A comparison of the persistence, toxicity, and exposure to high-volume natural plant-derived and synthetic pesticides

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Abstract
The immobility of plants exerted evolutionary selection pressures resulting in the production of thousands of chemical substances thought to function as pesticides against predation by insects and animals. More than 10,000 plant-derived compounds have been isolated with the existence of about 100,000 such compounds postulated. In 1990, Ames et al. reported that 99.99% by weight of the pesticides ingested in a normal human diet are derived from natural plant-based sources. This surprising result raised the question as to whether these natural plant pesticides were toxic to humans. These authors examined a relatively small subset of natural pesticides and determined that their tumorigenicity in rodent cancer bioassays was similar to synthetic pesticides. In this analysis, we used standard United States Environmental Protection Agency programs to estimate the toxicity (T.E.S.T. 4.2) and persistence (EPI Suite 4.1) of a series of high-volume synthetic and natural pesticides. On average, synthetic pesticides were more persistent in the environment than were natural pesticides. This result is consistent with cost, time, and logistical constraints under which farmers apply a limited number of applications of pesticides during a crop cycle. Synthetic and natural pesticides are predicted to possess toxicities including mutagenicity and developmental toxicity. Synthetic pesticides are less often mutagenic.

Keywords
Natural plant pesticides, synthetic pesticides, persistence, Ames mutagenicity, rodent carcinogenicity, developmental toxicity

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Introduction
DNA evidence suggests that the first plants might have colonized land about 700 million years ago. The first fossil evidence of land plants dates from 510 to 439 million years ago (Ordovician Period) in the form of wind-dispersed spores believed to have been produced by submerged plants that raised their sporangia above the water.¹ Flowering plants, termed angiosperms, are a more recent but still ancient arrival with the first fossil evidence appearing about 125 million years ago during the Lower Cretaceous, with a high degree of diversification by the Middle Cretaceous about 100 million years ago.² Insects coevolved with plants with the earliest fossilized insects dating from about 412 million years ago during the Early Devonian Period. However, phylogenetic data suggest that Hexapoda, the largest group of insects, might have evolved about 479 million years ago during the Early Ordovician Period.³

Pesticides are applied to prevent or control pests, diseases, weeds, and other plant pathogens to ameliorate or eliminate yield losses and maintain high agricultural production quality. Pesticides (both natural and synthetic) are regulated by governments and are premarket tested by employing standardized test methods aimed at achieving

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minimal impacts on human health and the environment. Under conditions of inappropriate application, unacceptable residue levels can accumulate in water, soil, or ambient air. Contamination from soil leaching, field runoff water, and spray drift, as well as adverse effects on wildlife, fish, plants, and other nontarget organisms can potentially occur. Actualization of potential effects depends on the specific toxicity, quantity and potency of the applied pesticide, safety precautions taken during application, adsorption onto soil colloids, weather conditions prevailing after application, and how long the pesticide persists in the environment. Potential health effects of pesticide exposures are dependent on the biological pathways and organ systems affected. Potential adverse health effects include skin and eye irritation, carcinogenicity (as estimated by rodent cancer bioassay), disruption of endocrine pathways, and interference with neural transmission in the case of some of the organophosphates and carbamates. The immobility of plants exerted evolutionary selection pressures resulting in the production of thousands of chemical substances thought to function as pesticides against predation by insects and animals. In 1990, Ames et al. reported that 99.99% of pesticide exposure experienced by humans (via diet) comes from natural pesticides produced by plants in contrast with trace residues of synthetic pesticides applied to the plants. This contention by Ames et al. is supported by a comprehensive review by Duke. Duke noted that tens of thousands of secondary products of plants have been identified as pesticides. Plant-produced compounds and derivatives with pesticidal activity include 1,8-cineole, cinnamon, hypericin, and pyrethrins. Plant-produced compounds with insecticidal activity include camphene, nicotine, anabasine, and rotenone. Plant-produced compounds with fungicidal, nematicidal, and rodenticidal activity include pisatin, juglone, alpha-terthienyl, and strychnine. It has been estimated that hundreds of thousands of these secondary plant products exist. The majority of this huge number of chemicals produced by plants “are involved in the interaction of plants with other species—primarily the defense of the plant from plant pests.” Anyone who eats vegetables is exposed to a subset of these natural plant pesticides.

Farmers apply pesticides to improve crop yield. Most pesticides used today are synthetic. However, smaller quantities of both organic and inorganic natural pesticides are also employed. These natural pesticides derive from biochemical, microbial, botanical, or mineral sources. Biochemical pesticides, for example phenomones, can disrupt mating behavior thereby controlling insect populations. Bacteria (e.g. δ-aminolevulinic acid), fungi, algae, and naturally occurring viruses or protozoans can be used to produce microbial pesticides. These natural plant pesticides either introduce a pathogen to a particular insect population (e.g. Milky spore), produce a substance toxic to insects, or limit reproduction. A number of plant-derived botanical pesticides have been isolated including nicotine, anabasine, and nornicotine from tobacco; azadirachtin B from neem seeds; linalool from tree bark; rotenone from derris plant; 1,8-cineole from eucalyptus tree; physostigmine from Calabar bean or manchineel tree; pyrethrins, jasminolins, and cinerins from chrysanthemum plant; and α-limonene from citrus peels. Also, mineral-based sulfur and lime-sulfur can be sprayed for insect control. The 34 natural plant pesticides evaluated for persistence and toxicity in this study were derived from either microbial or botanical sources.

The purpose of this study was to determine whether there are differences in persistence and toxicity between high-volume synthetic and natural pesticides. In this analysis, we used standard United States Environmental Protection Agency (US EPA) programs to estimate the toxicity (Toxicity Estimation Software Tool (T.E.S.T.)) and persistence and bioaccumulation (Estimation Programs Interface (EPI) Suite™) of a series of synthetic and natural pesticides. Thirty-four natural plant pesticides and 32 synthetic pesticides were included in this analysis. These subsets of natural and synthetic pesticides were selected because of their relatively high volume as compared with other members of the class, and widely distributed patterns of use. As such, the natural and synthetic pesticides studied herein represent leaders in the respective classes regarding their commercial importance and toxicological relevance to environmental and human health.

Methods

Compilation of natural and synthetic pesticides

A literature search of the databases Google, PubMed (National Library of Medicine), and the Hazardous Substances Data Bank (National Library of Medicine) was conducted. Key search words included the following: natural plant pesticides, natural pesticides, synthetic pesticides, pesticides, and persistent organic pollutants (POPs). This search strategy identified four major publications describing naturally occurring pesticides: Duke, McLaren, Russell, and Mpumi et al. The synthetic pesticides that are identified as POPs are listed within the United Nations Environment Programme, Stockholm Convention (POP chemicals are listed in both Annex A and Annex C) and/or the United Nations Economic Commission for Europe Protocol. Information on the Top 10 pesticides (poundage of active ingredient) was obtained from EPA and was based on Paisley-Jones.

