Maine border). In that event, 47 people died and 26,000 gallons of oil contaminated the Chaudiere River. Also in 2013, a crude oil train exploded on collision with a derailed train full of grain; luckily, this happened in a relatively unpopulated North Dakota area. 2005 saw the crash, in South Carolina, of a train carrying chlorine gas (a chemical highly poisonous to skin and the respiratory tract).

California's worst train debacle happened in 1991 near Dunsmuir, when roughly 19,000 gallons of metam sodium, a highly toxic pesticide still used as a fungicide and herbicide, flowed into the Sacramento River near the iconic Mt. Shasta. Nearly every living organism in a 38-mile stretch of the river died from the chemical's toxicity; fortunately, the river and its inhabitants were largely restored within three to four years, according to California Department of Fish and Game spokesperson Mark Stopher. These are just a handful of transportation accidents that released toxic chemicals, harming (and sometimes killing) people, and contaminating the environment.

Rail has often been considered preferable to (and cheaper than) trucking or flying. Long-haul trains, after all, do much of their travel through non- or less-populated areas, whereas trucks on crowded highways present their own significant safety risks, and planes filled with toxic chemicals would be, more or less, flying bombs.

The menu of toxic chemicals on board the Norfolk Southern train was an unsavory one. Of greatest concern has been vinyl chloride, a highly flammable compound used to make polyvinyl chloride (PVC) plastics; when exposed to sunlight, it generates toxic gases, including formaldehyde. When burned, vinyl chloride becomes hydrogen chloride and phosgene; the latter is a deadly gas that was used in World War I chemical warfare and is used in the manufacture of plastics and pesticides.

To boot, any vinyl chloride that seeped into the trench soil can persist for long periods and continue to volatilize, and can migrate into groundwater. Exposure to it has acute effects on people, and can lead to cardiovascular, developmental, hepatic, and immune problems, and to some nasty cancers. After three rounds of evacuation efforts, the five cars carrying it were breached by emergency responders who discharged the chemical to a trench and burned it.

Northeast University environmental toxicologist Kimberly Garrett, PhD explained the extreme concern about phosgene: "It disrupts the interaction between the lungs and the bloodstream. It makes it so oxygen can't get into the blood and carbon dioxide can't get out." The wildlife deaths in the area, including fish, squirrels, turtles, and foxes, were likely caused by phosgene. She added, "The risk of exploding was so high and the consequences so severe that it's better to do it under controlled conditions," and suggested that, because of the potential for long-term effects of vinyl chloride (with its carcinogenic impacts) migrating into groundwater (where it is notoriously difficult to clean up), officials likely opted for one of two bad options—a controlled burn rather than the explosive and migratory risks of leaving it alone.

Butyl acrylate is an explosive and flammable liquid used in manufacturing sealants, adhesives, and paints; it can lead to skin, eye, and respiratory irritation. Ethylhexyl acrylate is used similarly, and can cause the same kinds of irritation, as well as gastrointestinal problems if ingested; it is also a potential human carcinogen. Ethylene glycol monobutyl ether (EGBE) is neurotoxic; it can lead to irritation of the skin, nose, and throat, damage to red blood cells, hepatic, renal, and reproductive harms, and vomiting after exposure. Isobutylene is used in many industrial applications, is highly flammable, and is neurotoxic.

One might reasonably wonder why such dangerous chemicals (some of which are on their way to becoming pesticides) are allowed to be transported by rail through populated areas and vulnerable environments alike. The reality is that this is the chemically dependent state of the world (and for pesticides, of most agriculture and land management).

The manufacture of pesticides and plastics (and many other products) requires that toxic chemicals be transported . . . somehow.

Rail has often been considered preferable to (and cheaper than) trucking or flying. Long-haul trains, after all, do much of their travel through non- or less-populated areas, whereas trucks on crowded highways present their own significant safety risks, and planes filled with toxic chemicals would be, more or less, flying bombs (and a very pricey form of transport). In the wake of this tragic derailment, some public health advocates say it should be a wake-up call on the potential for far-more-deadly freight rail accidents, particularly in light of the petrochemicals (e.g., ethanol and other fuels) and their chemical derivatives that are transported by rail.

