Toxicological Aspects of Pesticides

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Abstract In 2022, 3.7 million tons of pesticide active ingredients were used worldwide, about 50% in the Americas. Pesticides are primarily used in agriculture, but also to control disease insect vectors, domestic pests, and home gardening, among other uses. General population is exposed to pesticides mainly through the consumption of treated food. Dietary intake assessment can be performed for specific population groups, such as toddlers, teenagers, and seniors, considering chronic and/or acute exposure, and may be combined with residential and water exposure. Most dietary exposure assessments conducted worldwide indicate no health risks to consumers. The primary exposure route of pesticides for the occupational population is through skin contact, which occurs mainly from spilling pesticides and drifting while mixing or applying pesticides. Epidemiological studies have shown an association between pesticide exposure and various diseases, mainly cancer, although there is a lack of consensus among scientists on the link between pesticide exposure and cancer. The environment can also be affected by pesticide use, as the products may move off-site via spray drift, leaching, and runoff and affect non--target aquatic and terrestrial organisms. Pesticides with high-water solubility and *mobility have the potential* to reach groundwater, *and those with low mobility* have a tendency to remain in soil/sediments, but they can reach water systems through superficial runoff. Exposure of the biota to pesticides at sublethal levels during the embryonic period may interfere with the development and survival of embryos and hatchlings, with a potential impact on population survival, biodiversity, and ecological equilibrium.

Keywords Toxicity · Dietary exposure · Occupational exposure · Environment · Biota

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1 Definition of Main Terms in Toxicology

Acceptable daily intake (ADI) or reference dose (RfD)—Estimated maximum amount of an agent, expressed on a body mass basis, to which individuals in a (sub)population may be exposed daily over their lifetimes without appreciable health risk.

Active ingredient—Component responsible for the biological effects of pesticides.

Acute/short-term exposure—Exposure of short duration, normally a single event or during the period of 24 h.

Acute reference dose (ARfD)—Estimate of the amount of a substance in food and/or drinking water, normally expressed on a body-weight basis, that can be ingested in a period of 24 h or less, without appreciable health risk to the consumer, on the basis of all the known facts at the time of the evaluation.

Adverse effect—Change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.

Benchmark dose (BMDL)—Statistically calculated lower 95% confidence limit on the dose that produces a defined response (usually 5 or 10%) of an adverse effect compared to background.

Bioaccumulation—Progressive increase in the amount of a substance in an organism or part of an organism that occurs because the rate of intake exceeds the organism's ability to remove the substance from the body.

Biodegradation—breakdown of a substance catalyzed by enzymes in vitro *or* in vivo.

Codex Alimentarius—Collection of internationally adopted food standards drawn up by the Codex Alimentarius Commission, the principal body implementing the joint FAO/WHO Food Standards Program.

Chronic/long-term exposure—Continued exposure or exposures occurring over an extended period of time, or a significant fraction of the test species' or of the group of individuals', or of the population's lifetime.

Effective concentration (EC)—Concentration of a substance that causes a defined magnitude of response in a given system. EC50 is the median concentration that causes 50% of maximal response.

Ecotoxicologically relevant concentration (ERC)—Concentration of a pesticide (active ingredient, formulations, and relevant metabolites) that is likely to affect a determinable ecological characteristic of an exposed system.

Estimated/expected environmental concentration (EEC)—Predicted concentration of a substance, typically a pesticide, within an environmental compartment based on estimates of quantities released, discharge patterns, and inherent disposition of the substance (fate and distribution) as well as the nature of the specific receiving ecosystems.

Good agricultural practice (GAP) in the use of pesticides—Nationally authorized safe uses of pesticides under actual conditions necessary for effective and reliable pest control.

Half-life, $t_{1/2}$—Time required for the concentration of a substance in a given reaction to reach a value that is the arithmetic mean of its initial and final (equilibrium) values.

Hazard—Set of inherent properties of a substance, mixture of substances, or a process involving substances that, under production, usage, or disposal conditions, make it capable of causing adverse effects to organisms or the environment, depending on the degree of exposure; in other words, it is a source of danger.

Hazard quotient (HQ)—Ratio of toxicant exposure to a reference value regarded as corresponding to a threshold of toxicity. A hazard quotient of less than 1.0 indicates that no adverse effects are likely over a lifetime of exposure.

Lethal concentration (LC_{50})—Statistically derived median concentration of a substance in an environmental medium expected to kill 50% of organisms in a given population under a defined set of conditions.

Lethal dose (LD_{50})—Statistically derived median dose of a chemical or physical agent (radiation) expected to kill 50% of organisms in a given population under a defined set of conditions.

Maximum residue limit (MRL)—Maximum contents of a pesticide residue (mg kg^{-1}) to be legally permitted in or on food commodities and animal feeds. MRLs are based on data obtained following good agricultural practice. Foods derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable.

Non-target organism—Organism affected by a pesticide, although not the intended object of its use.

No-observed-adverse-effect concentration or level (NOAEC/NOAEL)—Greatest concentration or dose of a substance which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of an organism under defined conditions of exposure.

Octan-1-ol–water partition coefficient, Kow—Ratio of the solubility of a chemical in octan-1-ol divided by its solubility in water.

Pesticide residue—Any substance or mixture of substances found in humans or animals or in food and water following use of a pesticide: the term includes any specified derivatives, such as degradation and conversion products, metabolites, reaction products, and impurities considered to be of toxicological significance.

Risk—Probability of adverse effects caused under specified circumstances by an agent in an organism, a population, or an ecological system.

Safety/uncertainty factor—Value used in extrapolation from experimental animals to man (assuming that man may be more sensitive) or from selected individuals to the general population. For example, a value applied to the no-observed-adverse-effect-level (NOAEL) to derive an acceptable daily intake (ADI) or tolerable daily intake (TDI).

2 Human Exposure to Pesticides

In 2022, 3.7 million tons of pesticide active ingredients were used worldwide, and Brazil was the world's largest user, with 801 ktons of pesticide applications, followed by the United States of America (468 kt) (FAO 2024). Among the top 10 users, China, Colombia, Vietnam, and Brazil had the highest use per crop land area (16.7 to 11.6 kg ai/ha) (FAO 2024). The proportion of the population involved in agricultural activities varies widely around the world, ranging from <1% (e.g., Belgium, Israel, Singapore) to over 50% in African countries (WPR 2025). Pesticide use occurs in rural and urban areas, during the production, storage, and transport of food commodities, in wood production, for the control of human disease insect vectors, in domestic settings for killing nuisance pests, in home gardening, and in veterinary medicine. Some pesticide products are also used directly on humans for lice and mite control (WHO 2006a).

Adverse health effects due to pesticides can occur after short-term (acute) up to long-term (chronic) exposure, which can occur through three main routes—oral, dermal, and respiratory (inhalation). Although all populations are exposed to some extent to all routes, oral exposure is primarily relevant to the general population, mainly through the consumption of treated food and contaminated water, and dermal and inhalation routes are more relevant to the occupational population. In addition to the use of pesticides during farming, occupational activities that are sources for pesticide exposure include public health campaigns to control insect-borne diseases, wood preservation, park maintenance, and pesticide manufacture (Gangemi et al. 2016). Additionally, the general population can be exposed to domestic and residential pesticides (e.g., treatment of insects or weeds in the garden), and non-occupational exposure can occur to those living in agricultural areas or residences nearby.

The level of pesticide exposure can be estimated by measuring concentrations in food, water, residential and occupational environments to which a population or an individual is in contact (external exposure approach), or to monitor the levels of pesticides, and/or their metabolites, in biological samples (internal exposure approach).

2.1 Oral Exposure to Pesticides

Human exposure to pesticides starts in the uterus because of the mother's exposure to these compounds from all sources (dietary, environmental, residential, and, in some cases, occupational), continues during lactation in early infancy and throughout life, mainly from the consumption of treated food.

The dietary risks from exposure to pesticides can be estimated within the context of the risk (or safety) assessment process, which also includes hazard identification and characterization, and risk characterization steps (IPCS 2009). Pesticide dietary

risk assessment is conducted at the international level by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) (FAO and WHO 2025) and by national or regional authorities within the regulatory process (Humphrey et al. 2017). Pesticide dietary risk assessment conducted by the JMPR supports the establishment of maximum residue limits (MRL) by the Codex Alimentarius, which has the objective of guaranteeing a fair international trade of food commodities and safe food to consumers (Codex Alimentarius 2018).

In the identification/hazard characterization steps, the no-observed-adverse-effect level (NOAEL) found for the identified critical effect, usually in animal model (mostly rodents), is divided by a safety factor, generally 100, which accounts for the extrapolation between the rodent specie to human (10x) and the variability within the human species (10x) to derive the accepted daily intake (ADI) or reference dose (RfD) for chronic exposure and the acute reference dose (ARfD) for acute exposure (WHO 2015).

The exposure assessment (dietary intake) is estimated using information on food consumption per body weight (bw) for a given population and the levels of pesticide residues in the food, according to Eq. (1).

$$\text{Intake} = \frac{\text{food consumption X pesticide residue concentration}}{\text{body weight}} \tag{1}$$

The estimation can be performed for the total population, or for specific population groups, such as toddlers, teenagers, and seniors, who have different dietary patterns. The estimation can consider long-term (chronic, lifetime) and/or short-term (acute, within 24 h) exposure. More recently, a less-than-lifetime exposure has also been considered (FAO & WHO JMPR 2025).

Food consumption information can be obtained at a population level from food production statistics, which represent foods available for consumption by the whole population, typically in the form in which the food is produced, and include the 17 GEMS/Food Cluster Diets used by the JMPR to estimate pesticide dietary exposure at international level (Caldas 2017; FAO and WHO 2025). However, more refined data can be obtained through household budget and individual food consumption surveys conducted at the national level (Valsta et al. 2017).

Pesticide residue data in food to estimate dietary intake can be obtained from various sources. For chronic exposure, MRL can be used in a tier 1 approach, although it greatly overestimates the exposure. The MRL reflects the maximum level of a pesticide expected to be found in a food when treated according to most critical Good Agricultural Practice (cGAP), including a maximum application rate, and the shortest application and post-harvest intervals. Using MRL as a proxy for concentration of the residue in Eq. (1) assumes a daily consumption of all foods for which the pesticide is registered, that all foods contain residue levels at the MRL, and that there is no degradation of the pesticide during transport, storage, or food processing (e.g., peeling, milling, cooking) (IPCS 2009). The JMPR uses the supervised trial median residue (STMR) from trials conducted according to the cGAP to estimate the International Estimated Daily Intake (IEDI) for chronic exposure to

pesticides at the international level, and STMR and/or HR (highest residue) to estimate the International Estimate of Short-Term Intake (IESTI) for acute exposure (Ambrus 2016; FAO and WHO 2025). At the national or regional level, the best approach is to use pesticide residue monitoring data (Boon et al. 2015; Sieke et al. 2018; Jardim et al. 2018a, b; EFSA 2022).

Exposure assessment can be performed for a single pesticide or a group of compounds with the same mechanism of action or based on common effect on target organ/system (cumulative dietary exposure), and may be combined with other routes (aggregate exposure, which includes residential and water) (IPCS 2009; US EPA 2001; Caldas 2023). The Environmental Protection Agency of the United States (US EPA) has established cumulative assessment groups (CAGs) based on mechanism of action for organophosphorus, N-methyl carbamates, pyrethrins/pyrethroids, triazines, and chloroacetanilides (US EPA 2025), and a CAG for triazole compounds was proposed by the European Food Safety Authority (EFSA 2009). Some authors grouped nicotinoid pesticides (Chang et al. 2018a), dithiocarbamates (Jardim et al. 2018a; Sieke et al. 2018), and succinate dehydrogenase inhibitors (Trenteseaux et al. 2024). More recently, CAGs based on the common effects of pesticides have been developed by the EFSA, such as for cranium facial alterations (29 pesticides and metabolites, such as triazoles, dithiocarbamates, organophosphorus, and 2,4-D; EFSA 2022), nervous system effects (up to 119 compounds; EFSA 2020a), thyroid effects (up to 128 compounds; EFSA 2020b) and liver steatosis (144 compounds; Crépet et al. 2019).