Thirty-two synthetic pesticides were included in this analysis. The 32 represent the Top 10 pesticides (poundage of active ingredient) sold worldwide and 22 other popular pesticides used internationally. There are only 8 pesticides common to the set of 32 synthetic pesticides considered in this study, and 514 pesticides previously tested by US EPA (2,4-dichlorophenoxyacetic acid (2,4-D); acetochlor; atrazine; chloropiricin; chlorothalonil; glyphosate; metolachlor; and pentachlorophenol). Seven of the eight common...
synthetic pesticides are on the Top 10 list (poundage of active ingredient) of pesticides sold worldwide. Of the 32 synthetic pesticides evaluated in this study, 62% are rodent carcinogens as determined by chronic cancer bioassays. Of the Top 10 pesticides by poundage of active ingredient sold worldwide, 30% are rodent carcinogens (Table 1). The 34 natural plant and bacterial extracts analyzed in this study represent the high-volume botanicals and microbial extracts used as commercial pesticides. The 34 natural pesticides described herein represent only a small fraction of the natural products extracted from plants and bacteria that have been employed as a pesticide, albeit usually under limited circumstances and at relatively low levels. The 1975 Farm Chemicals Handbook listed the following plant-derived materials as pesticides: tobacco alkaloids (nicotine, nornicotine, anabasine); rotenone (cube); rotenone (derris); hellebore; ryania (ryanodine); sabadilla; and pyrethrum (jasmol I, cinerin I, pyrethrin I, jasmolin II, cinerin II, pyrethrin II). Many of these same natural pesticides (noted in italics) are still in use and are numbered among the 34 pesticides analyzed herein.

### Computer programs for estimating persistence, bioaccumulation, and toxicity

Two computer programs were used to develop the tables of data on naturally occurring pesticides and the synthetic pesticides—T.E.S.T. and EPI Suite. T.E.S.T. (version 4.2) was used to determine the toxicity of several natural pesticides, the Top 10 synthetic pesticides used worldwide, and synthetic pesticides on the Stockholm list of POPs. The T.E.S.T. program contains experimental values for the toxicity endpoints. It also can estimate toxicity from molecular structure. T.E.S.T. was developed by the US EPA to allow users to easily acquire experimental data or estimate the toxicity of chemicals using quantitative structure activity relationships (QSARs) methodologies. In QSAR mode, T.E.S.T. estimates the toxicity values and physical properties of organic chemicals based on the molecular structure of the organic chemical entered by the user. T.E.S.T. allows a user to estimate toxicity without requiring any external programs. Users input a chemical to evaluate by drawing into an included chemical sketcher window, entering a structure text file, or importing from an included database of structures. Once entered, toxicity is either provided from experimental data or estimated using one of several advanced QSAR methodologies. The required molecular descriptors are calculated within T.E.S.T. The Consensus method was shown to achieve the best prediction results as determined by external validation.

The endpoints of toxicity contained in, or calculated by, T.E.S.T. are the following:

- 96 h fathead minnow 50% lethal concentration (LC50).
- 48 h Daphnia magna 50% lethal concentration (LC50).
- Tetrahymena pyriformis 50% growth inhibition concentration (IGC50).
- Oral rat 50% lethal dose (LD50).
- Bioconcentration Factor (BCF)—the BCF data set was compiled by researchers at the Mario Negri Istituto Di Ricerche Farmacologiche. The bioaccumulation factor (BAF) is the ratio of the chemical concentration in fish as a result of absorption via the respiratory surface to that in water at steady state.
- Developmental Toxicity (DevTox).
- Ames Mutagenicity (Mutagenicity).

### Table 1. Information on synthetic and natural pesticides examined in this study.

| Categories                                      | Synthetic pesticides (n = 32) | Natural pesticides (n = 34) |
|------------------------------------------------|-------------------------------|-----------------------------|
| Top 10 synthetic pesticides (by poundage)      | 10                            |                             |
| Most common pesticides used internationally    | 22                            |                             |
| Pesticides tested by the US EPA                | >500                          | 2                           |
| Pesticides tested by US EPA among the pesticides studied | 8 (2,4-D; acetochlor; atrazine; chloropicrin; chlorothalonil; glyphosate; metolachlor; and pentachlorophenol) | 2 (pyrethrins, rotenone) |
| Number of common pesticides on the Top 10 list  | 7                             | 0                           |
| Percentage of pesticides that are rodent carcinogens | 62                            | 30                          |

US EPA: United States Environmental Protection Agency; 2,4-D: 2,4-dichlorophenoxyacetic acid.

In all cases, the experimental values for the toxicity endpoints were used when available. These were obtained from US EPA programs including ECOTOX, TETRATOX, ChemIDPlus, data from Dimitrov et al., Arnot and Gobas, Zhao et al., and the Toxicity Benchmark Study for Ames Mutagenicity. When experimental values were not provided in T.E.S.T., the QSAR calculated values were used.

The EPI Suite is a computer program designed to derive physical/chemical property and environmental fate properties of organic chemicals based on the molecular structure of the organic chemical entered by the user.
estimations.\textsuperscript{11,24} It was developed by US EPA and the Syracuse Research Corp. (SRC). EPI Suite is a screening-level tool and should not be used if acceptable measured values are available.

For this analysis of natural and synthetic pesticides, the following EPI Suite modules were used:

- **BIOWIN3**: BIOWIN\textsuperscript{TM} estimates aerobic and anaerobic biodegradability of organic chemicals using seven different models. Biowin3 (Ultimate Survey Model) and Ready Biodegradability modules were used.\textsuperscript{11,24}
- **KOWWIN**: KOWWIN\textsuperscript{TM} estimates the log octanol–water partition coefficient, log KOW, of chemicals using an atom/fragment contribution method. Many of the log octanol–water partition coefficients have been experimentally measured. When experimental values were available these were used rather than the calculated log KOW values.\textsuperscript{11,24}
- **BCFBAF**: BCFBAF\textsuperscript{TM} is the calculated fish BCF and its logarithm using two different methods. The first is a traditional regression based on log KOW plus any applicable correction. The second is the Arnott–Gobas method, which calculates BCF from mechanistic first principles. BCFBAF also incorporates prediction of apparent metabolic half-life in fish and estimates BCF and BAF for three trophic levels.\textsuperscript{11,24}
- **Level III Fugacity Model—LEV3EPI**: This program contains a level III multimedia fugacity model and predicts partitioning of chemicals among air, soil, sediment, and water under steady state conditions for a default model “environment.” Additionally, a composite value of persistence is calculated. This composite persistence value was used in the tables of this analysis.\textsuperscript{11,24}

**Mathematical treatments**

**Hypothesis tests for multiple proportions.** Given more than one sample from which proportions are observed, a hypothesis test is usually used to assess whether differences in the proportions are statistically significant. The different samples may be taken from the same population at different times, from the same population with different experimental treatments, or from different groups.

The methods described in the following text are among those designed according to the “classical approach to hypothesis testing.” In the “classical approach,” an exact assumption is made about the population’s characteristics, usually but not always, restricted to an assumption about the value of a population parameter such as the true proportion, mean or standard deviation. This assumption is called the null hypothesis and is so named because it is usually an assumption of either no difference or no change. A test statistic is chosen that will have an exact distribution, or at least be close to the same distribution, when the null hypothesis is true. The probabilities of the values of the test statistic that are less likely than the value calculated from the sample(s) are summed to obtain what is termed the \( p \) value. The null hypothesis is rejected when the \( p \) value is small. The test statistic is designed so that when the null hypothesis is untrue, that the more untrue the null hypothesis is in the sense of the difference between the true and the hypothesized parameter, the more likely the correct conclusion will be made.

**Commonly used tests for two proportions.** Given two samples of sizes \( n_1 \) and \( n_2 \) with occurrences \( x_1 \) and \( x_2 \), the notation \( \hat{p}_1 = \frac{x_1}{n_1} \) and \( \hat{p}_2 = \frac{x_2}{n_2} \) will be used for the proportions. The true population proportions from which the first and second samples were drawn will be denoted by \( p_1 \) and \( p_2 \). The following tests are most commonly used to assess the statistical significance of differences in two proportions.