The Guardian reports, "By one estimate, 25 million Americans live in an oil train blast zone, and had the derailment occurred just a few miles east, it would be burning in downtown Pittsburgh, with tens of thousands of residents in immediate danger. Ineffective oversight and a largely self-monitoring industry that has cut the nation's rail workforce to the bone in recent years as it puts record profits over safety is responsible for the wreck, said Ron Kaminkow, an Amtrak locomotive engineer and former Norfolk Southern freight engineer.

"The Palestine wreck is the tip of the iceberg and a red flag," said Mr. Kaminkow, who is secretary for the Railroad Workers United, a nonprofit labor group that coordinates with the nation's rail unions. 'If something is not done, then it's going to get worse, and the next derailment could be cataclysmic.'"

These toxic chemicals are generally deemed necessary to "modern life." But there are, at least for pesticides and their precursor and ingredient compounds, other and better options. One would be for EPA to take into account, in its evaluation of pesticides for registration, the very real cradle-to-grave issues related to pesticide use—including transportation disasters that seriously threaten health and the environment.

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The *Federal Insecticide, Fungicide, and Rodenticide Act* (FIFRA)—the base federal statute that controls pesticide regulation—requires that pesticide use "will not generally cause unreasonable adverse effects on the environment." The statute defines "unreasonable adverse effects," in part, as "any unreasonable risk to man [*sic*] or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide."

A protective reading of this statute and definition would cause EPA to evaluate such risks from "cradle to grave," meaning from the sourcing of chemical ingredients through their manufacture, transportation, use, and ultimate disposal. The disaster in Ohio is a glaring example of EPA's failure to use a protective and precautionary approach; instead, the agency's history often shows an industry-friendly reluctance to do so.

SOURCE: Department of Environmental Protection, State of Pennsylvania, *East Palestine Train Derailment: What DEP Is Doing*, Ohio Train Derailment (pa.gov)

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Office of the Inspector General Slams EPA for Betraying Scientific Integrity . . . Again

A report from the Office of the Inspector General (OIG) for the U.S. Environmental Protection Agency (EPA) identifies the most recent event in the very long chronicle of EPA dysfunction that—put charitably—constitutes failures to enact its mission, and more accurately, sometimes crosses the line into malfeasance. In the report, OIG concludes that EPA's 2021 PFBS Toxicity Assessment failed to "uphold the agency's commitments to scientific integrity and information quality," and that the agency's actions "left the public vulnerable to potential negative impacts on human health." PFBS (perfluorobutane sulfonic acid) is a member of a larger group of per- and polyfluorinated substances (PFAS). As reported by *The Guardian*, "Trump administration appointees at . . . EPA meddled in agency science to weaken the toxicity assessment of a dangerous chemical." Last year, Beyond Pesticides' concerns about the myriad risks and harms of pesticides intersected with those about the PFAS family of chemical compounds, when a study found very high levels of PFAS in multiple pesticide products.

The EPA OIG explains why it undertook the evaluation that led to this report: "[T]o determine whether the EPA followed applicable policies and procedures to develop and publish the January 19, 2021 perfluorobutane sulfonic acid toxicity assessment. Two weeks after publication, the EPA removed the toxicity assessment from its website, citing political interference and Scientific Integrity Policy violations. . . . The EPA's Scientific Integrity Policy, established in 2012, states that science is the backbone of the EPA's decision making and that the Agency depends on the integrity of its science to protect human health and the environment. All EPA employees—including scientists, managers, and political appointees—must follow the Scientific Integrity Policy."