The dietary intake can be estimated using deterministic (point estimate) or probabilistic approaches. In the deterministic approach, a single value for each parameter in Eq. (1) is used for the estimation. For chronic exposure, the mean food consumption and body weight, and mean or median pesticide residue values are used, and the intakes from each food are added to calculate the dietary exposure. The JMPR uses the deterministic approach to estimate chronic (IEDI) and acute exposures (IESTI). The IEDI is the summation of the intakes from the consumption of all foods for which an MRL was recommended, using the 17 Cluster diets and the STMR values. The IESTI is calculated for each food crop using the 97.5th percentile of a consumption distribution (provided by national authorities) and the highest residue (HR) or the STMR value from supervised trials (FAO and WHO 2025). In the IESTI, a variability factor (equal to 3) of the residues in individual units of a food (e.g., apple) is also considered by the JMPR.

In the probabilistic approach to estimate dietary exposure to pesticides, at least one variable is represented by a distribution of values, rather than a single value, and a total dietary intake distribution (chronic or acute) is generated after several thousand iterations. This approach represents a more refined and realistic assessment as it considers individual members of the population who experience different levels of exposure, mainly due to personal dietary preferences (IPCS 2009). There are many models used for probabilistic dietary exposure to pesticides, including the Monte Carlo Risk Assessment (MCRA) software, developed by Biometris, Wageningen University and Research Centre, and the National Institute for Public Health and the Environment (RIVM) in the Netherlands (MCRA 2024), and the DEEM (Dietary

Exposure Evaluation Model)/CALENDEX™–FCID developed by the US EPA (2018a).

The last step of the dietary risk assessment of pesticides is the risk characterization, when the estimated intake is compared with the Health-Based Guidance Values (HBGV), the ADI, or the RfD for chronic exposure and ARfD for acute exposure. Risk may exist when the intake exceeds the ADI/RfD and/or the ARfD. When a cumulative assessment is performed, the ADI or ARfD is one of the CAG index compound (Caldas 2023). When the probabilistic approach is used in the exposure assessment, a given percentile of the intake distribution (normally higher than 95th) is used for the risk characterization. Another approach is to consider all the pesticides together, regardless of the mechanism of action or effect, and to estimate the hazard index (HI); risk may exist when the HI is higher than 1 (Larsson et al. 2018).

Another approach to characterize the risk from exposure to pesticides is to divide the toxicological parameter, normally the benchmark dose (BMDL), by the total intake to estimate the margin of exposure (MOE) or total margin of exposure (MOET). Risk may exist when the MOE/MOET is lower than a target value (Colnot and Dekant 2017; EFSA 2022). This approach is used by the US EPA to estimate the cumulative/aggregated exposure to pesticides using probabilistic models (US EPA 2017). For the CAG of pyrethroids/pyrethrins (deltamethrin as index compound), the minimum MOE at the 99.9th percentile (dietary and residential acute exposures) was 420 for children (1 to 2 years) and 810 for adults, higher than the target levels of 300 and 100, respectively, indicating no potential risks. For the N-methyl carbamate CAG (oxamyl as index compound), the MOE at the 99.9th percentile (dietary, residential, and water acute exposures) was approximately 8 for all populations, lower than the target value of 10. Food was the primary source of exposure in both cases, followed by residential and water (from surface water sources) (US EPA 2007).

Table 1 summarizes some dietary risk assessment studies conducted worldwide and by the JMPR using different approaches (probabilistic, deterministic, cumulative with different CAGs) and scenarios (acute or chronic). The exposure was below the HBGV (ADI, RfD, ARfD), or above the threshold for the MOE or MOET, or the HI was below one, indicating no health concern, except for the IEST estimated by the JMPR in 2024, which was higher than the ARfD for three compounds in various crops.

Exposure to pesticides from different sources can also be estimated by analyzing biological samples for pesticides and their metabolites (internal exposure), mainly urine. With this purpose, Sinha and Banda (2018) analyzed dialkyl phosphate metabolites (DAP) of organophosphorus pesticides (OP) in urine samples from 377 Indian children aged 6 to 15 years. Girls showed higher DAP detection frequency than boys, and those aged 11 to 15 years had significantly higher mean levels than boys (4.98 and 2.48 μmol L^{-1}, respectively), probably due to their higher fruit consumption. DAP levels found in this study were much higher than what was found in Canada, USA, and Italy (< 0.4 μmol L^{-1}; Sinha and Banda 2018). Using literature data on the urinary DAP excretion in various countries (occupational and environmental exposure), Katsikantami et al. (2019) estimated the highest intake of OP for

Table 1 Summary results of dietary risk assessment of pesticides conducted worldwide[a]

Country, reference	Method; model	Pesticide or CAG	Results
China, Li et al. (2017)	Probabilistic/ cumulative; MCRA[b] (F&V)	Organophosphorus and carbamates	Up to 36.6% ARfD (<7 to >18 years)
Brazil, Jardim et al. (2018a, b)	Probabilistic/ cumulative; MCRA[b]	Organophosphorus	36% ARfD
		Carbamates	9% ARfD
		Pyrethroids	2% ARfD
		Triazoles	0.9% ADI; 0.5%ARfD[c]
		Dithiocarbamates	5.3% ADI
USA, Chang et al. (2018a)	Probabilistic/ cumulative; MIXTRAN[b] (F&V)	Neocotinoids	35% RfD (chronic)
Europe, EFSA (2022)	Probabilistic/ cumulative SAS®	CAG for craniofacial alterations	MOET at P99.9 > 100
Denmark, Larsson et al. (2018)	Deterministic/ cumulative, HI	42 pesticides	43.6% ADI (4–6 years) 15.9% ADI (adults)
Germany, Sieke et al. (2018)	Probabilistic; MCRA[b]	Dithiocarbamates Imazalil Chlorpyrifos	32% ADI 46% ADI; 23% ARfD 21% ADI; 99% ARfD
France, Trenteseaux et al. (2024)	Deterministic and probabilistic, cumulative, HI	Succinate dehydrogenase inhibitors	HI = 0.12 MOE at P99.9 > 100
International FAO & WHO JMPR (2025)	Deterministic		
	IEDI (17 Cluster diets)	25 pesticides	From 0 to 100% ADI
	IESTI (STMR or HR)	19 pesticides	>% ARfD for fenpyroximate, phosmet, and pydiflumetofen (various crops)

ADI accepted daily intake, *ARfD* acute reference dose, *RfD* reference dose, *CAG* cumulative assessment group, *MOE* margin of exposure, *MOET* total margin of exposure, *IEDI* International Estimated Daily Intake Estimation, *IESTI* International Estimate of Short-Term Intake

[a]Unless specified, individual consumption and monitoring residue data were considered to estimate the intake for the total population, and include all foods for which data are available

[b]Risk characterization performed at 99.9th percentile of the intake distribution

[c]For women of child-bearing age

farmers, followed by children and pregnant women; in all cases, the hazard index was below 1, indicating no health concerns.

Yusà et al. (2022) reviewed 12 studies published between 2011 and 2021 that analyzed the biomarkers of OP and pyrethroid in the urine of the Spanish population. Between 65% and 100% of the samples analyzed contained OP biomarkers, and the pyrethroid metabolite 3-phenoxybenzoic acid was present in more than 65% of the samples. The mean Hazard Quotient (HQ), used as a metric for the individual risk, ranged from 0.0006 (glyphosate) to 0.93 in farm workers (parathion), indicating no potential health risk (HQ < 1).

2.2 Dermal and Inhalation Exposures to Pesticides

The main exposure route for occupational pesticide users is through skin contact, which occurs from spilling pesticides on unprotected skin, by drift while mixing or applying pesticides, by wearing pesticide-contaminated clothing, and during cleaning of application equipment (MacFarlane et al. 2013). Furthermore, agricultural workers are also exposed to pesticides during re-entry activities, such as removing branches and wires, and during crop harvesting. The amount of pesticide absorbed depends on the pesticide formulation (emulsifiable concentrates are mostly readily absorbed) and on the part of the body affected (the genital area and the scalp are highly absorptive, while the hands are more resistant to absorption) (WHO 2006b). Although absorption by the respiratory tract appears to be more limited due to the low vapor pressures of most pesticides, protecting the lungs is especially important since pesticide powders, dusts, gases, vapors, or tiny spray droplets can be inhaled during pesticide handling, especially in confined areas.

During occupational agricultural activities, the use of automated equipment can minimize pesticide exposure, including closed mixing and loading systems and spray tractors with enclosed cabs. Closed transfer systems allow pesticides to be transferred directly from the container into the sprayer via a closed route, and air-filtering systems in enclosed tractor cabs also provide respiratory protection for the pesticide applicator. Other engineering control systems, such as low-drift nozzles, hand-wash water supply, and tank rinse systems, are also important to reduce exposure during pesticide handling (Coffman et al. 2009).

Personal protective equipment (PPE), such as respirators with appropriate filters, gloves, coveralls, chemically resistant aprons, boots, and eyewear, can protect in situations where closed systems are not available (IPCS 2004). Figure 1 shows farmers applying pesticides using a backpack sprayer (top) or with the help of a tractor (below). The farmer applying pesticides using a backpack sprayer uses a mask, but an inappropriate cap, clothes, and boots. The farmer behind the truck uses a mask (not shown), but the truck driver is exposed to pesticide spray.

Tsakirakis et al. (2014) estimated the dermal and inhalation exposure of operators during fungicide application to Greek vineyards using a hand-held single nozzle spray gun connected to a tractor tank. The dermal exposure was measured using the whole-body dosimetry method, and the inhalation exposure was measured with the personal air sample devices with XAD tubes on the operator's breathing zone. Pesticide dermal exposure levels were mostly derived from the exposure of the head (89%), with hand exposure accounting for less than 10%. The mean inhalation exposure accounted for about 0.2% of the total exposure and the use of protective coveralls provided about 98.4% protection for the operators. A study conducted with 702 certified pesticide applicators in the USA showed that applicators working on large farms, users of boom and hydraulic sprayers, and growers of field crops were more likely to use engineering devices. Respondents reported a high level of PPE use, with chemical-resistant gloves showing the highest level of compliance (Coffman et al. 2009).

Fig. 1 Application of pesticides using a backpack sprayer in a Brazilian papaya orchard (top), and a farmer applying the pesticide carried by a tractor in a mango orchard (below). (*Photographs taken by the author*)

In a review of 39 studies conducted worldwide, primarily in developing countries, Kangavari et al. (2024) demonstrated that compliance with the use of PPE by farmers varies significantly and is influenced by various factors, including education level, knowledge, and attitudes toward safety measures. Tsakiris et al. (2025) found that most Greek farmers (82.6%) showed adequate use of PPE, which was positively correlated with education and risk perception. In Cameron, about 90% of

the farmers, mostly smallholders (< 1 ha), did not use PPE (Tache et al. 2023). In Morocco, although the farmers were aware of the adverse health effects caused by pesticide use, PPE was not used by most of them (Ben Khadda et al. 2021). In a study conducted in the Federal District of Brazil, over half rarely (48.2%) or never (7.2%) use complete PPE, and 16.7% of them showed blood acetylcholinesterase depletion over 30% (a biomarker of organophosphorus and carbamate exposure) during the exposure period compared with the baseline level (non-exposure period), which indicates a health risk (Pasiani et al. 2012). In this situation, the worker should be removed from the activities involving pesticides until the blood levels return to normal (OEHHA 2015). In Iran, about one-third of the farmers showed unwillingness or were unsure about using PPE, mainly due to the low availability and high price of these devices (Sharifzadeh et al. 2017).