**Pooled test**

The null hypothesis is

\[
H_0 : p_1 - p_2 = 0
\]

The formula for the pooled test statistic comparing two proportions is

\[
z = \frac{\hat{p}_1 - \hat{p}_2 - 0}{\sqrt{\hat{p}(1 - \hat{p}) \left( \frac{1}{n_1} + \frac{1}{n_2} \right)}}
\]

where \( \hat{p} \) is the proportion in the first sample with the characteristic of interest, \( \hat{p}_2 \) is the proportion in the second sample with the characteristic of interest, \( \hat{p} \) is the proportion in the combined sample (all the individuals in the first and second samples together) with the characteristic of interest, and \( z \) is a value on the \( Z \)-distribution

\[
\hat{p} = \frac{x_1 + x_2}{n_1 + n_2}
\]

The standard error is

\[
\sqrt{\hat{p}(1 - \hat{p}) \left( \frac{1}{n_1} + \frac{1}{n_2} \right)}
\]

**Unpooled test**

The null hypothesis is

\[
H_0 : \ p_1 - p_2 = 0
\]

\[
z = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\frac{\hat{p}_1(1 - \hat{p}_1)}{n_1} + \frac{\hat{p}_2(1 - \hat{p}_2)}{n_2}}}
\]

**Chi-squared statistic.** The Chi-squared (\( \chi^2 \)) statistic is defined as the sum of the squares of the \( Z \) squared values. If there are \( d \) degrees of freedom, then let this process of calculating \( \chi^2 \)
continue until $d$ different $Z$ values are selected from the distribution. If $Z_1, \ldots, Z_4$ are independent, standard normal random variables, then the sum of their squares

$$Q = \sum_{i=1}^{k} z_i^2$$

is distributed according to the $\chi^2$ distribution with $k$ degrees of freedom. This is usually denoted as

$$Q \sim \chi^2(k) \text{ or } Q \sim \chi_1^2$$

The $\chi^2$ distribution has one parameter: $k$ — a positive integer that specifies the number of degrees of freedom (i.e. the number of $Z_i$’s).31

$p$ Values from binomial tail probabilities. Given two samples of sizes $n_1$ and $n_2$ with occurrences $x_1$ and $x_2$, let $H_0$, the null hypothesis, be that the two samples were drawn independently from a population with the same true proportion $p$ estimated by

$$\hat{p} = \frac{x_1 + x_2}{n_1 + n_2}$$

that is

$$H_0 : p_1 = p_2 = \hat{p}$$

The test statistic is simply the outcome $(x_1, x_2)$ with probability, assuming $H_0$, given by

$$\left(\begin{array}{c} n_1 \\ x_1 \end{array}\right) \hat{p}^{x_1} (1 - \hat{p})^{(n_1 - x_1)} \left(\begin{array}{c} n_2 \\ x_2 \end{array}\right) \hat{p}^{x_2} (1 - \hat{p})^{(n_2 - x_2)}$$

$$= \left(\begin{array}{c} n_1 \\ x_1 \end{array}\right) \left(\begin{array}{c} n_2 \\ x_2 \end{array}\right) \hat{p}^{(x_1 + x_2)} (1 - \hat{p})^{(n_1 + n_2 - (x_1 + x_2))}$$

The $p$ value for this test is the sum of the probabilities of the possible outcomes whose probability is less than that of the observed outcome.31 That is

$$p \text{ Value} = \sum_{(x, y) : p(i, j) < p(x, y)} \left(\begin{array}{c} n_1 \\ x \end{array}\right) \hat{p}^{x} (1 - \hat{p})^{(n_1 - x)} \left(\begin{array}{c} n_2 \\ y \end{array}\right) \hat{p}^{y} (1 - \hat{p})^{(n_2 - y)}$$

here $P(x, y) = \left(\begin{array}{c} n_1 \\ x \end{array}\right) \hat{p}^{x} (1 - \hat{p})^{(n_1 - x)} \left(\begin{array}{c} n_2 \\ y \end{array}\right) \hat{p}^{y} (1 - \hat{p})^{(n_2 - y)}$

This summarizes to

$$p \text{ Value} = \sum_{(i, j) : p(i, j) < p(x, y)} p(i, j), \text{ with}$$

$$p(x, y) = \left(\begin{array}{c} n_1 \\ x \end{array}\right) \left(\begin{array}{c} n_2 \\ y \end{array}\right) \hat{p}^{(x+y)} (1 - \hat{p})^{(n_1+n_2-(x+y))}$$

Table 15 (Online Supplement) shows the statistics on the comparison of characteristics for all natural and synthetic pesticides studied.

Results

Tables 2 to 4 summarize the persistence, biodegradability, bioaccumulation, toxicity and carcinogenicity data on the 34 relatively high-volume natural pesticides, the 22 high-volume synthetic pesticides, and the Top 10 commercial pesticides sold worldwide. With the exception of rodent carcinogenicity data available on the Internet, the data in Tables 2 to 4 were derived from EPI Suite 4.1.

Table 2 summarizes the persistence, biodegradability, bioaccumulation, toxicity, and carcinogenicity data on the 34 natural pesticides. For the 34 natural pesticides, the maximum persistence time (half-life in the environment) was 15,000 h, the minimum persistence time was 101 h, and the average persistence time 2402 h.

Table 3 summarizes the persistence, biodegradability, bioaccumulation, toxicity, and carcinogenicity data on the 22 high-volume synthetic pesticides. The maximum, minimum, and average persistence for these 22 synthetic pesticides were 9730, 144, and 4579 h.

Table 4 summarizes the persistence, biodegradability, bioaccumulation, toxicity, and carcinogenicity data on the Top 10 synthetic pesticides sold worldwide. The maximum, minimum, and average persistence for the Top 10 synthetic pesticides were 5180, 144, and 1506 h. The average persistence time for the 34 natural pesticides was statistically significantly lower than for the 32 synthetic pesticides ($p < 0.0039$).

Only 3 of the 34 natural pesticides were biodegradable, that is, δ-aminolevulinic acid, juglone, and geraniol. None of the 22 synthetic pesticides were biodegradable. Only 1 of the Top 10 synthetic pesticides were biodegradable (glyosphate). The difference in tendency to biodegrade between the 34 natural pesticides and 32 synthetic pesticides was not statistically significant ($p < 0.332$) (Tables 2 to 4).

For the natural pesticides, the maximum log KOW was 8.22, the minimum $-4.4$, and the average 3.41 (Table 2). The log KOW for the 22 high-volume synthetic pesticides had a maximum, minimum, and average value of 6.91, 3.44, and 5.47, respectively (Table 3). The log KOW for the Top 10 synthetic pesticides had a maximum, minimum, and average value of 3.05, $-5.4$, and 1.10, respectively (Table 4). On average, the 32 synthetic pesticides were more lipophilic than the 34 natural plant pesticides, although this difference was not statistically significant ($p < 0.275$).