PFBS is one of thousands of PFAS "forever chemicals" that are emerging as a ubiquitous and serious threat to human and organismic health. These compounds do not break down in the environment, and can move through soils, contaminate water resources, and bioaccumulate in aquatic and terrestrial organisms. *The Guardian* writes that PFBS "is toxic at low levels. Research has linked the chemical to kidney disease, reproductive problems and thyroid damage, and it has been found throughout the environment, including in an estimated 860,000 Americans' drinking water."

Concurrent with the recent Biden administration's EPA announcement of new proposed federal standards for PFAS compounds in drinking water, the Environmental Working Group published an interactive map of the nearly 3,000 (and rising) number of sites in the U.S. (and two territories) contaminated by PFAS chemicals. EPA warned, in June 2022, that PFAS

compounds, linked to reproductive, immune, cardiovascular, and endocrine (especially thyroid) anomalies and to several kinds of cancer, are an even greater health threat than was previously known. Many advocates have noted that the proposed new federal standards are still inadequate because they are less stringent than the interim advisory levels for safe consumption EPA set out last year—lifetime exposures of no more than 0.004 to 0.02 ppt (parts per trillion), depending on the type of PFAS compound.

The OIG report notes "unprecedented" interference on the part of Trump EPA Administrator Andrew Wheeler and other political appointees in the PFBS assessment. At the 11th hour, Mr. Wheeler ordered the insertion of a range of toxicity values, rather than a specific limit. The compromised assessment, which would have guided drinking water standards for the chemical, as well as targets that polluters would need to meet in pollution cleanup—thus, allowing companies to remediate PFBS to higher, more-dangerous levels—was published just four days prior to the inauguration of President Biden. The OIG report notes that, "The new numbers were inserted without being fully scientifically vetted, and they lacked 'technical and quality assurance review.'" Kyla Bennett, PhD, of Public Employees for Environmental Responsibility (PEER), notes that "[t]hey were trying so hard to get [the assessment] out before Trump left office."

The Biden administration yanked the 2021 PFBS assessment in February 2021 because of its determination that there had been political interference. According to *The Guardian*, it was republished several months later "using what it said is sound science, and declared it had resolved the issue." But some EPA scientists related to the newspaper that "several employees willingly worked with the Trump appointees to weaken the assessment, and they were never reprimanded or fired. The scientists say the controversy is part of a deeper problem afflicting EPA: industry influence on career staff, and an unwillingness from the EPA to address it.

"'The issue is part of the larger rot at the agency of career staff working with industry to weaken the EPA,' a current agency scientist familiar with the situation said. The scientist did not use their name for fear of reprisal."

After the 2021 assessment was pulled, the Biden administration declared in a statement that the EPA evaluation of PFBS had been "compromised by political interference as well as infringement of authorship." *The Guardian* reports that, "During its review, the administration took no action against career employees who implemented the political appointees' changes. Those employees 'made the changes happily,' according to [Dr.] Bennett, but remained at the agency."

According to *The Guardian's* coverage, internal emails from the ebbing days of the Trump EPA, as well as comments in the OIG report, indicate that career employees in the agency's OCSPP [Office of Chemical Safety and Pollution Prevention] either asked for the toxicity metric changes or did not object to them. Reportedly, the sole career employee who opposed the order for changes to the PFBS assessment was Orme-Zavaleta, who told *The Guardian* that Administrator Wheeler's order "flew in the face of scientific integrity." Former EPA scientist Betsy Southerland told the paper that the changes were "something that industry has always wanted."