Dermal contact and inhalation of dust in the residence can be an important source of exposure to pesticides for the non-occupational population and the occupational population out of working hours, mainly due to spray drifting from the field (Pasiani et al. 2012; Butler-Dawson et al. 2018; Deziel et al. 2017, 2018). Using data from studies conducted in the United States from 1995 to 2015, Deziel et al. (2017) found that homes near treated fields, homes of farmers who applied pesticides more frequently or recently, and of those who used pesticides around the house had higher pesticide concentrations in the dust compared to their reference groups. In the study conducted by Pasiani et al. (2012), one-third of the residents living on the farms had significant blood acetylcholinesterase depletion compared with their control group and with their baseline level measured when the farmers were not exposed. Figure 2 shows a Brazilian farmer using no PPE when applying the pesticide in a field very close to the residence.

Pesticides used in and around homes, schools, offices, golf courts, and other urban areas may result in potential human exposure via the oral (hand-to-mouth activity by children), dermal, and inhalation routes, during or after the application. Examples of post-application activities include weeding and harvesting gardens, mowing and playing on lawns, and playing golf. Furthermore, some pesticides

Fig. 2 Application of pesticides using a backpack sprayer in a familiar system. (*Photograph taken by the author*)

(such as the N-methyl carbamates carbaryl and propoxur) are formulated as impregnated pet collars, and adults and children can be exposed to them when in contact with pets (US EPA 2007).

Hung et al. (2018) found cypermethrin (a pyrethroid) and chlorpyrifos (an organophosphorus) in indoor and outdoor dust collected from homes in a rural county of Taiwan (80% of the indoor samples and 40 to 48% of outdoor samples, respectively). Permethrin, prallethrin, and tetramethrin, other pyrethroid residential insecticides, were also frequently found in indoor dust. Permethrin and cypermethrin were the main pyrethroids found in residential material, including carpet dust, hard floor surface wipes, vacuum dust bags, food, and air from various USA locations, at levels that may represent a risk to the children (Morgan 2012; Lu et al. 2013). The pyrethroid metabolite 3-phenoxybenzoic acid were detected in over 67% of the urine samples from children 2–11 years of age (Morgan 2012).

3 Toxicological Effects of Pesticides to Humans

All pesticides possess an inherent toxicity to some living organism to be of practical use. However, their selectivity to the target species is not always totally developed, and they can present a health risk to humans and other organisms. Pesticides can cause a wide range of effects on humans, including cancer, neurotoxicity, pulmonotoxicity, reproductive and developmental toxicity, and metabolic toxicity. Common mechanisms include oxidative stress, mitochondrial dysfunction, inflammatory responses, immune dysregulation, and endocrine disruption. Most of the evidence comes from epidemiological studies with the occupational population, but studies with the general population are also reported, including children (Mostafalou and Abdollahi 2017; Wan et al. 2022; Costas-Ferreira et al. 2022; Wolfe and Marsit 2023).

3.1 Cancer

In a review conducted by Mostafalou and Abdollahi (2017), most of the epidemiological studies (54%) that investigated the health impact of pesticides are related to cancer, including brain cancer (adult and children), leukemia (adult and children), esophageal, stomach and colorectal cancers, liver cancer, non-Hodgkin lymphoma, and bladder cancer.

Bonner et al. (2017) evaluated the association of 43 pesticides and 654 lung cancer cases after 10 years of additional follow-up in the Agricultural Health Study, a prospective cohort study comprising 57,310 pesticide applicators from Iowa and North Carolina, USA. The authors found additional evidence for an association between pendimethalin, dieldrin, and parathion use and lung cancer risk, in addition to chlorimuron ethyl, an herbicide for which lung cancer had not been previously reported. Another cohort study (AGRIculture & CANcer) followed for about 7 years

181,842 French farmers, and found 381 incident cases of brain tumors, with hazard ratios for gliomas ranging from 1.18 for thiofanox to 4.60 for formetanate, and for meningiomas, ranging from 1.51 for carbaryl to 3.67 for thiofanox (Piel et al. 2018). van Maele-Fabry et al. (2017, 2019) found associations between residential exposure to pesticides and childhood leukemia and brain tumors, and although causality could not be established, the results indicated the need for limiting the use of household pesticides during pregnancy and childhood.

DDT (*p,p´*-dichloro-diphenyl-trichloroethane) is a very efficient insecticide introduced in the early 1940s to control agricultural pests and vectors for diseases, such as malaria. The compound was widely used until it was banned for agricultural use in most countries in the 1970s and 1980s due to its environmental impact (Jarman and Ballschmiter 2012). DDT is highly persistent in the environment and biological system, with DDE (*p,p´*-dichloro-diphenyl-dichloroethylene) the main degradation product/metabolite. Due to its estrogenic properties, since the early 1990, various studies have investigated the association between DDT and/or DDE and the risk of cancer, particularly breast cancer, although the subject still lacks a consensus among researchers. To elucidate the contradicting results, which may be due to methodological differences, López-Cervantes et al. (2004) conducted a meta-analysis of 22 studies from various countries published up to 2001 on DDT and breast cancer. The summary odds ratio was 0.97, and the authors concluded that there was substantial evidence to discard the relationship between DDE and breast cancer risk. Ingber et al. (2013) updated this meta-analysis by including studies published through June 2012 and confirmed the previous conclusion that the existing information does not support the hypothesis that exposure to DDT/DDE increases the risk of breast cancer in humans.

In the study conducted by Cohn et al. (2007), which was included in the meta-analysis conducted by Ingber et al., blood samples collected from women during the peak DDT use period in the USA (1959–1967) showed high levels of serum DDT. The authors reported a statistically significant fivefold increased risk of breast cancer among women who were born after 1931. Furthermore, Cohn et al. (2018) revisited the same study and suggested that vulnerability to breast cancer before the age of 50 may be associated with an inverse correlation between body mass index and serum DDTs. Chang et al. (2018b) found that women born between 1951 and 1959 exposed to DDT (for malaria control) in Taiwan had an increased risk of breast cancer in adulthood. Cohn et al. (2015) linked the o,p′-DDT (a minor constituent of technical DDT) exposure in utero to risk of breast cancer, a result that needs further investigation (Paumgartten 2015).

Another controversial issue is glyphosate, the most widely used herbicide worldwide. In 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as "probably carcinogenic to humans" (Group 2A), due to *sufficient evidence* of carcinogenicity in animals, *limited evidence* of carcinogenicity in humans (increased risks for non-Hodgkin lymphoma, NHL), and *strong* evidence for two carcinogenic mechanisms (Guyton et al. 2015). Although this conclusion had support from many researchers (Portier et al. 2016; Myers et al. 2016), others contested the IARC classification (Acquavella et al. 2016; Tarone 2018) and national

authorities, including the USA EPA (2017) and the Australian Pesticides and Veterinary Medicines Authority (APVMA 2016), the EFSA (2015), the European Chemical Agency (ECHA 2017), and the FAO and WHO (2016), which have concluded that current data support the conclusion that glyphosate is unlikely to cause cancer in human. Weisenburger (2021) reviewed studies linking exposure to glyphosate and its formulations (GBF) to the development of NHL, with emphasis on new findings since publication of the IARC report. The studies have shown that glyphosate is carcinogenic in rodents and causes NHL in mice, and that glyphosate and GBFs are genotoxic to human lymphocytes, both in vitro and in vivo. The author claimed that the evaluation provides evidence that glyphosate and GBFs are a cause of NHL in exposed humans and should prompt new reviews by pesticide regulatory agencies. The glyphosate status was reconsidered by the European Commission, which confirmed its registration until December 2033, under certain use conditions and restrictions (EU 2025). The reevaluation of glyphosate performed by the Brazilian Government in 2019 also maintained the registration, but prohibited its use in amateur gardening (ANVISA 2020a).

Table 2 summarizes IARC classification of the 33 pesticides evaluated by the Agency (as of August 2025), including the persistent organochlorine insecticides banned in most countries. Lindane is the only one classified as carcinogenic to humans (Group 1A), and most were classified in Group 3.

3.2 Neurotoxicity

The organophosphorus (OP), N-methyl carbamates (NMC), and pyrethroids (PY) insecticides are neurotoxic compounds that act in mammals, including humans, through the same mechanism by which they exert their acute toxic effects on the target insects (Casida and Durkin 2013; Soderlund 2012). OP and NMC inhibit the acetylcholinesterase (AChE) in the central and peripheral (humans only) nervous systems, an enzyme that hydrolyses the neurotransmitter acetylcholine, and PY interacts with the voltage-gated sodium channels, leading to delayed repolarization of the nervous signal. High acute exposure to AChE inhibitors results in accumulation of acetylcholine at the synaptic cleft, leading to excessive stimulation and impairment of the physiological functions controlled by the cholinergic, muscarinic, and central nervous systems, and can be fatal (Peter et al. 2014). Symptoms of intoxication include salivation, gastric cramps, emesis, neuromuscular weakness, respiratory, and cardiovascular effects. Fatal poisonings with AChE inhibitors have been reported worldwide, mainly suicide, but also accidental cases involving children and under occupational circumstances (Dawson et al. 2010; Yimaer et al. 2017; Magalhães and Caldas 2018).

Various studies have shown an association between pesticide exposure, mainly OP, and neurodegenerative diseases, including Alzheimer's, Parkinson's, and Amyotrophic Lateral Sclerosis (Mostafalou and Abdollahi 2017, 2018). In a systematic review and meta-analysis, Vaccari et al. (2019) found a positive association

Table 2 Classification of pesticides regarding their carcinogenicity to humans according to the International Agency for Research on Cancer (IARC 2025)

Pesticide (evaluated/published)	Classification	Criteria
Lindane (2015/2018)	I (carcinogenic)	Sufficient evidence of carcinogenicity in humans
DDT (2015/2018)	2A (probably carcinogenic)	Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals
Diazinon (2015/2017)		
Dieldrin and aldrin metabolized to dieldrin (2016/2019)		
Glyphosate (2015/2017)		
Malathion (2015/2017)		
Chlordane (200/2001)	2B (possibly carcinogenic)	Limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals
2,4 D (2015/2018)		
Dichlorvos (1990/1991)		
Heptachlor (2000/2001)		
Hexachlorocyclohexanes (1987/1987)		
Tetrachlorvinphos (2015/2017)		
Parathion (2015/2017)		
Aldicarb (1990/1991)	3 (not classifiable as to its carcinogenicity)	Evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals
Atrazine (1998/1999)		
Captafol (1990/1991)		
Captan (1987/1987)		
Carbaryl (1987/1987)		
Deltamethrin (1990–1991)		
Dicofol (1987/1987)		
Endrin (1987/1987)		
Fenvalerate (1990/1991)		
Ferbam (1987/1987)		
Maneb (1987/1987)		
Methyl parathion (1987)		
Methoxychlor (1987/1987)		
Permethrin (1990/1991)		
Picloram (1990/1991)		
Simazine (1998/1999)		
Thiram (1990/1991)		
Trifluralin (1990/1991)		
Zineb (1987/1987)		
Ziram (1990/1991)		

between occupational exposure to paraquat and Parkinson's disease, but the authors concluded that the weight-of-evidence did not allow an indisputable cause–and–effect relationship.

Koh et al. (2017) found a significant positive association between at least a 20-year period of pesticide use and depression among Korean adults. In a

systematic review of epidemiological studies, Freire and Koifman (2013) found an association between pesticide exposure and either depression or suicide in some populations, although the authors recognized that the evidence is still very limited and inconclusive. In another systematic review, Zanchi et al. (2023) showed an increased prevalence of depressive disorders, increased self-reported prevalence of depression, and a higher suicide risk among farmers.