The BAF (biotransformation half-life normalized to 10 g fish) for the natural pesticides ranged from 113 days to 0.00001233 days, with an average of 5.83 days (Table 2). The BAF for the high-volume pesticides ranged from 252 days to 1.66 days, with an average of 62.2 days (Table 3). The BAF for the Top 10 synthetic pesticides ranged from 10.1 days to 0.0016 days, with an average of 1.28 days (Table 4). The BAF of the 32 synthetic pesticides was statistically significantly higher than the comparable value of the 34 natural plant pesticides ($p < 0.0009$).
| Chemical | Formula | Molecular weight | CAS RN | Canonical SMILES | Ultimate biodegradability (BioWin3)—time (h) | BioWin3—anaerobic biodegradability (yes/no) | Log KOW | BAF biotransformation half-life (normalized to 10 g fish) | Toxicity (mg/kg) (rats) | Rodent carcinogen |
|----------|---------|-----------------|--------|------------------|---------------------------------------------|--------------------------------------------|---------|-----------------------------------------------|----------------------|------------------|
| N,N,N',N'-Tetramethylethylenediamine | C8H16N4 | 150.21 | 227-34-8 | CC(=O)(C(N)=C(N)=C(=O)) | 3.28 days—39 h | Yes | -4.1 | 0.028 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | Y |
| 2,4-Dichlorophenoxyacetic acid | C₈H₇Cl₂O₂ | 247.06 | 128-92-5 | CC(=O)(O)(Cl)C=C(=N)(O)Cl | 2.65 weeks—160 h | No | 0.97 | 0.069 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |
| 2,4-Dinitrophenol | C₈H₄N₂O₃ | 152.12 | 88-90-6 | C(=O)(N)=C(N)=C(=O) | 2.88 weeks—340 h | No | 2.9 | 0.20 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |
| camphor | C₁₀H₁₆O | 156.21 | 156-28-6 | C₁₀H₁₆O | 2.17 weeks—360 h | No | 2.0 | 0.12 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |
| Cinnamaldehyde | C₁₀H₁₂O₂ | 156.19 | 106-20-9 | (C₆H₅)C(=O)(C)C(=O)(C) | 2.70 weeks—380 h | No | 2.77 | 0.12 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |
| N,N-Dimethylformamide | C₃H₆N₂O | 75-09-2 | 75-09-2 | C₃H₆N₂O | 1.91 weeks—305 h | No | 3.38 | 0.012 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |
| 2,4-Dichlorophenol | C₈H₄Cl₂O₂ | 192.93 | 89-69-3 | C₈H₄Cl₂O₂ | 2.59 weeks—600 h | No | 4.64 | 3.68 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |
| Inositol | C₆H₁₂O₆ | 182.15 | 87-86-5 | C₆H₁₂O₆ | 1.91 weeks—305 h | No | 3.38 | 0.012 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |
| Phosphorous acid | H₃PO₃ | 97.99 | 77-94-2 | H₃PO₃ | 2.83 weeks—776 h | Yes | 1.92 | 0.07 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N/A |
| Nicotinamide | C₇H₉N₄O₇ | 162.13 | 59-88-8 | C₇H₉N₄O₇ | 2.37 weeks—1610 h | No | 1.17 | 0.0072 days | Oral LD₅₀ = 50–60; Dermal LD₅₀ = 50 | N |
| N,N-Dimethylformamide | C₃H₆N₂O | 75-09-2 | 75-09-2 | C₃H₆N₂O | 2.68 weeks—1700 h | No | 0.17 | 0.084 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |
| Phenolphthalein | C₁₅H₁₀O₃ | 230.23 | 59-88-8 | C₁₅H₁₀O₃ | 2.08 weeks—4370 h | No | 4.88 | 0.038 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |
| Phenylstigmine | C₁₅H₁₃N₂O₂ | 335.31 | 292-58-7 | C₁₅H₁₃N₂O₂ | 1.82 weeks—2340 h | No | 1.58 | 0.0045 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | Y |
| Phosphorus oxychloride | C₁₅H₆O₅ | 161.08 | 100-43-5 | C₁₅H₆O₅ | 3.44 weeks—1590 h | Yes | 1.92 | 0.07 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N/A |
| Retinoic acid | C₂₁H₂₀O₂ | 314.34 | 112-89-0 | C₂₁H₂₀O₂ | 2.00 weeks—2960 h | No | 2.58 | 0.015 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |
| Strychnine | C₂₁H₂₂N₂O₂ | 334.38 | 57-24-9 | C₂₁H₂₂N₂O₂ | 1.86 weeks—4900 h | No | 4.1 | 0.083 days | Oral LD₅₀ = 60–150; dermal LD₅₀ = 940–3000 | N/A |
| Thymol | C₁₀H₁₆O | 156-83-5 | 156-83-5 | C₁₀H₁₆O | 3.14 weeks—1500 h | No | 1.75 | 0.015 days | Oral LD₅₀ = 750–1200; dermal LD₅₀ = 4000 | N |
| Thymol | C₁₀H₁₆O | 156-83-5 | 156-83-5 | C₁₀H₁₆O | 3.14 weeks—1500 h | No | 1.75 | 0.015 days | Oral LD₅₀ = 750–1200; dermal LD₅₀ = 4000 | N |
| Wyeone | C₁₅H₁₄O | 258.28 | 20079-30-5 | C₁₅H₁₄O | 3.04 weeks—661 h | No | 2.68 | 0.064 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | Y |
| α-Terpentinol | C₁₂H₂₀O₂ | 248.38 | 108-13-4 | C₁₂H₂₀O₂ | 2.65 weeks—1320 h | No | 5.57 | 3.96 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |
| Lantadene A | C₃₂H₃₂O₅ | 512.8 | 30545-82-5 | C₃₂H₃₂O₅ | 4.57 weeks—1700 h | No | 8.22 | 1.13 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |
| Geraniol | C₁₀H₁₈O | 154.28 | 106-24-1 | C₁₀H₁₈O | 3.02 weeks—424 h | Yes | 3.47 | 1.96 days | The LD₅₀ for rats was 800–3000 mg kg⁻¹ for pure compounds | N |

(continued)
### Table 2. (continued)