Beyond Pesticides has repeatedly highlighted the too-cozy relationship between the chemical industry and EPA, with particular attention to the impacts on EPA's registration and regulation of pesticides. A 2021 press release on a letter sent to the Biden Administration by Beyond Pesticides and PEER (with 35 other groups) summarized the issues: "The Office of Pesticides Programs within the U.S. Environmental Protection Agency has become so captured by industry that it has lost sight of its health and environmental mission. . . . [T]he groups are urging the Biden administration to adopt reforms within OPP to ensure pesticide approval and use decisions are science-based." It continues, "Inside OPP [EPA's Office of Pesticide Programs], marginalization of science remains cause for celebration and the result has been repeated ecological and public health disasters. . . . The letter recounts a litany of improper pesticide approval decisions, some of which were blocked in court, while still others are being reversed under Biden. But the groups say these cases are symptomatic of a larger institutional illness that calls for thoroughgoing reforms. The cumulative effects of years and decades of this regulatory abuse are untold human deaths, disabilities, and illnesses. Industry has been forced to pay out billions of dollars for damages claims over OPP-approved products. The groups also point to the decline of pollinators—the key to American food security—due to the indiscriminate application of highly potent pesticides. The health of non-target wildlife, as well as our soil and waters, is under chemical siege."

Beyond Pesticides has covered many of the transgressions of EPA during the Trump administration, including those related to pesticides (e.g., dicamba, pyrifos), scientific integrity, lack of transparency and accountability, poor enforcement of regulations, and water protection, among others. Investigative journalists Cary Gillam, Sharon Lerner, and PEER have all bird-dogged EPA on its chemical and pesticide policies and regulations; Beyond Pesticides has featured their work (and others') in various *Daily News* entries. See, for example, coverage on EPA's ongoing failures and malfeasance: EPA reliance on industry research; the "revolving door" between industry and EPA; chemical industry influence on the agency; the corrupt alteration of scientific information, as related to the pesticide dicamba; and so many instances of EPA disregarding scientifically demonstrable harms that they cannot reasonably be listed here.

Beyond Pesticides' three-part series, based in part on Ms. Lerner's work, goes directly to these issues: undermining of EPA function by industry influence, the susceptibility of EPA officials and managers to corrupt behavior, and the ongoing failure of the agency to align

its efforts with its own 2012 Scientific Integrity Policy, here and here. Further, the many transgressions of the Trump EPA are a dramatic demonstration of how whipsawed EPA's operations and approach can be with the advent of administrations whose politics harbor animus toward regulation—even though the agency's job is to protect human and environmental health.

As is the practice for the offices of federal Inspectors General in reports on their internal agency investigations, the EPA OIG made recommendations to the agency. Three of those are directed to the Assistant Administrator for Research and Development; they (1) "aim to reduce procedural confusion and strengthen existing policies, procedures, and guidance by clarifying if and when comments expressing scientific disagreement can be expressed; (2) making clear if and when toxicity ranges are acceptable; and (3) using the OIG as a resource for high-profile scientific integrity concerns that relate to political interference or that assert risk to human health or the environment." Another is directed to the assistant administrator for Mission Support: "to update policies and procedures on environmental information quality to require additional quality assurance reviews for EPA products." The last goes to the deputy administrator of EPA: "to strengthen the EPA's culture of scientific integrity, transparency, and accountability of political leadership actions when changes occur as a result of policy decisions."

Whether and how EPA chooses to adopt these recommendations remains to be seen. Yet even this OIG report—though potentially helpful in righting EPA's ship—does not address the comprehensive overhaul needed at EPA to ensure it pursues its mission with integrity, based in science, and with protection of health and environment at the helm.

As Beyond Pesticides recently wrote, "[EPA's] track record, on so many pesticides [and chemicals broadly], is to deal with one compound (under a narrow range of circumstances and/or narrow time frame and/or specific exposure levels) at a time. Beyond Pesticides has dubbed this the 'whack-a-mole' struggle on pesticides. Each regulatory baby step at EPA, each judicial settlement or knock-down of a particular pesticide, each bit of research demonstrating harms—these represent small, incremental advances on a pesticide [and broad "chemical saturation"] problem that is vast in scope. But this approach is wholly inadequate to the devastation that [dangerous chemicals] are causing, and it continues the "collision course" we are on re: human health and well-being, biodiversity collapse, and the climate crisis. A precautionary approach . . . is far more suited to the task of genuinely protecting public health and the environment."