3.3 Reproductive and Developmental Toxicity

Many studies have investigated the association between exposure to pesticides and an increased risk of developing reproductive and developmental disorders, mainly endocrine-disrupting pesticides. In a population-based case-control study conducted by García et al. (2017) on pregnant women in Spain and male children found significantly higher prevalence rates and risk of miscarriage, low birth weight, hypospadias, cryptorchidism, and micropenis in areas of higher pesticide use in relation to those with lower use. Various studies have shown the association between pesticide exposure and low semen quality and/or sperm concentration (Melgarejo et al. 2015; Perry et al. 2011; Zamkowska et al. 2018).

Epidemiological studies reviewed by Burke et al. (2017) reported statistically significant

correlations between prenatal exposures to chlorpyriphos and postnatal neurological deficit, including impaired cognition and motor function, attention deficit hyperactivity disorder, deficits in working memory, and reduced full-scale intelligence quotient. Kongtip et al. (2017) found higher DEP and/or total DAP organophosphorus metabolite levels from the mother at 28 weeks' gestation in Taiwan, which were significantly associated with reduced motor and cognitive composite scores of the infants.

Carbendazim is a benzimidazole fungicide with a potential for endocrine-disrupting (ED) properties and classified as mutagenic and toxic for reproduction (category 1B), which was the basis for its cancelation by the European Commission in 2014, when all the MRLs were withdrawn (EFSA 2024), and other countries, including Brazil (ANVISA 2022). More recently, EFSA concluded that the criteria for ED are not met for carbendazim and that the compound is not clastogenic, i.e., it does not induce chromosomal aberrations (EFSA 2024). As a risk assessor, the Agency confirmed its previous ADI, ARfD, risk assessment, and MRL recommendations, although the compound registration status is still canceled in the region.

3.4 Toxicity to the Respiratory Tract

The link between occupational exposures to chemicals, including pesticides, with asthma, bronchitis, and other respiratory diseases has long been reported (Ye et al. 2017; Mostafalou and Abdollahi 2017). In the USA, from an estimated 2.1 million farm operators, 40.0% used pesticides; insecticide and herbicide uses were significantly associated with lifetime allergic rhinitis and current asthma (Patel et al. 2018). A cohort study conducted with Canadian grain farmers also showed that lifetime exposure to phenoxy herbicides, including 2,4-D, is associated with an increased risk of asthma (Cherry et al. 2018). In a study conducted with children (3–10 years old) living in a French vineyard rural area, there was an association between ethylenethiourea urinary concentration, a metabolite of dithiocarbamate fungicides, asthma, and rhinitis symptoms (Raherison et al. 2018).

Paraquat is a highly toxic herbicide to humans, and its use has been restricted or withdrawn in many countries, including the European Union (EC 2009) and Brazil (ANVISA 2020b). However, it is still used in the United States (US EPA 2025). Paraquat is not well absorbed by inhalation in agricultural/occupational settings, but inhalation of paraquat droplets may produce nasal and tracheobronchial irritation. Most of the poisoning cases occur by self-poisoning, when it accumulates in the lungs and death occurs by respiratory failure, particularly due to pulmonary fibrosis (Dinis-Oliveira et al. 2008). A retrospective study of 62 paraquat poisoning cases in French Guiana from 2008 to 2015 included 44 adults and 18 children younger than 16 years of age; 48% of them died (Elenga et al. 2018). In Korea, the mean mortality rate of 1056 cases that occurred from 2010 and 2014 was 73.0%, with a significant decrease after the compound was banned in the country in 2012 (Ko et al. 2018).

4 Environmental Fate of Pesticides and Impact on the Biota

The fate of the pesticide in the various environmental compartments is illustrated in Fig. 3. The chemical may move off-site via spray drift, volatilization, leaching, and runoff, degraded in the air by photolysis, water, and in the soil to less or more toxic products, and can affect aquatic and terrestrial organisms, and non-target insects, such as bees. Additionally, predatory invertebrates may become contaminated by consuming pests such as leafhoppers or aphids that feed on treated crops, and other beneficial plant-feeding invertebrates may be exposed directly through the diet. Other routes of exposure include contact with treated surfaces, exposure to sprays, or consumption of guttation droplets (Khani et al. 2012; Pisa et al. 2015).

The fate of chemicals depends primarily on their physical-chemical and other properties, as well as soil characteristics (Table 3), which provide information on their persistence, potential transport pathways, and bioavailability in the environment (US EPA 2009).

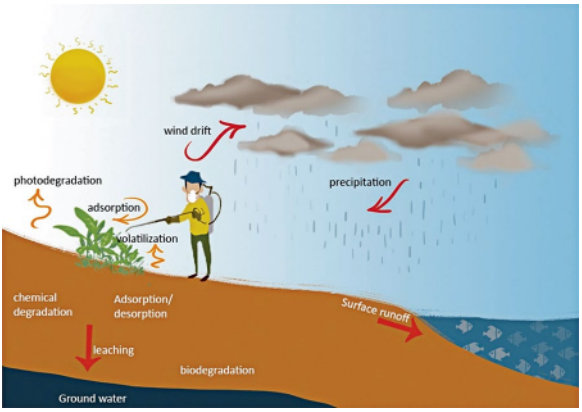

Fig. 3 Fate of pesticides in the environment

Table 3 Summary of information needed to predict the fate of a pesticide in the environment (US EPA 2009)

Physical--chemical properties	Solubility in water, octan-1-ol-water partition coefficient (K_{ow}/log K_{ow}), vapor pressure/volatility, Henry's Law Constant (air-water partition coefficient), octan-1-ol-air partition coefficient (K_{OA}), dissociation constant in water for weak acids and bases (pK_a or pK_b), UV/visible light absorption
Other properties	Degradation (water and/or soil): Hydrolysis, photolysis, aerobic, and anaerobic Sorption: Soil/sediment-water distribution coefficients (K_d and K_f) and organic carbon normalized distribution coefficient (K_{OC}). The pesticide can be classified as highly mobile in the soil (K_{oc} < 10 mL g^{-1}) to immobile (K_{oc} > 100,000 mL g^{-1}) Field dissipation: Half-lives ($t_{1/2}$) in terrestrial and aquatic media Bioconcentration in fish
Soil characteristics	pH, hydroxyl radical concentration, microbial community organic carbon content

Table 4 shows the main properties of some pesticides, in addition to toxicological benchmarks for non-target organisms. Compounds with high-water solubility and *mobility (low* K_{OC}), such as 2,4-D, have the potential to reach groundwater. Those with a higher K_{OC} (very low mobility), such as flumetralin and glyphosate, tend to remain in soil/sediments, but they can reach water systems through superficial runoff (Fig. 3). Pesticides with high vapor pressure are likely to be transported over long distances, which is not the case of any pesticide shown in Table 4.

4.1 Impact of Pesticides on Aquatic Organisms

Pesticides reach surface waters mainly through atmospheric deposition (spray drift) and by surface runoff (Fig. 3). Uptake of pesticides by aquatic invertebrates occurs through respiration (gills and trachea), feeding, and through the epidermis (Pisa

Table 4 Physical-chemical properties and acute toxicity of some pesticides of ecotoxicological relevance[a]

Pesticide (class)	Physical-chemical and other properties	Toxicological benchmark
Ametryn (triazine herbicide)	MM: 227.3 g mol^{-1} Sol_w: 170–200 mg L^{-1} Log k_{ow}: 2.63 Vapor pressure 2.74×10^{-6} mmHg at 25 °C K_{OC}:170–390 mL g^{-1} $t_{1/2}$ (soil): 60 days	Algae: EC_{50} = 3.6–4.06 µg L^{-1} Microcrustaceans: EC_{50} = 28–45.29 mg L^{-1} Fish: LC_{50} = 4.24–14.1 mg L^{-1}
2,4-Dichloro-phenoxy acetic acid (2,4 D) (Phenoxy acetic herbicide)	MM: 221.0 g mol^{-1} Sol_w: 23180 mg L^{-1} Log k_{ow}: −0.83 Vapor pressure: 1.4×10^{-7} mmHg at 20 °C K_{OC}: 70–117 mL g^{-1} $t_{1/2}$ (soil): 1–14 days $t_{1/2}$ (water): 15 days	Algae: EC_{50} = 24.2 mg L^{-1} Microcrustaceans: EC_{50} = 100 mg L^{-1} Fish: LC_{50} = 63.4 mg L^{-1} Earthworms (*Lumbricus rubellus*) LC_{50}: 61.6 µg cm^{-1} Bees (*Apis mellífera*) LD_{50}: 10 µg per bee (oral)
Glyphosate (glycine herbicide)	MM: 169.1 g Mol^{-1} Sol_w: 12 g L^{-1} Log k_{ow}: −3.4 Vapor pressure: 9.8×10^{-8} mmHg at 25 °C K_{OC}: 300–20,100 mL g^{-1} $t_{1/2}$ (soil): 77 days $t_{1/2}$ (water): up to 91 days	Crustaceous (*Palaemonetes vulgaris*) LC_{50} = 281 mg L^{-1} Fish (rainbow trout): LC_{50} = 140 mg L^{-1} Earthworm (biomass) EC_{50}: >5000 µg g^{-1} soil Bee (*Apis mellífera*) LD_{50}: > 100 µg per bee (oral)
Carbendazim (benzimidazole fungicide)	MM: 191.2 g mol^{-1} Sol_w: 7.0 mg L^{-1} Log k_{ow}:1.51 Vapor pressure: 7.5×10^{-10} mmHg at 20 °C K_{OC}: 200 mL g^{-1} $t_{1/2}$ (soil): 120 days	Algae: EC_{50} = 2.57–7.7 mg L^{-1} Microcrustaceans: EC_{50} = 0.11–0.19 mg L^{-1} Fish: LC_{50} = 0.36–5.5 mg L^{-1}
Flumetralin (2,6-dinitroaniline herbicide)	MM: 421.7 g mol^{-1} Sol_w: 5.85 µg L^{-1} Log k_{ow}: 5.45 Vapor pressure: 1.3×10^{-8} mmHg at 20 °C K_{OC}: 100000 mL g^{-1} $t_{1/2}$ (soil): 20 days	Algae: EC_{50} = 0.85–8.58 mg L^{-1} microcrustaceans: EC_{50} = 0.0028–0.42 mg L^{-1} Fish: LC_{50} = 0.014–0.024 mg L^{-1}

(continued)

Table 4 (continued)

Pesticide (class)	Physical-chemical and other properties	Toxicological benchmark
Imidacloprid (neonicotinoid insecticide)	MM: 255.7 g mol^{-1} Sol_w: 610 mg L^{-1} Log k_{ow}: 0.57 Vapor pressure: 3×10^{-12} mmHg at 20 °C K_{OC}: 249–336 mL g^{-1} $t_{1/2}$ (field dissipation): 40–124 days $t_{1/2}$ (water/sediment): 30–162 days	Algae: EC_{50} = 10–389 mg L^{-1} Crustaceans (*Americamysis bahia)* EC_{50} = 34.6 µg L^{-1} Fish (rainbow trout): LC_{50} = 21 mg L^{-1} Earthworm (biomass) EC_{50}: 0.8 mg kg^{-1} dry soil Bees (*Apis mellífera*) LD_{50}: 3.7–40.9 ng per bee (oral) LD_{50}: 59.7–242.6 ng per bee (contact)

MM molar mass, Sol_w water solubility, at 20 °C, K_{ow} *n*-octanol-water partition coefficient, pK_a dissociation constant, K_{OC} organic carbon normalized distribution coefficients, CE_{50} effective concentration, LC_{50} lethal concentration, LD_{50} lethal dose

[a]Information obtained from: https://pubchem.ncbi.nlm.nih.gov/; http://npic.orst.edu/factsheets/archive/; Rebelo and Caldas 2014

et al. 2015). Toxic pesticide residues in aquatic systems may eliminate aquatic species, reduce biodiversity, and compromise the functioning of ecosystems (Carvalho 2017). Toxicological benchmarks for aquatic organisms are shown in Table 4 for some pesticides. Ametryn is the most toxic to algae (LC_{50} ~ 4 µg L^{-1}), flumetralin and carbendazim are the most toxic to crustaceans (EC_{50} < 1 mg L^{-1}), and flumetralin is the most toxic to fish (LC_{50} < 0.05 mg L^{-1}).