| Chemical     | Formula  | Molecular weight | CAS RN | Canonical SMILES | Ultimate biodegradability (BioWin3)—persistence time (h) = half-life in environment | BioWin—anaerobic biodegradability (yes/no) | Log KOW | BAF biotransformation half-life (normalized to 10 g fish) | Toxicity (mg/kg) (rats) | Rodent carcinogen |
|--------------|----------|------------------|--------|------------------|-----------------------------------------------------------------------------------|----------------------------------------|---------|---------------------------------------------------------|--------------------------|------------------|
| 6-Methoxyapigenin | C16H12O6 | 300.26           | 1447-88-7 | \( \text{COC}_1\text{C}2\text{C}3\text{C}_1\text{O} \text{OC}_1\text{C}3\text{C} \text{C}_1\text{O} \text{CC}_1\text{O} \text{OCC}_1\text{C} \) | 2.57 weeks—1860 h | No | 2.67 | 0.014 days | The LD\(_{50}\) for rats were 800–3000 mg kg\(^{-1}\) for pure compounds | N/A |
| Jasmin I     | C21H30O3 | 330.5            | 4466-14-2 | \( \text{CCC}_1\text{C}2\text{C}3\text{C}_1\text{O} \text{OC}_1\text{C}3\text{C}_1\text{O} \text{C}_2\text{C}2\text{C}_1\text{C}_2\text{C}_1\text{O} \text{CC}_1\text{O} \text{OCC}_1\text{C} \) | 2.67 weeks—1140 h | No | 6.42 | 2.153 days | The LD\(_{50}\) for rats were 800–3000 mg kg\(^{-1}\) for pure compounds | N |
| Cinerin I    | C20H28O3 | 316.4            | 25402-06-6 | \( \text{CC}_1\text{C}2\text{C}3\text{C}_1\text{O} \text{OC}_1\text{C}3\text{C}_1\text{O} \text{C}_2\text{C}2\text{C}_1\text{C}_2\text{C}_1\text{O} \text{CC}_1\text{O} \text{OCC}_1\text{C} \) | 2.70 weeks—1100 h | No | 5.93 | 1.563 days | The LD\(_{50}\) for rats were 800–3000 mg kg\(^{-1}\) for pure compounds | N |
| Pyrethrin I  | C21H28O3 | 338.4            | 121-21-1 | \( \text{CC}_1\text{C}2\text{C}3\text{C}_1\text{O} \text{OC}_1\text{C}3\text{C}_1\text{O} \text{C}_2\text{C}2\text{C}_1\text{C}_2\text{C}_1\text{O} \text{CC}_1\text{O} \text{OCC}_1\text{C} \) | 2.37 weeks—1150 h | No | 5.9 | 1.485 days | Oral LD\(_{50}\) = 1200–1500; Dermal LD\(_{50}\) ≥ 1800 | N |
| Jasmin II    | C22H30O5 | 374.5            | 1172-63-0 | \( \text{CC}_1\text{C}2\text{C}3\text{C}_1\text{O} \text{OC}_1\text{C}3\text{C}_1\text{O} \text{C}_2\text{C}2\text{C}_1\text{C}_2\text{C}_1\text{O} \text{CC}_1\text{O} \text{OCC}_1\text{C} \) | 2.72 weeks—1390 h | No | 5.47 | 0.147 days | The LD\(_{50}\) for rats were 800–3000 mg kg\(^{-1}\) for pure compounds | N |
| Cinerin II   | C21H28O5 | 340.4            | 121-20-0 | \( \text{CC}_1\text{C}2\text{C}3\text{C}_1\text{O} \text{OC}_1\text{C}3\text{C}_1\text{O} \text{C}_2\text{C}2\text{C}_1\text{C}_2\text{C}_1\text{O} \text{CC}_1\text{O} \text{OCC}_1\text{C} \) | 2.75 weeks—1450 h | No | 4.98 | 0.107 days | The LD\(_{50}\) for rats were 800–3000 mg kg\(^{-1}\) for pure compounds | N |
| Pyrethrin II | C22H28O5 | 372.5            | 121-29-9 | \( \text{CC}_1\text{C}2\text{C}3\text{C}_1\text{O} \text{OC}_1\text{C}3\text{C}_1\text{O} \text{C}_2\text{C}2\text{C}_1\text{C}_2\text{C}_1\text{O} \text{CC}_1\text{O} \text{OCC}_1\text{C} \) | 2.42 weeks—1110 h | No | 4.3 | 0.064 days | Oral LD\(_{50}\) = 1200–1500; dermal LD\(_{50}\) ≥ 1800 | N |
| Tagitins C   | C19H12O6 | 348.4            | 59979-56-5 | \( \text{CC}_1\text{C}2\text{C}3\text{C}_1\text{O} \text{OC}_1\text{C}3\text{C}_1\text{O} \text{C}_2\text{C}2\text{C}_1\text{C}_2\text{C}_1\text{O} \text{CC}_1\text{O} \text{OCC}_1\text{C} \) | 2.48 weeks—1390 h | No | 1.08 | 0.0093 days | The LD\(_{50}\) for rats were 800–3000 mg kg\(^{-1}\) for pure compounds | N/A |
| ß-Caryophyllene | C15H24  | 204.35           | 87-44-5 | \( \text{CC}_1\text{C}2\text{C}3\text{C}_1\text{O} \text{OC}_1\text{C}3\text{C}_1\text{O} \text{C}_2\text{C}2\text{C}_1\text{C}_2\text{C}_1\text{O} \text{CC}_1\text{O} \text{OCC}_1\text{C} \) | 2.54 weeks—207 h | No | 6.3 | 57.98 days | The LD\(_{50}\) for rats were 800–3000 mg kg\(^{-1}\) for pure compounds | N |
| Linalool     | C10H18O  | 154.23           | 78-70-6 | \( \text{CC}_1\text{C}2\text{C}3\text{C}_1\text{O} \text{OC}_1\text{C}3\text{C}_1\text{O} \text{C}_2\text{C}2\text{C}_1\text{C}_2\text{C}_1\text{O} \text{CC}_1\text{O} \text{OCC}_1\text{C} \) | 2.65 weeks—792 h | No | 2.97 | 0.726 days | Oral LD\(_{50}\) = 2440–3180; dermal LD\(_{50}\) = 3578-8374 | N |
| o-Limonene   | C10H16   | 136.23           | 5989-27-3 | \( \text{CC}_1\text{C}2\text{C}3\text{C}_1\text{O} \text{OC}_1\text{C}3\text{C}_1\text{O} \text{C}_2\text{C}2\text{C}_1\text{C}_2\text{C}_1\text{O} \text{CC}_1\text{O} \text{OCC}_1\text{C} \) | 2.90 weeks—123 h | No | 4.57 | 3.53 days | Oral LD\(_{50}\) ≥ 5000 | N |

**BAF**: bioaccumulation factor.
Table 3. Persistence, biodegradability, bioaccumulation, toxicity, and carcinogenicity data on synthetic pesticides (data from EPI Suite 4.1).