SOURCE: Office of Inspector General, U.S. Environmental Protection Agency, *The EPA's January 2021 PFBS Toxicity Assessment Did Not Uphold the Agency's Commitments to Scientific Integrity and Information Quality*, Report no. 23-E-0013, March 7, 2023.

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Int'l Group of Scientists Calls for Restraints on Conflicts of Interest in Publications and Regulation

Drawing on a recent gathering of international scientists, a group of 34 scientists published a call for much stricter scrutiny of researchers' conflicts of interest by agencies that regulate and register chemicals, with recommendations for the newly formed Intergovernmental Science Policy Panel. Writing in *Environmental Science & Technology*, the authors, led by Andreas Schäffer, PhD of Aachen University in Germany and Martin Scheringer, DSc of Masaryk University in the Czech Republic, cite an abundance of examples of chemical companies and their trade associations manufacturing doubt via an array of techniques, resulting in agencies such as the U.S. Environmental Protection Agency (EPA) dropping certain provisions from rulemaking, ignoring scientific consensus, and keeping chemicals on the market—and in the environment—that many scientists say should be entirely banned. The authors produced the article in response to this webinar to discuss how to ensure that United Nations' panels dealing with global crises get the most sound scientific advice conducted by the International Panel on Chemical Pollution.

Over the last four decades or so, the notion that conflicts of interest affect the validity of scientific research and professional opinions has been steadily eroded. Regulators wallow in compromised research, hamstrung by political pressure and pinched funding even as they face some 350,000 chemicals registered for use globally, only a tiny fraction of which have been tested for safety. Arguments in favor of enforcing rigorous conflict of interest (COI) policies in evaluation and registration of pesticides and other industrial chemicals have been repeatedly emphasized in scientific journals and the press, yet almost nothing has reduced the amount of industry influence over that process. In 2022, the United Nations Environment Assembly decided to create a new advisory group called the Intergovernmental Science Policy Panel to provide expert advice to the U.N.'s existing intergovernmental panels on climate change and biodiversity.

The problem of industry interference applies to almost every industrial

chemical, including pesticides, pharmaceuticals, plastics, flame retardants, and asbestos. The tactics remain the same across fields, and are derived from the campaigns waged by climate deniers, tobacco companies, and fossil fuel companies as detailed in 2010 in Merchants of Doubt by Naomi Oreskes and Erik M. Conway.

One of the most obvious routes to affect policy, namely lobbying, cost chemical interests $65.9 million in 2022, according to an Open Secrets report. The American Chemistry Council's pressure on legislators accounted for $19.8 million of that.

But more subtle industry influences also pervade the regulatory process. There are at least 24 strategies industry uses to disguise its conflicts of interest and further its economic goals, according to Rebecca Goldberg and Laura Vandenberg, researchers at the University of Massachusetts Amherst. These include, the authors write, "'revolving doors' between a regulatory authority and the industry it is meant to regulate; reliance for safety data on unpublished industry documents while largely ignoring publications by independent scientists; and covert influence by the industry." They also often threaten lawsuits against researchers whose work conflicts with their goals.

More types of industry manipulation were offered in 2019 by Xaver Baur, MD, Colin Soskolne, PhD, and Lisa Bero, PhD in *Environmental Health*: Practices of corporate malfeasance include the orchestrated contamination of editorial boards of peer-reviewed scientific journals with industry apologists; interference with activities of national regulatory bodies and international review panels engaged in safeguarding occupational and public health; constructing roadblocks by capitalizing on uncertainty to undermine scientific consensus for much-needed government regulation of carcinogenic, endocrine-disrupting and/or immunotoxic agents; promoting "causation" criteria that lack foundation and effectively block workers' access to legal remedies for harms from occupational exposures resulting in morbidity and premature mortality; and violating standards of professional conduct by seducing reputable scientists with financial incentives that make them beholden to corporate agendas.