To estimate the exposure of aquatic organisms, computer simulation models (e.g., GENeric Estimated Environmental Concentration, GENEEC) can be used to estimate the environmental concentrations (EECs) in surface water using degradation data (half-life) and organic carbon normalized distribution coefficient (K_{OC}), considering that the pesticide is applied at its maximum application rates (US EPA 2018b). A more refined assessment can be performed based on actual use site conditions. To characterize the risk of a given pesticide to the organisms, the EEC is compared to the toxicological benchmark values (e.g., LC50) to estimate the risk quotient (RQ). This RQ is then compared with the Levels of Concern (LOCs) for direct effects, which can be defined by the environmental agency to analyze potential risk to non-target organisms under the pesticide regulatory process. Table 5 shows the LOCs defined by the EPA (US EPA 2018b). A regulatory action (e.g., use restriction) can be taken when the RQ is higher than the LOC.

Various studies have been conducted to evaluate the pesticide environmental concentrations and the potential impact on aquatic organisms worldwide. In a study conducted in the Great Barrier Reef, Australia, the runoff of pesticides, mainly herbicides from sugar cane cultivation, resulted in the presence of several pesticides (mainly herbicides) in both freshwater and coastal marine waters with a potential to reduce the productivity of marine plants and corals (Lewis et al. 2009). Chen et al.

Table 5 Levels of concern for the risk characterization of pesticides for aquatic organisms (US EPA 2018b)

Risk presumption	Risk quotient	Level of concern
Acute risk	EEC/LC_{50} or EC_{50}	0.5
Acute restricted use	EEC/LC_{50} or EC_{50}	0.1
Acute endangered species	EEC/LC_{50} or EC_{50}	0.05
Chronic risk	EEC/NOAEC	1

EEC estimated environmental concentrations and lowest tested EC_{50}, $LC_{50,}$ or NOAEC for freshwater fish and invertebrates and estuarine/marine fish and invertebrates from acute toxicity tests

(2018) investigated 31 pesticides in the water of the Dongjiang River (China), including persistent organochlorines, organophosphorus, N-methyl carbamates, and pyrethroid insecticides, and found residues at levels up to 1198 ng L^{-1}. Ecological risk assessments indicated that most of the pesticides posed a high level of risk to the aquatic organisms.

Ernst et al. (2018) reported multiple pesticide residues in muscle tissue of wild fish species from two large rivers in South America (Uruguay and Negro Rivers) at levels up to 194 μg kg^{-1}, with the incidence directly related to the properties of the chemical (K_{ow}, environmental persistence, and mobility), pesticide use, and cultivated land area. Trifloxystrobin, metolachlor, and pyraclostrobin showed the highest rates of occurrence, and the results suggest a regular exposure of aquatic wild biota to sublethal concentrations of multiple pesticides.

Using a dynamic multimedia model for the Caño Azul River drainage area (Costa Rica), which is heavily influenced by banana and pineapple plantations, Mendez et al. (2018) estimated the levels of diuron, ethoprophos, and epoxiconazole in water, air, soil, and sediments based on pesticide properties, emission patterns, and environmental conditions. Concentration in the environment was highly variable, reaching peak concentrations in water that can exceed thresholds for ecosystem health. Another study conducted in Costa Rica (Tempisque river basin) during 2007 and 2012 found the pesticides carbendazim, diuron, endosulfan, epoxiconazole, propanil, triazophos, and terbutryn showing non-acceptable risk for the ecosystem (Carazo-Rojas et al. 2018).

A monitoring study conducted in 2010 and 2011 in the Guadalquivir River Basin (Spain) showed that pesticides are widespread in surface waters and sediments, with organophosphorus, triazines, and carbamates the most detected (Masiá et al. 2013). Atrazine and terbuthylazine degradation products were found at higher concentrations than parent pesticides**.**

In a study conducted in a Brazilian Midwestern region agricultural area, Pires et al. (2023) found all 52 groundwater samples and 30% of the 90 surface water samples collected in 20021/2022 contaminated with glyphosate and its metabolite AMPA, but at levels lower than the most critical toxicological endpoints for aquatic organisms. In further work, the samples were also analyzed for the presence of 77 pesticides and metabolites, and 19 compounds were detected (Pires et al. 2025).

The highest concentrations found in surface water were of atrazine-2-hydroxy, a degradate of atrazine, at levels that may represent a potential risk to aquatic organisms.

In a review of 146 studies conducted worldwide from 1976 to 2021, de Araújo et al. (2022) found that the concentrations exceeded the toxicological endpoint for at least 11 pesticides, including atrazine (Daphnia, LC50 and fish NOAEC), cypermethrin (algae EC50, Daphnia and fish LC50; fish NOAEC), and chlorpyrifos (Daphnia and fish LC50; fish NOAEC).

4.2 Impact on Non-Target Insects

Wild bee communities are important agricultural pollinators, and bee abundance and diversity are of great benefit to farms (Eilers et al. 2011). Many studies have shown that chronic exposure to multiple stressors is driving honeybee colony losses and declines of wild pollinators, including habitat loss, owing to agricultural intensification and exposure to pesticides, in addition to parasites and pathogens (Goulson and Nicholls 2016; Park et al. 2015). Bees are exposed to pesticides through direct contact with dust during drilling, guttation drops from seed-treated crops, and consumption of pollen and nectar from wild flowers and trees growing near-treated crops (Bonmatin et al. 2015). Pesticide exposure can impair detoxification mechanisms and immune responses, rendering bees more susceptible to parasites, and can affect bee behavior, including mobility, learning, and orientation (Pisa et al. 2015; Goulson and Nicholls 2016; Thorbek et al. 2017).

Among the pesticides, the neonicotinoid insecticides, including thiamethoxam and imidacloprid, and fipronil, are considered the most toxic to bees (Bonmatin et al. 2015; Pisa et al. 2015). These pesticides are generally used as seed coating/dressing treatment, generating a "toxic" dust around the planting machine at a concentration enough to kill bees passing through the cloud (Girolami et al. 2012). In response to the concern over honeybee colony declines and of wild bee distribution and abundance, the European Commission (EC 2013) prohibited the use and sale of seeds treated with imidacloprid, thiamethoxam, and clothianidin. However, the impact of this regulatory action on bee colonies in Europe is still unclear and probably can only be assessed in the future (Blacquière and van der Steen 2017).

Thorbek et al. (2017) found that contact with oilseed rape or sunflower treated with neonicotinoids affected bee behavior, with poor brood care impacting the colony the most; good forage mitigated the effects substantially. Queenless bumblebee (*Bombus terrestris*) micro-colonies exposed to thiamethoxam, pollen paste, and sugar for a 28-day period up to 10 ng g^{-1} (which corresponds to the maximum field application) consumed significantly less sugar solution than control colonies, and colonies fed at the highest concentration had reduced nest-building activity and produced significantly fewer eggs and larvae (Elston et al. 2013).

An extensive review on the impact of neonicotinoid use on bee colonies and other organisms conducted by Wood and Goulson (2017) showed that proximity to treated flowering crops increases bee exposure to neonicotinoids, mainly through pollen and nectar. In general, wild bees have similar sensitivity to neonicotinoids compared to honeybees when considering direct mortality, although there is a wide variability between bee species, genera, and families. In addition to bees, correlational studies conducted in various countries have suggested a link between neonicotinoid use and the population of butterflies and insectivorous birds. The authors suggested that bee declines are indicators of environmental damage that is likely to have a broad impact on biodiversity and the ecosystem services it provides. Hisamoto et al. (2024) found that paddy and orchard fields, and urban areas resulted in higher bee pesticide exposure compared to forests. The authors concluded that to control pesticide exposure levels in bees effectively, it is essential to understand pesticide use patterns and to develop appropriate regulatory systems in non-agricultural lands, similar to those in agricultural lands.

4.3 Impact on Non-Target Terrestrial Organisms

Earthworms constitute an important part of agricultural soil animal biomass, playing a critical role in the development and maintenance of soil properties and fertility (Sharma et al. 2017). They are one of the most important bioindicators in the terrestrial environment and can be exposed to pesticides by direct contact with the applied granules or treated seeds, or contaminated soil and water (Katagi and Ose 2015; Pisa et al. 2015).

Populations with short generation times and/or high dispersal capacity are likely to recover from pesticide-induced toxicity, although soil-persistent pesticides, such as neonicotinoids, may impact subsequent generations (Pisa et al. 2015). Wang et al. (2012) investigated the toxicity of 45 pesticides to *Eisenia fetida* and found that clothianidin (a neonicotinoid), fenpyroximate, and pyridaben were the most toxic after dermal exposure (LC_{50} lower than 1 μg cm^{-2}), and clothianidin and picoxystrobin showed the highest toxicity after oral exposure (LC_{50} lower than 10 μg kg^{-1}).

Arbuscular mycorrhizal (AM) fungi are ubiquitous soil micro-organisms that facilitate plant uptake of water and nutrients and receive carbohydrates from the plant in return to complete their life cycle. Helander et al. (2018) showed that glyphosate reduced the mycorrhizal colonization and growth of both target and non-target grasses, and the magnitude of reduction depended on tillage and soil properties due to the cultivation history of the endophyte symbiotic grass. Li et al. (2013) demonstrated that the herbicides prometryn and acetochlor exerted negative effects on the AM fungus and symbiosis at increasing concentrations, with prometryn apparently being more toxic.

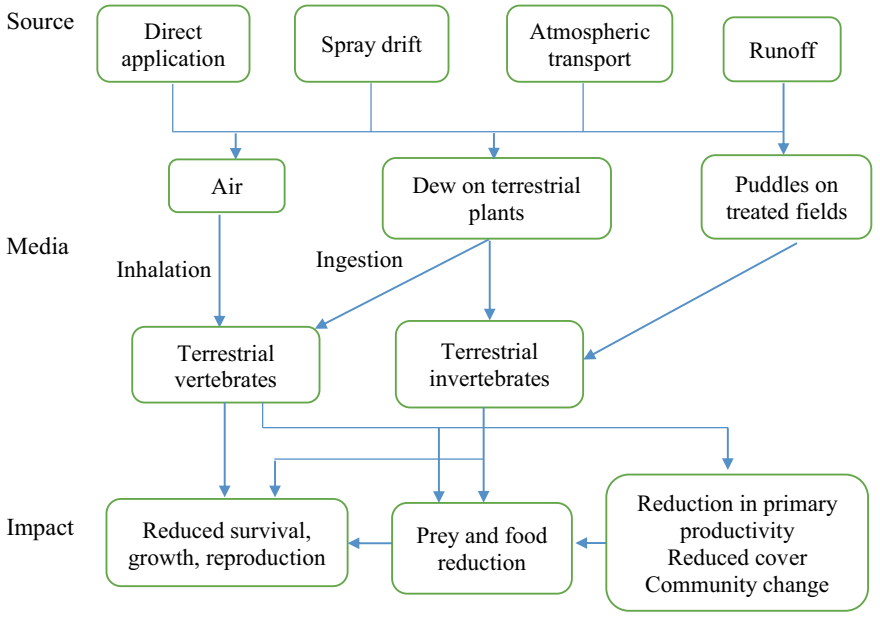

Fig. 4 Major routes of potential exposure for terrestrial organisms. (Adapted from US EPA 2018c)

Some argue that pesticides of natural origin are an environmentally friendly alternative to synthetic pesticides. Romdhane et al. (2019) applied leptospermone, a natural β-triketone herbicide, and sulcotrione, a synthetic one, to soil microcosms at recommended field doses. Both compounds fully dissipated over the incubation period of 45 days, but CMBA, the major metabolite of sulcotrione, remained in soil microcosms. For both herbicides, the diversity of the soil bacterial community was still not entirely recovered by the end of the experiment.