| Chemical          | Formula | Molecular weight | CAS RN      | Canonical SMILES | Ultimate biodegradability (BioWin3)— persistence time (h) = half-life in environment | BioWin aerobic/anaerobic biodegradability (yes/no) | Persistence half-life (time) in soil sediment. | Log KOW | BAF biotransformation half-life (normalized to 10 g fish) | Toxicity | Rodent carcinogen |
|-------------------|---------|------------------|-------------|------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------|---------|----------------------------------------------------------------|---------|------------------|
| Aldrin            | C12 H8 CL6 | 344.92          | 309-00-2    | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C)=C       | Recalcitrant—5290 h                                                                      | No                                                                         | 4–7 years                                      | 6.06    | 73.7 days                                      | Rot oral: 39 to 60 mg/kg, dermal: 100 mg/kg, mouse oral: 44 mg/kg | Y      |
| Dieldrin          | C12 H8 CL6 O1 | 380.91          | 60-57-1     | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=C=CC=C(C=O)       | Recalcitrant—5070 h                                                                      | No                                                                         | 9 months                                      | 5.4     | 62.7 days                                      | Rot oral: 46 mg/kg, dermal: 50–120 mg/kg, mouse oral: 38–77 mg/kg | Y      |
| Chlordane         | C10 H6 CL8  | 409.78          | 57-74-9     | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=C=CC=C(C=O)       | Recalcitrant—6750 h                                                                      | No                                                                         | 10 years                                      | 6.22    | 129 days                                       | Rot oral: 200 to 700 mg/kg, dermal: 530–490 mg/kg, mice oral: 145–430 mg/kg, dermal: 153 mg/kg | Y      |
| α-Endosulfan      | C9 H6 CL6 O3 | 406.92          | 332-13-65-9 | C1=C(C=C(C)=C(C=O))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—4460 h                                                                      | No                                                                         | 35 days                                       | 3.83    | 5.39 days                                      | Rot oral: 18–220 mg/kg, dermal: 74 mg/kg | N      |
| β-Endosulfan      | C9 H6 CL6 O3 | 406.92          | 959-98-8    | C1=C(C=C(C)=C(C=O))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—4460 h                                                                      | No                                                                         | 130 days                                      | 3.83    | 5.39 days                                      | Rot oral: 18–220 mg/kg, dermal: 74 mg/kg | N      |
| Endrin            | C12 H8 CL6 O1 | 380.91          | 72-30-8     | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=C=CC=C(C=O)       | Recalcitrant—5070 h                                                                      | No                                                                         | 1 Day to 12 Years                              | 5.4     | 62.7 days                                      | Rot oral: 3 mg/kg, dermal: 15 mg/kg, mouse oral: 1.37 g/kg, intravenous: 2300 g/kg | N      |
| Mirex             | C10 CL12  | 545.55          | 2385-85-5   | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—8770 h                                                                      | No                                                                         | 10 years                                      | 6.89    | 109 days                                       | Rot oral: 600–740 mg/kg             | Y      |
| Heptachlor        | C10 H5 CL7 | 373.32          | 76-44-8     | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—5040 h                                                                      | No                                                                         | 2 years                                       | 6.1     | 50.1 days                                      | Rot oral: 40–220 mg/kg, dermal: 119–320 mg/kg, mouse oral: 30–68 mg/kg | Y      |
| Hexachlorobenzene (HCB) | C6 CL6 | 284.78          | 118-74-1    | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—4800 h                                                                      | No                                                                         | 3–6 years                                     | 5.73    | 21.5 days                                      | Rot oral: 4000–10,000 mg/kg, guinea pigs oral: <3000 mg/kg             | Y      |
| γ-Lindane (γ-HCH); δ-Lindane (δ-HCH) | C6 H6 CL6 | 230.83          | 58-88-9; 319-84-6; 319-85-7 | C1=C(C(C=OC)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—4610 h                                                                      | No                                                                         | 15 months                                     | 3.78    | 17 days                                        | Rot oral: 88–270 mg/kg, mouse oral: 59–246 mg/kg | Y      |
| Toxaphene         | C10 H8 CL8 | 411.8           | 8001-35-2   | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—9020 h                                                                      | No                                                                         | 11 Years                                      | 6.75    | 124 days                                       | Rot oral: 80–293 mg/kg, dogs: 25 mg/kg | Y      |
| Dibromodichloromethane (DDT) | C14 H9 CL5 | 354.49          | 50-29-3     | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—9730 h                                                                      | No                                                                         | 2–15 years                                    | 6.91    | 161 days                                       | Rot oral: 113–130 mg/kg, dermal: 2130 mg/kg, mice oral: 150–300 mg/kg | Y      |
| 1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene (DDD) | C14 H10 OCH4 | 310.05         | 72-54-8     | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—7530 h                                                                      | No                                                                         | 5–10 years                                    | 6.02    | 58.8 days                                      | Rot oral: 4000 mg/kg               | Y      |
| Dibromodichloromethane (DDD) | C14 H8 CL4 | 318.03          | 72-35-9     | C1=C(C(C=OC)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—8470 h                                                                      | No                                                                         | 10 years                                      | 6.51    | 252 days                                       | Rot oral: 800–1240 mg/kg            | Y      |
| p, p'-DDE         | C14 H9 CL5 O1 | 370.49          | 115-32-2    | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—6000 h                                                                      | No                                                                         | 60 days                                       | 5.02    | 37.4 days                                      | Rot oral: 684–1495 mg/kg           | Y      |
| o, p'-DDT         | C14 H9 CL5 O1 | 370.49          | 10606-46-9 | C1=C(C(C=OC)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—6000 h                                                                      | No                                                                         | 60 days                                       | 5.81    | 65.2 days                                      | Rot oral: 684–1495 mg/kg           | Y      |
| Methoxychlor      | C16 H72 CL3 O2 | 357.75          | 72-48-5     | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—5330 h                                                                      | No                                                                         | <120 Days                                     | 6.45    | 242 days                                       | Rot oral: 5000–6000 mg/kg, mice oral: 2000 mg/kg             | Y      |
| Isodrin           | C12 H8 CL6 | 364.92          | 465-73-6    | C1=C(C=C(C)=CC(COC))=CC=C(C)=CC=C(C)=CC=C(C=O)       | Recalcitrant—6220 h                                                                      | No                                                                         | 0.5–6 years                                    | 6.06    | 73.7 days                                      | Rot oral: 8.8 mg/kg               | Y      |

(continued)
| Chemical          | Formula | Molecular weight | CAS RN   | Canonical SMILES                                                                 | Ultimate biodegradability (BioWin3)—persistence time (h) | BioWin—aerobic/anaerobic biodegradability (yes/no) | Persistence half-life (time) in soil/sediment | Log KOW | BAF biotransformation half-life (normalized to 10 g fish) | Toxicity | Rodent carcinogen |
|-------------------|---------|------------------|----------|----------------------------------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------|-----------------------------------------------|--------|------------------------------------------------|----------|------------------|
| Isobenzan         | C₉H₄Cl₈O₁ | 411.76           | 297-78-9 | C₁₂C(C(O)C(C)C(C)(C(C(C(C(OC₁Cl)Cl)Cl)Cl)Cl)Cl)Cl                                   | Recalcitrant—6430 h                                      | No                                                | 2.8 years                                      | 4.51   | 28.8 days                                      | Rat oral: 4.8 mg/kg | N                |
| Chloropropylate   | C₁₇H₁₆Cl₂O₃ | 339.22           | 5836-10-2 | CC(C)OC(O)C(C₁Cl)(C₂CC(C(C₂Cl)Cl)O                                          | 1.9644 months—2580 h                                   | No                                                | 50 days                                        | 4.41   | 1.66 days                                      | Rat oral: 5000 mg/kg | N                |
| 1,4-Dichlorobenzene | C₆H₄Cl₂  | 147              | 106-46-7 | C₁=CC(C=CC=C=CC=CC=CC=O)                                                                 | 2.4611 weeks—563 h                                     | No                                                | < 50 days                                      | 3.44   | 3.44 days                                      | Rat oral: 1516–2138 mg/kg | Y                |
| Pentachlorophenol | C₆H₅Cl₅O₁  | 266.34           | 87-86-5  | C₁(C=C(C=C(C=C(C=O)O)O)O)C₃O                                                                 | Recalcitrant—8150 h                                    | No                                                | 45 days                                        | 5.12   | 22 days                                        | Rat oral: 27–31.1 mg/kg; dermal: 98–330 mg/kg; mice oral: 74–130 mg/kg | Y                |

BAF: bioaccumulation factor.
Table 4. Persistence, biodegradability, bioaccumulation, toxicity, and carcinogenicity data on Top 10 pesticides worldwide (data from EPI Suite 4.1).