And yet another perspective on the problem was offered by University of Notre Dame biologist Jason Rohr, PhD in a 2021 article: The first tool is shaping science, which is the art of creating research to produce a desired outcome, often referred to as outcome-oriented research. When efforts to shape science fail, advocates will often attempt to hide science associated with unwelcome information or attack this science by launching illegitimate critiques in an effort to turn reliable science into "junk" [references omitted]. To discourage future damaging research, advocates will also harass or bully scientists who produce damaging research. Packaging science is the art of assembling an expert group to advance a favored outcome, whereas spinning science is the art of manipulating public perception about credible science.

For a painful example of the personal toll such practices take on individual scientists, read Herbert Needleman's (MD) 1992 story of persecution by fossil fuel interests when he published research showing that inner-city children's teeth contained high levels of lead. This was 14 years *after* lead was banned in paint, but just the beginning of the fight to further reduce children's lead exposure, which has seen considerable

success. However, the lead industry was still lobbying against regulation by 1996, and today there are still nearly half a million U.S. children with elevated levels.

Beyond Pesticides has covered many aspects of industry influence at EPA, FDA, USDA and other regulatory agencies. See the organization's 2017 commentary for more details. That year Beyond Pesticides also critiqued the nomination of Michael L. Dourson, PhD to be assistant administrator for chemical safety on the grounds that he had spent years "helping companies resist constraints on their use of potentially toxic compounds in consumer products." Dr. Dourson founded a consultancy whose clients included Dow Chemical Company, Koch Industries, Inc. and Chevron Corporation. His research funders included the American Chemistry Council, which endorsed his EPA nomination. However, vigorous resistance from Beyond Pesticides and many other advocate groups and unflattering press coverage led Dr. Dourson to withdraw his nomination. Thus, the revolving door did not operate as intended this time.

Pesticide regulation is a major target for industry influence. For example, the herbicide atrazine, which EPA acknowledges is an endocrine disrupter, is very common in U.S drinking water. The E.U. banned it in 2004, but it remains the second most-used herbicide in the U.S. Atrazine's manufacturer, Syngenta, notoriously attacked University of California Berkeley professor and researcher Tyrone Hayes, PhD, when he published results of atrazine's hormonal effects on frogs. The company went so far as to hire a public relations flack to gin up rumors about Hayes's mental health in order to discredit his work.

One of industry's most appalling successes has been keeping asbestos on the market despite reams of evidence that it is extremely damaging to humans, causing mesothelioma, asbestosis, and other respiratory diseases, and it has been associated with ovarian, colorectal, stomach and pharyngeal cancers. In an especially scurrilous turn of events, from 2012 to 2016 an international corporate intelligence firm called K2 hired a former television producer to misrepresent himself as a crusading filmmaker eager to document the tragic effects of asbestos in India. The firm was working for asbestos interests. The so-called filmmaker, Robert Moore, ingratiated himself with anti-asbestos activists, recording phone calls and meetings and reporting to K2. The World Health Organization hired him to make a film called "Victims of Chrysotile Asbestos." The whole story unraveled in court in 2018, but even this outrage did not overcome industry influence. EPA tried to ban asbestos in the U.S. in 1989 but caved to political pressure from the George H.W. Bush administration. It remains importable and usable in the U.S. today.

Not all biases create conflicts of interest. The Schäffer group distinguishes three different conditions that affect scientific validity, namely conflicts of interest, bias and just plain interest. The latter two are unavoidable, as they arise from professional obligations or participation in the work of activist groups advocating for public health. The authors cite the Intergovernmental Panel on Climate Change's definition of bias as "a point of view or perspective" that "every expert holds" by virtue of his or her expertise. They support IPCC's statement that "Holding a view that one believes to be correct, but that one does not stand to gain from personally, is not a conflict of interest." In contrast, a true conflict derives from "a direct and material gain" in the form of money, political loyalties, or social connections. The conflicts that do the real damage are those associated with for-profit entities, their linked nonprofit trade groups, and the consultancies they hire. Money, prestige and power are tempting rewards.