Figure 4 shows a generic conceptual model used by the US EPA for pesticide effects on terrestrial organisms, considering drinking water and inhalation exposure pathways for vertebrates, and ingestion of dew by invertebrates (US EPA 2018c). Additionally, dermal exposure can occur in the treated field during pesticide application or in adjacent areas, during contact with contaminated soils or with contaminated puddle water on the treated field or in areas impacted by drift and runoff. In addition to death, exposure to pesticides can affect the food chain, food availability, growth, and reproduction. Schaumburg et al. (2016) showed that glyphosate-based formulations have genotoxic effects on the tegu lizard (*Salvator merianae*) at sublethal concentrations during the embryonic period, which may interfere with the development and survival of embryos and hatchling, with a potential impact on population survival, affecting the local biodiversity and ecological equilibrium.

References

Acquavella J, Garabrant D, Marsh G, Sorahan T, Weed DL (2016) Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma. Crit Rev Toxicol 46(sup1):28–43

Ambrus Á (2016) FAO manual on the submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed, 3rd edn. Food and Agriculture Organization, Rome

ANVISA (Agência Nacional de Vigilância Sanitária) (2020a). https://antigo.anvisa.gov.br/documents/10181/5344168/Nota+T%C3%A9cnica+Final+-+Reavalia%C3%A7%C3%A3o+do+Glifosato.pdf/9f513821-c4e5-4be3-a538-ef1947034272

ANVISA (Agência Nacional de Vigilância Sanitária) (2020b). https://www.gov.br/anvisa/pt-br/setorregulado/regularizacao/agrotoxicos/monografias/monografias-excluidas/p01-paraquate-monografia-excluida.pdf

ANVISA (Agência Nacional de Vigilância Sanitária) (2022) Nota Técnica Conclusiva de Reavaliação do Carbendazim. https://www.gov.br/anvisa/pt-br/acessoainformacao/perguntasfrequentes/agrotoxicos/reavaliacao-de-agrotoxicos-copy_of_NotaTcnicaFinaldeReavaliaodoCarbendazimcomseusAnexos.pdf

APVMA (2016) Regulatory position: consideration of the evidence for a formal reconsideration of glyphosate. Australian Pesticides and Veterinary Medicines Authority. https://apvma.gov.au/sites/default/files/publication/20701-glyphosate-regulatory-position-report-final.pdf

Ben Khadda Z, Fagroud M, El Karmoudi Y, Ezrari S, Berni I, De Broe M, Behl T, Bungau SG, Sqalli Houssaini T (2021) Farmers' knowledge, attitudes, and perceptions regarding carcinogenic pesticides in fez Meknes region (Morocco). Int J Environ Res Public Health 18(20):10879

Blacquière T, van der Steen JJ (2017) Three years of banning neonicotinoid insecticides based on sub-lethal effects: can we expect to see effects on bees? Pest Manag Sci 73(7):1299–1304

Bonmatin J-M, Giorio C, Girolami V, Goulson D, Kreutzweiser D, Krupke C, Liess M, Long E, Marzaro M, Mitchell E, Noome D, Simon-Delso N, Tapparo A (2015) Environmental fate and exposure; neonicotinoids and fipronil. Environ Sci Pollut Res 22:35–67

Bonner MR, Freeman LE, Hoppin JA, Koutros S, Sandler DP, Lynch CF, Hines CJ, Thomas K, Blair A, Alavanja MC (2017) Occupational exposure to pesticides and the incidence of lung cancer in the agricultural health study. Environ Health Perspect 125(4):544–551

Boon PE, van Donkersgoed G, Christodoulou D, Crépet A, D'Addezio L, Desvignes V, Ericsson BG et al (2015) Cumulative dietary exposure to a selected group of pesticides of the triazole group in different European countries according to the EFSA guidance on probabilistic modelling. Food Chem Toxicol 79:13–31

Burke RD, Todd SW, Lumsden E, Mullins RJ, Mamczarz J, Fawcett WP, Gullapalli RP, Randall WR, Pereira EFR, Albuquerque EX (2017) Developmental neurotoxicity of the organophosphorus insecticide chlorpyrifos: from clinical findings to preclinical models and potential mechanisms. J Neurochem 142(Suppl 2):162–177

Butler-Dawson J, Galvin K, Thorne PS, Rohlman DS (2018) Organophosphorus pesticide residue levels in homes located near orchards. J Occup Environ Hyg 23:1–24

Caldas ED (2017) Principles of safety assessment of pesticides at National Levels. In: Food safety assessment of pesticide residues. Chapter 3. World Scientific Publishing Europe Ltd, Hackensack, NJ

Caldas ED (2023) Approaches for cumulative dietary risk assessment of pesticides. Curr Opin Food Sci 53:101079

Carazo-Rojas E, Pérez-Rojas G, Pérez-Villanueva M, Chinchilla-Soto C, Chin-Pampillo JS, Aguilar-Mora P, Alpízar-Marín M, Masís-Mora M, Rodríguez-Rodríguez CE, Vryzas Z (2018) Pesticide monitoring and ecotoxicological risk assessment in surface water bodies and sediments of a tropical agro-ecosystem. Environ Pollut 241:800–809

Carvalho FP (2017) Pesticides, environment, and food safety. Food Energy Secur 6(2):48–60. https://doi.org/10.1002/fes3.108
Casida JE, Durkin KA (2013) Anticholinesterase insecticide retrospective. Chem Biol Interact 203(1):21–225
Chang CH, MacIntosh D, Lemos B, Zhang Q, Lu C (2018a) Characterization of daily dietary intake and the health risk of neonicotinoid insecticides for the U.S. population. J Agric Food Chem 66(38):10097–10105
Chang S, El-Zaemey S, Heyworth J, Tang MC (2018b) DDT exposure in early childhood and female breast cancer: evidence from an ecological study in Taiwan. Environ Int 121(Pt 2):1106–1112
Chen Y, Yu K, Hassan M, Xu C, Zhang B, Gin KY, He Y (2018) Occurrence, distribution and risk assessment of pesticides in a river-reservoir system. Ecotoxicol Environ Saf 166:320–327
Cherry N, Beach J, Senthilselvan A, Burstyn I (2018) Pesticide use and asthma in Alberta grain farmers. Int J Environ Res Public Health 15;15(3)
Codex Alimentarius (2018) Purpose of the Codex Alimentarius. http://www.fao.org/fao-who-codexalimentarius/about-codex/en/
Coffman CW, Stone J, Slocum AC, Landers AJ, Schwab CV, Olsen LG, Lee S (2009) Use of engineering controls and personal protective equipment by certified pesticide applicators. J Agric Saf Health 15:311–326
Cohn BA, Wolff MS, Cirillo PM, Sholtz RI (2007) DDT and breast cancer in young women: new data on the significance of age at exposure. Environ Health Perspect 115(10):1406–1414
Cohn BA, La Merrill M, Krigbaum NY, Yeh G, Park JS, Zimmermann L, Cirillo PM (2015) DDT exposure in utero and breast cancer. J Clin Endocrinol Metab 100(8):2865–2872
Cohn BA, Cirillo PM, La Merrill MA (2018) Correlation of body mass index with serum DDTs predicts lower risk of breast cancer before the age of 50: prospective evidence in the child health and development studies. J Expo Sci Environ Epidemiol 29(3):302–309
Colnot T, Dekant W (2017) Approaches for grouping of pesticides into cumulative assessment groups for risk assessment of pesticide residues in food. Regul Toxicol Pharmacol 83:89–99
Costas-Ferreira C, Durán R, Faro LRF (2022) Toxic effects of glyphosate on the nervous system: a systematic review. Int J Mol Sci 23(9):4605
Crépet A, Vanacker M, Sprong C, de Boer W, Blaznik U, Kennedy M, Anagnostopoulos C, Christodoulou DL, Ruprich J, Rehurkova I, Domingo JL, Hamborg Jensen B, Metruccio F, Moretto A, Jacxsens L et al (2019) Selecting mixtures on the basis of dietary exposure and hazard data: application to pesticide exposure in the European population in relation to steatosis. Int J Hyg Environ Health 222(2):291–306
Dawson AH, Eddleston M, Senarathna L, Mohamed F, Gawarammana I, Bowe SJ, Manuweera G, Buckley NA (2010) Acute human lethal toxicity of agricultural pesticides: a prospective cohort study. PLoS Med 7(10):e1000357
de Araújo EP, Caldas ED, Oliveira-Filho EC (2022) Pesticides in surface freshwater: a critical review. Environ Monit Assess 194(6):452
Deziel NC, Freeman LE, Graubard BI, Jones RR, Hoppin JA, Thomas K, Hines CJ, Blair A, Sandler DP, Chen H, Lubin JH, Andreotti G, Alavanja MC, Friesen MC (2017) Relative contributions of agricultural drift, para-occupational, and residential use exposure pathways to house dust pesticide concentrations: meta-regression of published data. Environ Health Perspect 125:296–305
Deziel NC, Beane Freeman LE, Hoppin JA, Thomas K, Lerro CC, Jones RR, Hines CJ, Blair A, Graubard BI, Lubin JH, Sandler DP, Chen H, Andreotti G, Alavanja MC, Friesen MC (2018) An algorithm for quantitatively estimating non-occupational pesticide exposure intensity for spouses in the agricultural health study. J Expo Sci Environ Epidemiol. https://doi.org/10.1038/s41370-018-0088-z
Dinis-Oliveira RJ, Duarte JA, Sánchez-Navarro A, Remião F, Bastos ML, Carvalho F (2008) Paraquat poisonings: mechanisms of lung toxicity, clinical features, and treatment. Crit Rev Toxicol 38(1):13–71

EC (European Commission) (2009) Active substance: Paraquat https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/start/screen/active-substances/details/952

EC (European Commission) (2013) Commission implementing regulation (EU) no 485/2013 of 24 may 2013 amending implementing regulation (EU) no 540/2011, as regards the conditions of approval of the active substances clothianidin, thiamethoxam and imidacloprid, and prohibiting the use and sale of seeds treated with plant protection products containing those active substances. J Eur Union 139:12–26

ECHA (European Chemical Agency) (2017) Glyphosate not classified as a carcinogen by ECHA. https://echa.europa.eu/-/glyphosate-not-classified-as-a-carcinogen-by-echa

EFSA (European Food Safety Authority) 2015 Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate EFSA J 13:4302

EFSA (European Food Safety Authority) (2009) Scientific Opinion on risk assessment for a selected group of pesticides from the triazole group to test possible methodologies to assess cumulative effects from exposure through food from these pesticides on human health. EFSA J 7(9):1167

EFSA (European Food Safety Authority), Craig PS, Dujardin B, Hart A, Hernández-Jerez AF, Hougaard Bennekou S, Kneuer C, Ossendorp B, Pedersen R, Wolterink G, Mohimont L (2020a) Cumulative dietary risk characterisation of pesticides that have acute effects on the nervous system. EFSA J 18(4):e06087