| Chemical         | Rank | Introduction date | Formula | Molecular weight | CAS RN  | Canonical SMILES                                                                 | Ultimate biodegradability (BioWin3)— persistence time (h) = half-life in environment | BioWin— aerobic/anaerobic biodegradability (Yes/No) | Log KOW | BAF biotransformation half-life (normalized to 10 g fish) | Toxicity (mg/kg) (Rats) | Rodent carcinogen |
|------------------|------|-------------------|---------|------------------|---------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------|---------|-------------------------------------------------------------|------------------------|-------------------|
| Glyphosate       | 1    | 1974              | C3H8NO5P| 169.07           | 1071-83-6 | C(C(=O)O)NCP(=O)(O)O                                                             | 3.21 weeks—587 h                                                                      | Yes                                            | −5.4    | 0.0016 days                                                  | Oral LD<sub>50</sub> = 4877 | N                 |
| Atrazine         | 2    | 1958              | C8H14ClN5 | 215.68           | 1912-24-9 | CCNC1=NC(=NC(=N1)C(NC(C)C)C1)                                                  | 2.00 months—2460 h                                                                    | No                                             | 2.61    | 0.1169 days                                                  | Oral LD<sub>50</sub> = 673–3000 | N                 |
| Metolachlor-S    | 3    | 1997              | C15H22ClNO2 | 283.79           | 87392-12-9 | CCC1=CC=CC(=C1N(C(C)C)OC)C                                                  | 2.19 months—2270 h                                                                    | No                                             | 2.9     | 0.184 days                                                   | Oral LD<sub>50</sub> = 3621; Dermal LD<sub>50</sub> > 5000 | N                 |
| Dichloropropene  | 4    | 1982              | C3H4ClO2 | 110.97           | 10061-02-6 | C(C≡CC)Cl                                                                     | 2.61 weeks—144 h                                                                      | No                                             | 2.03    | 0.557 days                                                   | Oral LD<sub>50</sub> = 375–666 | Y                 |
| 2,4-D            | 5    | 1945              | C8H6Cl2O3 | 221.03           | 94-75-7   | C1=CC(=C(=C(C)O)Cl)OC(=O)O                                                   | 2.60 weeks—1190 h                                                                    | No                                             | 2.81    | 10.11 days                                                   | Oral LD<sub>50</sub> = 127–714 | N                 |
| Metam            | 6    | 1973              | C2H5NS2  | 107.2            | 144-54-7  | CNC(=S)S                                                                      | 2.96 weeks—308 h                                                                     | No                                             | 0.48    | 0.038 days                                                   | Oral LD<sub>50</sub> = 1700–1894 | N                 |
| Acetochlor       | 7    | 1994              | C14H20ClNO2 | 269.77           | 34256-82-1 | CCC1=CC=CC(=C1N(COCC)C(=O)C)C                                                   | 2.22 months—1970 h                                                                    | No                                             | 3.03    | 0.205 days                                                   | Oral LD<sub>50</sub> = 2953 | Y                 |
| Metam potassium  | 8    | 1973              | C2H4KNS2 | 145.29           | 137-41-7  | CNC(=S)[S-][K+]                                                                 | 2.96 weeks—726 h                                                                     | No                                             | −2.62   | 0.0304 days                                                  | Oral LD<sub>50</sub> = 630; Dermal LD<sub>50</sub> ≥ 1000 | N                 |
| Chloropirizin    | 9    | 1984              | C13NO2   | 164.37           | 76-06-2   | C([N+]1)[(=O)O]Cl(=O)O                                                        | 2.01 months—227 h                                                                    | No                                             | 2.09    | 0.294 days                                                   | Oral LD<sub>50</sub> = 251 | N                 |
| Chlorothalonil   | 10   | 1966              | C8CH4N2  | 265.9            | 1897-45-6 | C1#NCl=C1(=C(C(=C1)O)Cl)C(=C1)NCl                                               | Recalcitrant—5180 h                                                                   | No                                             | 3.05    | 1.29 days                                                    | Oral LD<sub>50</sub> ≥ 10000 | Y                 |

BAF: bioaccumulation factor; 2,4-D: 2,4-dichlorophenoxyacetic acid.
The toxicity in rats measured as the oral LD50 ranged from 5000 mg/kg to 0.4 mg/kg, with an average of 989 mg/kg on the basis of the minimum dose for the 34 natural pesticides (Table 2). The toxicity in rats measured as the oral LD50 ranged from 5000 mg/kg to 3 mg/kg, with an average of 1044 mg/kg on the basis of the minimum dose for the 22 high-volume pesticides (Table 3). The toxicity in rats measured as the oral LD50 ranged from 10,000 mg/kg to 127 mg/kg, with an average of 2521 mg/kg on the basis of the minimum dose for the 22 high-volume synthetic pesticides (Table 4). The toxicity as measured by the oral LD50 for rats was not statistically different. The aquatic toxicity of the 22 high-volume synthetic pesticides were rodent carcinogens (phaseolin and wyerone) (7%) (Table 2). Seventeen of the 22 high-volume synthetic pesticides were rodent carcinogens (77%) (Table 3). Only 3 of the Top 10 synthetic pesticides were rodent carcinogens (acetochlor, chlorothalonil, and dichloropropene) (30%) (Table 4). The overall percentage for the 32 synthetic pesticides for rodent carcinogenicity was 63% with the comparable value for the 34 natural pesticides at only 7%. This difference was statistically significant (p < 0.001).

Table 5 (Online Supplement) shows toxicity data from fathead minnow, D. magna, and T. pyriformis, oral toxicity in rats, bioaccumulation, developmental toxicity, and mutagenicity for the 34 natural pesticides. The majority of data in Table 5 (Online Supplement) were derived from T.E.S.T. 4.2. Table 8 (Online Supplement) summarizes the results found in Table 5 (Online Supplement).

Table 6 (Online Supplement) shows toxicity data from fathead minnow, D. magna, and T. pyriformis, oral toxicity in rats, bioaccumulation, developmental toxicity, and mutagenicity on the 22 high-volume synthetic pesticides. The data in Table 6 (Online Supplement) were mainly derived from T.E.S.T. 4.2. Table 9 (Online Supplement) summarizes the data in Table 6 (Online Supplement).

Table 7 (Online Supplement) shows toxicity data from fathead minnows, D. magna, and T. pyriformis, oral toxicity in rats, bioaccumulation, developmental toxicity, and mutagenicity on the Top 10 pesticides. The data in Table 7 (Online Supplement) were mainly derived from T.E.S.T. 4.2. Table 10 (Online Supplement) summarizes the results in Table 7 (Online Supplement).

In Tables 8, 9, and 10 (Online Supplement), toxicity data from fathead minnow, D. magna, and T. pyriformis are displayed. The aquatic toxicity of the 22 high-volume synthetic pesticides is greater than the comparable values for the Top 10 synthetic pesticides, and for the 34 natural pesticides (Table 11, Online Supplement). However, the aquatic toxicities of the 22 synthetic, Top 10 synthetic, and 34 natural pesticides did not significantly differ. The oral rat LD50 data calculated by T.E.S.T. corroborated the data from EPI Suite. Both data sets indicated that the oral LD50 data on rats for natural and synthetic pesticides were not significantly different.

Table 12 (Online Supplement) provides an overview of the average values of the calculations for the 34 natural pesticides and the 32 synthetic pesticides. Statistical significance of the data is noted at the 95% confidence level. The persistence of the natural pesticides is significantly shorter than for the synthetic pesticides (p < 0.0032). The biodegradability between natural and synthetic pesticides is not significantly different (p < 0.332). The biotransformation of natural pesticides is significantly shorter than for the synthetic pesticides (p < 0.0009). The log KOW for the natural versus synthetic pesticides is not significantly different (p < 0.275). Only 2 of the natural pesticides were found to be rodent carcinogens, while 20 of the synthetic pesticides were found to be rodent carcinogens. The increased tendency toward displaying rodent carcinogenicity in the synthetic pesticides as compared with the natural pesticides was highly statistically significant (p < 0.0001). The LC50 for fathead minnow and D. magna and the IGC50 for T. pyriformis were lower for the 32 synthetic pesticides versus the 34 natural pesticides but the difference was not significant. The BAF for the 34 natural pesticides was significantly lower than for the 32 synthetic pesticides (p < 0.0036). The percentage of the 34 natural pesticides with predicted positive developmental toxicity was significantly higher than for the synthetic pesticides (p < 0.0003). Similarly, the 34 natural pesticides tended to be positive in the Ames mutagenicity assay more often than the 32 synthetic pesticides and the difference was significant (p < 0.0018). The oral LD50 in rats (mg/kg) was not significantly different between the 34 natural and 32 synthetic pesticides.