Funding source has been identified numerous times as an indicator of industry influence. For example, a 2016 analysis of 39 studies of atrazine's effects on reproduction found that only 9.1 percent of industry-funded studies showed evidence of harm, compared to 50 percent of non-industry sponsored studies.

In the late 1990s bisphenol A (BPA) was shown to disrupt prostate development in animals. After these results were successfully replicated, the American Plastics Council paid the Harvard Center for Risk Analysis to produce an argument that the evidence of endocrine disruption was very weak. A subsequent analysis of the BPA literature by Frederick vom Saal, PhD and Claude Hughes, MD, PhD revealed that the 19 studies considered by Harvard were a small and cherry-picked fraction of the full range of studies available. Further, Drs. vom Saal and Hughes showed that out of 115 *in vivo* studies conducted by academic scientists, 94 found evidence of significant effects at low doses, yet none of the industry studies did so.

Clearly there has not been widespread progress on eliminating corporate and industrial interests' influence on chemical policies, including pesticides. But the body of evidence is large and eloquent. The newly-formed Intergovernmental Science Policy Panel proposes that its own membership be subject to rigorous conflict of interest disclosure and that experts who have such conflicts should participate only as observers. To ensure that the panel's work is "transparent, impartial, credible and scientifically robust," as specified by the United Nations resolution establishing the panel, monitoring by an independent audit team is typically needed for credibility. If scientists who are free of industry tentacles join with environmental groups and the global public to push back against manipulation and misinformation, progress will be achieved.

SOURCE: Andreas Schäffer et al., Conflicts of Interest in the Assessment of Chemicals, Waste, and Pollution, *Environ. Sci. Technol.* 2023, *57*, 48, 19066–19077, https://doi.org/10.1021/acs.est.3c04213.

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TOXICOLOGY | ELEVATED RISK AT GOLF COURSES | MARCH 22, 2023

Pesticide Dangers at Golf Courses Much Higher in the U.S. than Europe, Study Finds

Pesticide use on golf courses in the United States poses significantly more risk to human health than those in Europe, according to a study published in Science of the Total Environment. The findings highlight yet another area of land management where the U.S. is dangerously behind the European Union, as these countries are set to ban pesticides in parks, playgrounds, and playing fields, and have established a 50 percent reduction goal for agriculture by 2030.

Researchers found that pesticide risks from golf courses in the U.S. were on average 15 times higher than those in the EU. In order to come to that conclusion, surveys were sent out to courses in eight regions: East Texas, Florida, the Midwest, Northeast, and Northwest in the U.S., and the United Kingdom, Denmark, and Norway in Europe. Recorded answers (including product applied, date, rate, and area of application) were incorporated into the development of a hazard quotient (HQ), a ratio of pesticide exposure to a chemical's toxicity. High hazard quotients indicate high acute risks to human health.

The highest single HQ for a golf course was found in Florida at 40,806. While the region with the highest average hazard quotient was U.S. Northwest at 13,696, with the lowest found in Norway and Denmark at 64. In East Texas and Florida pesticide greens represented the greatest risk, but in all other locations fairways had the highest HQ. Fungicides pose the greatest health risk in Florida, the Midwest, Northeast, and Norway, while herbicides filled this role in East Texas, the Northwest, and Denmark. Insecticides posed the greatest risk for golf courses in the UK.

As the study explains, "Golf courses in regulatory environments where <100 pesticide products were available had a median CWA-HQ [component-weighted-average hazard quotient) of 248, which was significantly lower than mean pesticide risk on golf courses located in regulatory environments which allowed >100 pesticide products, which had a mean CWA-HQ of 7031."

"The risk based system used by the EPA has led to a much higher number of pesticides being available for golf courses in the US," the study notes.

SOURCE: MAH Bekken et al., Analyzing golf course pesticide risk across the US and Europe—The importance of regulatory environment. *Sci Total Environ.* 2023 May 20; 874:162498. https://doi:10.1016/j.scitotenv.2023.162498.