EFSA (European Food Safety Authority), Craig PS, Dujardin B, Har A, Hernandez-Jerez AF, Hougaard Bennekou S, Kneuer C, Ossendorp B, Pedersen R, Wolterink G, Mohimont L (2020b) cumulative dietary risk characterisation of pesticides that have chronic effects on the thyroid. EFSA J 18(4):e06088

EFSA (European Food Safety Authority), Anagnostopoulos C, Anastassiadou M, Castoldi AF, Cavelier A, Coja T, Crivellente F, Dujardin B, Hart A, Hooghe W, Jarrah S, Machera K, Menegola E, Metruccio F, Sieke C, Mohimont L (2022) Retrospective cumulative dietary risk assessment of craniofacial alterations by residues of pesticides. EFSA J 20(10):e07550

EFSA (European Food Safety Authority), Bellisai G, Bernasconi G, Binaglia M, Carrasco Cabrera L, Castellan I, Castoldi AF, Chiusolo A, Crivellente F, Del Aguila M, Ferreira L, Giner Santonja G, Greco L et al (2024) Updated reasoned opinion on the toxicological properties and maximum residue levels (MRLs) for the benzimidazole substances carbendazim and thiophanate-methyl. EFSA J 22(2):e8569

Eilers EJ, Kremen C, Greenleaf SS, Garber AK, Klein A-M (2011) Contribution of pollinator-mediated crops to nutrients in the human food supply. PLoS One 6:e21363

Elenga N, Merlin C, Le Guern R, Kom-Tchameni R, Ducrot YM, Pradier M, Ntab B, Dinh-Van KA, Sobesky M, Mathieu D, Dueymes JM, Egmann G, Kallel H, Mathieu-Nolf M (2018) Clinical features and prognosis of paraquat poisoning in French Guiana: a review of 62 cases. Medicine (Baltimore) 97(15):e9621

Elston C, Thompson HM, Walters KM (2013) Sublethal effects of thiamethoxam, a neonicotinoid pesticide, and propiconazole, a DMI fungicide, on colony initiation in bumblebee (Bombus terrestris) micro-colonies. Apidologie 44:563

Ernst F, Alonso B, Colazzo M, Pareja L, Cesio V, Pereira A, Márquez A, Errico E, Segura AM, Heinzen H, Pérez-Parada A (2018) Occurrence of pesticide residues in fish from south American rainfed agroecosystems. Sci Total Environ 631-632:169–179

EU (European Union) (2025) Status of glyphosate in the EU. https://food.ec.europa.eu/plants/pesticides/approval-active-substances-safeners-and-synergists/renewal-approval/glyphosate_en

FAO & WHO (2016) Pesticide residues in food 2016 Report of the special session of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues Geneva, Switzerland, 9–13 May 2016

FAO & WHO (2025) Pesticide residues in food: report 2024—Joint FAO/WHO Meeting on pesticide residues. Rome. https://doi.org/10.4060/cd5918en

FAO (Food and Agricultural Organization) (2024) FAOSTAT Pesticide use. https://wwwfaoorg/faostat/en/#data/RP
Freire C, Koifman S (2013) Pesticides, depression and suicide: a systematic review of the epidemiological evidence. Int J Hyg Environ Health 216(4):445–460
Gangemi S, Miozzi E, Teodoro M, Briguglio G, De Luca A, Alibrando C, Polito I, Libra M (2016) Occupational exposure to pesticides as a possible risk factor for the development of chronic diseases in humans (review). Mol Med Rep 14:4475–4488
García J, Ventura MI, Requena M, Hernández AF, Parrón T, Alarcón R (2017) Association of reproductive disorders and male congenital anomalies with environmental exposure to endocrine active pesticides. Reprod Toxicol 71:95–100
Girolami V, Marzaro M, Vivan L, Mazzon L, GreattiM, Giorio C, Marton D, Tapparo A (2012) Fatal powdering of bees in flight with particulates of neonicotinoids seed coating and humidity implication. J Appl Entomol 136:17–26
Goulson D, Nicholls E (2016) The canary in the coalmine; bee declines as an indicator of environmental health. Sci Prog 99(3):312–326
Guyton KZ, Loomis D, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Scoccianti C, Mattock H, Straif K (2015) International Agency for Research on Cancer monograph working group, IARC, Lyon, France. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. Lancet Oncol 16(5):490–491
Helander M, Saloniemi I, Omacini M, Druille M, Salminen JP, Saikkonen K (2018) Glyphosate decreases mycorrhizal colonization and affects plant-soil feedback. Sci Total Environ 15(642):285–291
Hisamoto S, Ikegami M, Goka K, Sakamoto Y (2024) The impact of landscape structure on pesticide exposure to honey bees. Nat Commun 15(1):8999
Humphrey P, Margerison S, van der Velde-Koerts T, Doherty MA, Rowland J (2017) Principles of Safety assessment of pesticides at National Levels. In: Food Safety assessment of pesticide residues. Chapter 3. World Scientific Publishing Europe Ltd, Hackensack, NJ
Hung CC, Huang FJ, Yang YQ, Hsieh CJ, Tseng CC, Yiin LM (2018) Pesticides in indoor and outdoor residential dust: a pilot study in a rural county of Taiwan. Environ Sci Pollut Res Int. https://doi.org/10.1007/s11356-018-2413-4
IARC (International Agency for Cancer Research) (2025) IARC monographs on the classification of cancer risks to human. World Health Organization. https://monographs.iarc.who.int/list-of-classifications
Ingber SZ, Buser MC, Pohl HR, Abadin HG, Murray HE, Scinicariello F (2013) DDT/DDE and breast cancer: a meta-analysis. Regul Toxicol Pharmacol 67(3):421–433
IPCS (International Programme on Chemical Safety) (2004) Guidelines on the prevention of toxic exposures. Education and Public Awareness Activities; World Health Organization, Geneva. https://www.who.int/ipcs/features/prevention_guidelines.pdf
IPCS (International Programme on Chemical Safety) (2009) Dietary exposure assessment of chemicals in food (chapter 6). In: Principles and methods for the risk assessment of chemicals in food. Environmental health criteria 240. International Programme on chemical Safety World Health Organization, Geneva
Jardim ANO, Mello DC, Brito AP, van der Voet H, Boon PE, Caldas ED (2018a) Probabilistic dietary risk assessment of triazole and dithiocarbamate fungicides for the Brazilian population. Food Chem Toxicol 118:317–327
Jardim ANO, Brito AP, van Donkersgoed G, Boon PE, Caldas ED (2018b) Dietary cumulative acute risk assessment of organophosphorus, carbamates and pyrethroids insecticides for the Brazilian population. Food Chem Toxicol 112:108–117
Jarman WM, Ballschmiter K (2012) From coal to DDT: the history of the development of the pesticide DDT from synthetic dyes till silent spring. Endeavour 36(4):131–142
Kangavari M, Sarvi M, Afshari M, Maleki S (2024) Understanding determinants related to farmers' protective measures towards pesticide exposure: a systematic review. PLoS One 19(2):e0298450

Katagi T, Ose K (2015) Toxicity, bioaccumulation and metabolism of pesticides in the earthworm. Pestic Sci 40:69–81

Katsikantami I, Colosio C, Alegakis A, Tzatzarakis MN, Vakonaki E, Rizos AK, Sarigiannis DA, Tsatsakis AM (2019) Estimation of daily intake and risk assessment of organophosphorus pesticides based on biomonitoring data - the internal exposure approach. Food Chem Toxicol 23:57–71

Khani A, Ahmadi F, Ghadamyari M (2012) Side effects of imidacloprid and abamectin on the mealybug destroyer, Cryptolaemus montrouzieri. Trakia J Sci 10:30–35

Ko DR, Chung SP, You JS, Cho S, Park Y, Chun B, Moon J, Kim H, Kim YH, Kim HJ, Lee KW, Choi S, Park J, Park JS, Kim SW, Seo JY, Park HY, Kim SJ, Kang H, Hong DY, Hong JH (2018) Effects of Paraquat ban on herbicide poisoning-related mortality. Yonsei Med J 58(4):859–866

Koh SB, Kim TH, Min S, Lee K, Kang DR, Choi JR (2017) Exposure to pesticide as a risk factor for depression: a population-based longitudinal study in Korea. Neurotoxicology 62:181–185

Kongtip P, Techasaensiri B, Nankongnab N, Adams J, Phamonphon A, Surach A, Sangprasert S, Thongsuksai A, Srikumpol P, Woskie S (2017) The impact of prenatal organophosphate pesticide exposures on Thai infant neurodevelopment. Int J Environ Res Public Health 14(6)

Larsson MO, Sloth Nielsen V, Bjerre N, Laporte F, Cedergreen N (2018) Refined assessment and perspectives on the cumulative risk resulting from the dietary exposure to pesticide residues in the Danish population. Food Chem Toxicol 111:207–267

Lewis SE, Brodie JE, Bainbridge ZT, Rohde KW, Davis AM, Masters BL, Maughan M, Devlin MJ, Mueller JF, Schaffelke B (2009) Herbicides: a new threat to the great barrier reef. Environ Pollut 157(8–9):2470–2484

Li X, Miao W, Gong C, Jiang H, Ma W, Zhu S (2013) Effects of prometryn and acetochlor on arbuscular mycorrhizal fungi and symbiotic system. Lett Appl Microbiol 57(2):122–128

Li F, Yuan Y, Meng P, Wu M, Li S, Chen B (2017) Probabilistic acute risk assessment of cumulative exposure to organophosphorus and carbamate pesticides from dietary vegetables and fruits in Shanghai populations. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 34(5):819–831

Lopez-Cervantes M, Torres-Sanchez L, Tobias A, Lopez-Carrillo L (2004) Dichlorodiphenyldichloroethane burden and breast cancer risk: a meta-analysis of the epidemiologic evidence. Environ Health Perspect 112:207–214

Lu C, Adamkiewicz G, Attfield KR, Kapp M, Spengler JD, Tao L, Xie SH (2013) Household pesticide contamination from indoor pest control applications in urban low-income public housing dwellings: a community-based participatory research. Environ Sci Technol 47(4):2018–2025

MacFarlane E, Carey R, Keegel T, El-Zaemay S, Fritschi L (2013) Dermal exposure associated with occupational end use of pesticides and the role of protective measures. Saf Health Work 4(3):136–141

Magalhães AFA, Caldas ED (2018) Underreporting of fatal poisonings in Brazil—a descriptive study using data from four information systems. Forensic Sci Int 287:136–141

Masiá A, Campo J, Vázquez-Roig P, Blasco C, Picó Y (2013) Screening of currently used pesticides in water, sediments and biota of the Guadalquivir River basin (Spain). J Hazard Mater 263(Pt 1):95–104

MCRA (Monte Carlo Risk Assessment) (2024). https://www.rivm.nl/en/food-safety/chemicals-in-food/monte-carlo-risk-assessment-mcra

Melgarejo M, Mendiola J, Koch HM, Moñino-García M, Noguera-Velasco JA, Torres-Cantero AM (2015) Associations between urinary organophosphate pesticide metabolite levels and reproductive parameters in men from an infertility clinic. Environ Res 137:292–298

Mendez A, Castillo LE, Ruepert C, Hungerbuehler K, Ng CA (2018) Tracking pesticide fate in conventional banana cultivation in Costa Rica: A disconnect between protecting ecosystems and consumer health. Sci Total Environ 613–614:1250–1262

Morgan MK (2012) Children's exposures to pyrethroid insecticides at home: a review of data collected in published exposure measurement studies conducted in the United States. Int J Environ Res Public Health 9(8):2964–2985

Mostafalou S, Abdollahi M (2017) Pesticides: an update of human exposure and toxicity. Arch Toxicol 91(2):549–599