Discussion

Persistence

Thirty-four natural plant pesticides and 32 synthetic pesticides were included in this analysis. On average, synthetic pesticides lasted longer in the environment than natural plant pesticides. The median persistence for synthetic pesticides was 5055 h (210.6 days) with an average persistence of 4578.9 h (190.8 days). In contrast, the median persistence for natural plant pesticides was 1600 h (66.7 days), with an average persistence of 2402.5 h (100.1 days). The increased persistence of the synthetic pesticides is statistically significant (p < 0.0039).

Application of synthetic pesticides and herbicides to agricultural fields is a precise, highly technical, expensive, and time-consuming process.32 The number of applications required is specific to the soil type and fertility, rainfall, erosion and weathering, field slope and runoff pathways, potency toward the intended pests, and crop type.33–39 US EPA and the European Union promulgate regulations toward minimization of pesticide use via programs of Integrated Pest Management.40,41

Agro-scientists and farmers, and the biological evolution of plants, share several of the same goals but operate
on different timescales. The goal of maximizing crop yield per unit cost has incentivized the design of fast-acting synthetic pesticides. 45 In contrast, although natural plant pesticides applied to agricultural crops can be effective, they are generally slower acting. 53,44 This kinetic difference is not unexpected as a particular natural plant pesticide is usually found in a vegetable along with a large number of other natural plant pesticides, for example, broccoli is known to contain approximately 40 different plant pesticides. 6 Therefore, most natural plant pesticides did not evolve as standalone deterrents to insect or animal predation, with several notable exceptions, for example, highly toxic nicotine in the tobacco plant.45,46

Toxicity

Using the T.E.S.T. program, the oral rat LD 50 (mg/kg body-weight) of the 34 natural plant pesticides and 32 synthetic pesticides were either directly obtained from experimental data or predicted. The median LD 50 for the synthetic pesticides is 176.9 mg/kg. This level of toxicity falls within Category II (moderately toxic) (Table 13, Online Supplement). 37,48 The mean LD 50 for the synthetic pesticides is 974.3 mg/kg, which falls within Category III (slightly toxic). 37,48 The median LD 50 for the natural pesticides is 569.6 mg/kg, which falls within Category III (slightly toxic). The mean LD 50 for the natural pesticides is 1431.9 mg/kg (Category III/slightly toxic). While the median and mean LD 50 values for the synthetic pesticides are lower (more toxic) than comparable values for the natural pesticides, neither type of pesticide is notably toxic as measured by oral rat LD 50 values. 47,48

Using the T.E.S.T. program, the Ames Salmonella bacterial reverse mutation results were available for 30 of the 34 natural plant pesticides. 49 Of the 30 natural plant pesticides tested in the Ames assay, 12 were positive, that is, mutagenic. Of the 32 synthetic plant pesticides, 31 had been tested in the Ames assay. Of the 31 synthetic pesticides tested in the Ames assay, only 2 were positive in the Ames test. The difference between the ratios of 12/30 (natural pesticides) and 2/31 (synthetic pesticides) is statistically significant (p < 0.0018), with natural pesticides displaying increased mutagenicity as determined by the Ames assay. The Salmonella bacterial reverse mutation test (Ames assay) is the most commonly required screening assay for the potential genotoxicity of agricultural and industrial chemicals, or therapeutics, in commerce.50 The chemical structural determinants underlying Ames activity have been well characterized in a series of QSAR studies.51–53 New product developers are cognizant of the chemical determinants of Ames mutagenicity, so it is not surprising that synthetic pesticides tend to be negative in the Ames test.

Chronic bioassays conducted in rats or mice for the purpose of assessing the tumorigenic or carcinogenic potential of a chemical are very expensive and time-consuming.54,55 The majority of chemicals evaluated in these resource-intensive bioassays are commercial products being tested either as part of product stewardship or regulatory compliance.56,57 As most natural plant pesticides are not commercial products, relatively few of the more than 10,000 identified have been tested for carcinogenic potential.58–62 Ames et al. 6 noted that up through 1990, 1052 chemicals had been tested in at least one species in chronic cancer tests. Of the 1052 chemicals, 52 were natural plant pesticides.58–61 Of the 52 natural plant pesticides tested, 27 were carcinogenic, that is, 27/52 (52%). However, the natural plant pesticides considered by Ames et al. 6 are found in commonly eaten vegetables and do not include the 34 commercial natural plant pesticides applied to crops and considered in this analysis. It is possible that the selection process that resulted in widespread use of the 34 natural plant pesticides used in commerce took carcinogenic potential into consideration thereby resulting in only 2/28 being reported as rodent carcinogens.

Over the last 33 years (1985–2018), the US EPA has evaluated over 500 pesticides for carcinogenic potential of pesticide chemicals via the US EPA’s Pesticide Program (US EPA 2018).18 The latest report was issued in late 2018.18 The list includes the chemical name, CAS RN, PC code (a unique chemical identifier used by the EPA Office of Pesticide Programs), EPA human cancer classification, and report date. In the 2018 report, approximately 520 pesticides were listed. Of these, 514 possessed sufficient information for analysis. Table 14 (Online Supplement) shows the relationship between the human cancer classification and data collected from rodent carcinogenicity testing. Of the 514 pesticides for which data were available, 36% were carcinogenic to rodents.18

The 32 synthetic pesticides in this analysis represent the Top 10 (poundage of active ingredient) pesticides sold worldwide17 and 22 other popular pesticides used internationally.15,16 Eight pesticides are common to the set of 32 synthetics in this study and the 514 synthetics tested by the US EPA, that is, 2,4-D, acetochlor, atrazine, chloropicrin, chlorothalonil, glyphosate, metolachlor, and pentachlorophenol. Seven of these pesticides are on the Top 10 (poundage of active ingredient) list of pesticides sold worldwide. The overall rodent carcinogen percentage of 62% for the 32 synthetic pesticides (Top 10 plus the 22 high-volume) is notably higher than the 30% rate reported for the just the Top 10 synthetic pesticides sold worldwide. It is possible that the relatively low rate of rodent carcinogenicity has been a factor in elevating this subset of pesticides into the Top 10 positions by poundage of active ingredient used.53,64

In addition to an increase in predicted or measured Ames mutagenicity, the T.E.S.T. program predicts a statistically significant increase in the probability that the 34 natural plant pesticides will induce developmental toxicity than the 32 synthetic pesticides. However, QSAR is generally considered less reliable in predicting effects on developmental toxicity than in predicting Ames mutagenicity.65–67
Conclusions

In 1990, Ames et al. evaluated the toxicological significance of exposures to synthetic pesticides as compared with naturally occurring pesticides. They calculated that 99.99% (by weight) of the pesticides ingested in the American diet are chemicals that plants produce to defend themselves. Of the natural pesticides tested in high-dose animal cancer tests, about half were rodent carcinogens found in many common foods. They concluded that natural and synthetic chemicals are equally likely to be positive in animal cancer tests. Based on the relative mass of ingested material, synthetic pesticides represented an insignificant health risk as compared to the risks posed by natural pesticides.

In conclusion, the current study suggests that persistence in the environment is higher for synthetic as compared with natural pesticides. Similarly, rodent carcinogenicity is also higher in synthetic pesticides. Acute toxicity as determined by LD50 values in rats did not differ between synthetic and natural pesticides. Natural pesticides display significantly higher developmental toxicity and mutagenicity as compared with synthetic pesticides. Based on these findings and the much higher level of ingestion of natural pesticides (via food ingestion), health risks to the general human population from natural pesticide exposure would be expected to be greater than risks expected from exposure to synthetic pesticides on average. However, individual fruits and vegetables should always be washed prior to ingestion to remove any potentially harmful organic material, or synthetic pesticide residues that might be extant at higher than average values.

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