Mostafalou S, Abdollahi M (2018) The link of organophosphorus pesticides with neurodegenerative and neurodevelopmental diseases based on evidence and mechanisms. Toxicology 409:44–52

Myers JP, Antoniou MN, Blumberg B, Carroll L, Colborn T, Everett LG, Hansen M, Landrigan PJ, Lanphear BP, Mesnage R, Vandenberg LN, Vom Saal FS, Welshons WV, Benbrook CM (2016) Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. Environ Health 15:19

OEHHA (Office of Environmental Health Hazard Assessment) (2015) California Environmental Protection Agency. https://oehha.ca.gov/pesticides/program/cholinesterase-monitoring-agricultural-pesticide-applicators

Park MG, Blitzer EJ, Gibbs J, Losey JE, Danforth BN (2015) Negative effects of pesticides on wild bee communities can be buffered by landscape context. Proc Biol Sci 282(1809):20150299

Pasiani JO, Torres P, Silva JR, Diniz BZ, Caldas ED (2012) Knowledge, attitudes, practices and biomonitoring of farmers and residents exposed to pesticides in Brazil. Int J Environ Res Public Health 9:3051–3068

Patel O, Syamlal G, Henneberger PK, Alarcon WA, Mazurek JM (2018) Pesticide use, allergic rhinitis, and asthma among US farm operators. J Agromedicine 23(4):327–335

Paumgartten FJ (2015) Letter to the Editor: DDT Exposure in Utero and Breast Cancer. J Clin Endocrinol Metab 100(11):L104–L105

Perry MJ, Venners SA, Chen X, Liu X, Tang G, Xing H, Barr DB, Xu X (2011) Organophosphorous pesticide exposures and sperm quality. Reprod Toxicol 31(1):75–79

Peter JV, Sudarsan TI, Moran JL (2014) Clinical features of organophosphate poisoning: a review of different classification systems and approaches. Indian J Crit Care Med 18(11):735–745

Piel C, Pouchieu C, Migault L, Béziat B, Boulanger M, Bureau M, Carles C, Grüber A, Lecluse Y, Rondeau V, Schwall X, Tual S, Lebailly P, Baldi I, AGRICAN Group (2018) Increased risk of central nervous system tumours with carbamate insecticide use in the prospective cohort AGRICAN. Int J Epidemiol. https://doi.org/10.1093/ije/dyy246

Pires NL, de Araújo EP, Oliveira-Filho EC, Caldas ED (2023) An ultrasensitive LC-MS/MS method for the determination of glyphosate, AMPA and glufosinate in water—analysis of surface and groundwater from a hydrographic basin in the Midwestern region of Brazil. Sci Total Environ 875:162499

Pires NL, de Araújo EP, DHF M, Oliveira-Filho EC, Caldas ED (2025) Pesticides in ground and surface water from the Rio Preto Hydrographic Basin, an important agricultural area in the Midwestern region of Brazil. Water 17(8):1186

Pisa LW, Amaral-Rogers V, Belzunces LP, Bonmatin JM, Downs CA, Goulson D, Kreutzweiser DP, Krupke C, Liess M, McField M, Morrissey CA, Noome DA, Settele J, Simon-Delso N, Stark JD, Van der Sluijs JP, Van Dyck H, Wiemers M (2015) Effects of neonicotinoids and fipronil on non-target invertebrates. Environ Sci Pollut Res Int 22(1):68–102

Portier CJ, Armstrong BK, Baguley BC, Baur X, Belyaev I, Bellé R, Belpoggi F et al (2016) Differences in the carcinogenic evaluation of glyphosate between the international. Agency for Research on cancer (IARC) and the European Food Safety Authority (EFSA). J Epidemiol Community Health 70(8):741–745

Raherison C, Baldi I, Pouquet M, Berteaud E, Moesch C, Bouvier G, Canal-Raffin M (2018) Pesticides exposure by air in vineyard rural area and respiratory health in children: a pilot study. Environ Res 169:189–195

Rebelo RM, Caldas ED (2014) Avaliação de risco ambiental de ambientes aquáticos afetados pelo uso de agrotóxicos. Quím Nova 37:1199–1208

Romdhane S, Devers-Lamrani M, Beguet J, Bertrand C, Calvayrac C, Salvia MV, Jrad AB, Dayan FE, Spor A, Barthelmebs L, Martin-Laurent F (2019) Assessment of the ecotoxicological impact of natural and synthetic β-triketone herbicides on the diversity and activity of the soil bacterial community using omic approaches. Sci Total Environ 651(Pt 1):241–249.

Schaumburg LG, Siroski PA, Poletta GL, Mudry MD (2016) Genotoxicity induced by roundup® (glyphosate) in tegu lizard (Salvator merianae) embryos. Pestic Biochem Physiol 130:71–78

Sharifzadeh MS, Damalas CA, Abdollahzadeh G (2017) Perceived usefulness of personal protective equipment in pesticide use predicts farmers' willingness to use it. Sci Total Environ 609:517–523

Sharma DK, Tomar S, Chakraborty D (2017) Role of earthworm in improving soil structure and functioning. Curr Sci 113:1064–1071

Sieke C, Michalski B, Kuhl T (2018) Probabilistic dietary risk assessment of pesticide residues in foods for the German population based on food monitoring data from 2009 to 2014. J Expo Sci Environ Epidemiol 28(1):46–54

Sinha SN, Banda VR (2018) Correlation of pesticide exposure from dietary intake and biomonitoring: the different sex and socio-economic study of children. Ecotoxicol Environ Saf 162:170–177

Soderlund DM (2012) Molecular mechanisms of pyrethroid insecticide neurotoxicity: recent advances. Arch Toxicol 86(2):165–181

Tache JIT, Fai PBA, Tamungang SA, Riegert J (2023) Use of pesticides and risk perception of environmental contamination by farmers surrounding the Menoua River (West Cameroon). Integr Environ Assess Manag 19(6):1600–1608

Tarone RE (2018) On the International Agency for Research on Cancer Classification of glyphosate as a probable human carcinogen. Eur J Cancer Prev 27(1):82–87

Thorbek P, Campbell PJ, Thompson HM (2017) Colony impact of pesticide-induced sublethal effects on honeybee workers: a simulation study using BEEHAVE. Environ Toxicol Chem 36(3):831–840

Trenteseaux C, Fontaine K, Chatzidimitriou E, Bouscaillou W, Mienné A, Sarda X (2024) Cumulative dietary risk assessment for French consumers exposed to succinate dehydrogenase inhibitor pesticides. Food Chem Toxicol 191:114890

Tsakirakis AN, Kasiotis KM, Charistou AN, Arapaki N, Tsatsakis A, Tsakalof A, Machera K (2014) Dermal & inhalation exposure of operators during fungicide application in vineyards. Evaluation of coverall performance. Sci Total Environ 470–471:282–289

Tsakiris P, Damalas CA, Koutroubas SD (2025) Risk perception and use of personal protective equipment (PPE) in pesticide use: does risk shape farmers' safety behavior? Int J Environ Health Res 35(2):453-463.

US EPA (Environmental Protection Agency) (2001) General principles for performing aggregate exposure and risk assessments for pesticides. https://www.epa.gov/sites/production/files/2015-07/documents/aggregate.pdf

US EPA (Environmental Protection Agency) (2007) Revised *N*-methyl carbamate cumulative risk assessment. Office of Pesticide Programs. https://archive.epa.gov/pesticides/reregistration/web/pdf/nmc_revised_cra.pdf

US EPA (Environmental Protection Agency) (2009) Guidance for reporting on the environmental fate and transport of the stressors of concern in problem formulations for registration review, registration review risk assessments, listed species litigation assessments, new chemical risk assessments, and other relevant risk assessments. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-reporting-environmental-fate-and-transport#I

US EPA (Environmental Protection Agency) (2017) Cumulative assessment of risk from pesticides. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides

US EPA (Environmental Protection Agency) (2025) Cumulative assessment of risk from pesticides. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides

USA EPA (Environmental Protection Agency) (2017) Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential EPA's Office of Pesticide Programs December 12, 2017. https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0073

USA EPA (Environmental Protection Agency) (2018a) Models for pesticide risk assessment. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#health

USA EPA (Environmental Protection Agency) (2018b) Technical overview of ecological risk assessment: risk characterization. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/technical-overview-ecological-risk-assessment-risk

USA EPA (Environmental Protection Agency) (2018c) Guidance for the development of conceptual models for a problem formulation developed for registration review. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-development-conceptual-models-problem#section2

USA EPA (Environmental Protection Agency) (2025) Paraquat Dichloride. https://www.epa.gov/ingredients-used-pesticide-products/paraquat-dichloride

Vaccari C, El Dib R, Gomaa H, Lopes LC, de Camargo J (2019) Paraquat and Parkinson's disease: a systematic review and meta-analysis of observational studies. J Toxicol Environ Health B Crit Rev 22(5–6):172–202

Valsta L, Ocké M, Lindtner O (2017) Towards a harmonized food consumption survey methodology for exposure assessment. In: Food Safety assessment of pesticide residues. Chapter 3. World Scientific Publishing Europe Ltd, Hackensack, NJ

van Maele-Fabry G, Gamet-Payrastre L, Lison D (2017) Residential exposure to pesticides as risk factor for childhood and young adult brain tumors: a systematic review and meta-analysis. Environ Int 106:69–90

van Maele-Fabry G, Gamet-Payrastre L, Lison D (2019) Household exposure to pesticides and risk of leukemia in children and adolescents: updated systematic review and meta-analysis. Int J Hyg Environ Health 222(1):49–67

Wan MLY, Co VA, El-Nezami H (2022) Endocrine disrupting chemicals and breast cancer: a systematic review of epidemiological studies. Crit Rev Food Sci Nutr 62(24):6549–6576. https://doi.org/10.1080/10408398.2021.1903382

Wang Y, Wu S, Chen L, Wu C, Yu R, Wang Q, Zhao X (2012) Toxicity assessment of 45 pesticides to the epigeic earthworm Eisenia fetida. Chemosphere 88:484–491

Weisenburger DD (2021) A review and update with perspective of evidence that the herbicide glyphosate (roundup) is a cause of non-Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk 21(9):621–630

WHO (World Health Organization) (2006a) Pesticides and their application for control of vectors and pests of public health importance, 6th edn WHO/CDS/NTD/WHOPES/GCDPP/2006.1

WHO (World Health Organization) (2006b) Dermal absorption. Environmental Health Criteria 235. World Health Organization, Geneva. http://www.who.int/iris/handle/10665/43542

WHO (World Health Organization) (2015) Pesticide residues in food. Guidance document for WHO monographers and reviewers WHO Core Assessment Group on Pesticide Residues. World Health Organization, Geneva. WHO/HSE/FOS/2015.1

Wolfe J, Marsit C (2023) Pyrethroid pesticide exposure and placental effects. Mol Cell Endocrinol 578:112070

Wood TJ, Goulson D (2017) the environmental risks of neonicotinoid pesticides: a review of the evidence post 2013. Environ Sci Pollut Res Int 24(21):17285–17325

WPR (World Population Review) (2025) Employment in Agriculture by Country. https://worldpopulationreview.com/country-rankings/employment-in-agriculture-by-country)

Ye M, Beach J, Martin JW, Senthilselvan A (2017) Pesticide exposures and respiratory health in general populations. J Environ Sci (China) 51:361–370

Yimaer A, Chen G, Zhang M, Zhou L, Fang X, Jiang W (2017) Childhood pesticide poisoning in Zhejiang, China: a retrospective analysis from 2006 to 2015. BMC Public Health 17:602

Yusà V, Fernández F, Dualde P, López A, Lacomba I, Coscollà C (2022) Exposure to non-persistent pesticides in the Spanish population using biomonitoring: a review. Environ Res 205:112437