Toxicology Research

REVIEW

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The ABCs of pesticide toxicology: amounts, biology, and chemistry

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Everyone is affected directly or indirectly by pesticide use and safety. The magnitude and perception of this effect depend on one's individual involvement or vantage point. The researcher seeks discovery and the entrepreneur goes after financial rewards. The general public wants food, health and safety. Pesticide toxicology is a core issue in these relationships. The three goals of toxicology research on pesticides are first to create new knowledge and chemicals, second to evaluate their effectiveness and safety and third to regulate their use. What amounts of pesticides are applied and do we really understand their biology and chemistry? This review addresses the ABCs of pesticide toxicology, *i.e.* their amounts, biology and chemistry.

1. Introduction

We live in a competitive environment with many species of pest insects (10 000), weeds (1800) and fungi (80 000) yet we survive and sometimes prosper by maintaining the balance in favor of people and their food supply. Pesticides are designed to control pests with minimal effects on people and the environment. This takes many millions of pounds of pesticide chemicals and constant updating of the pesticide arsenal to keep up with the development of resistant pest strains. The goal of this review is to briefly evaluate the current status of pesticide toxicology research which involves determining their mode of action, resistance mechanisms, secondary effects in mammalian systems, and environmental impact. It involves a different emphasis than recent reviews by the author[1–5] by focusing on amounts, biology and chemistry, the ABCs of pesticide toxicology (Fig. 1).

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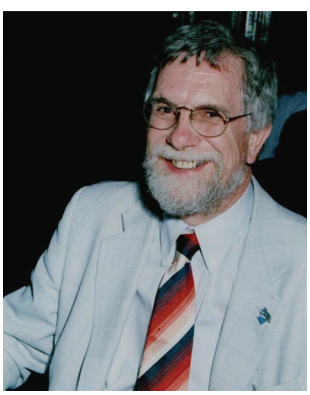

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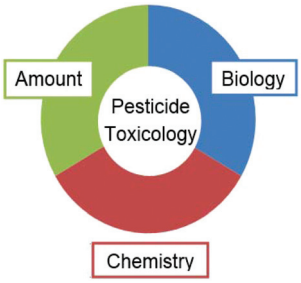

Fig. 1 The ABCs of pesticide toxicology.

2. Approach and data sources

This review relates the amounts, biology and chemistry of the top 30 pesticides, insecticides, herbicides and fungicides to their molecular targets and chemotypes. The data for amounts on a worldwide basis are ranked by volume in metric tons (m/t, one m/t is 2204.62 lbs) but sales values (dollars, millions) are also given for comparison using 2015 data.[6] The ranking by amounts favors high volume inexpensive compounds and by dollars emphasizes high value chemicals. The biological portion states the primary mechanisms of pesticidal action and the common modes of action with increased likelihood of cross-resistance assigned by the Resistance Action Committees for insecticides (IRAC),[7] herbicides (HRAC),[8] and fungicides (FRAC).[9] The toxicology and hazard ratings for acute toxicity and long-term effects in mammals and the environment (pollinators, aqueous organisms, and bioaccumulation) are based on the 2016 compilations of the Pesticide Action Network (PAN) international list of most hazardous pesticides.[10] PAN states their goals as to "challenge the global proliferation of pesticides, defend basic rights to health and environmental quality, and work to ensure the transition to a just and viable food supply". Judgements from this international citizens' action network must be balanced against those of toxicologists and chemists in appropriate regulatory agencies. Extensive evaluations are made by the Environmental Protection Agency (EPA) in the Federal Register and in a variety of reviews (*e.g.* ref. 11) and position statements by registration agencies of many countries and regions. The chemistry aspects relate to chemical types (chemotypes) for each type of pesticidal activity and comments on bioaccumulation, persistence and special features. The goal is to highlight the impact of the pesticides of current importance more than historical significance. Structures of four or five major compounds in amount of each type are shown in Fig. 2. Structures of the other compounds considered are given in The Pesticide Manual.[12]

3. Pesticides

The worldwide use of the top 30 pesticides based on 2015 data for amounts was about 2 million mt (4 billion pounds) divided between insecticides (5.7%), herbicides (55.4%), fungicides (28.6%) and others (10.3%). The overall corresponding values

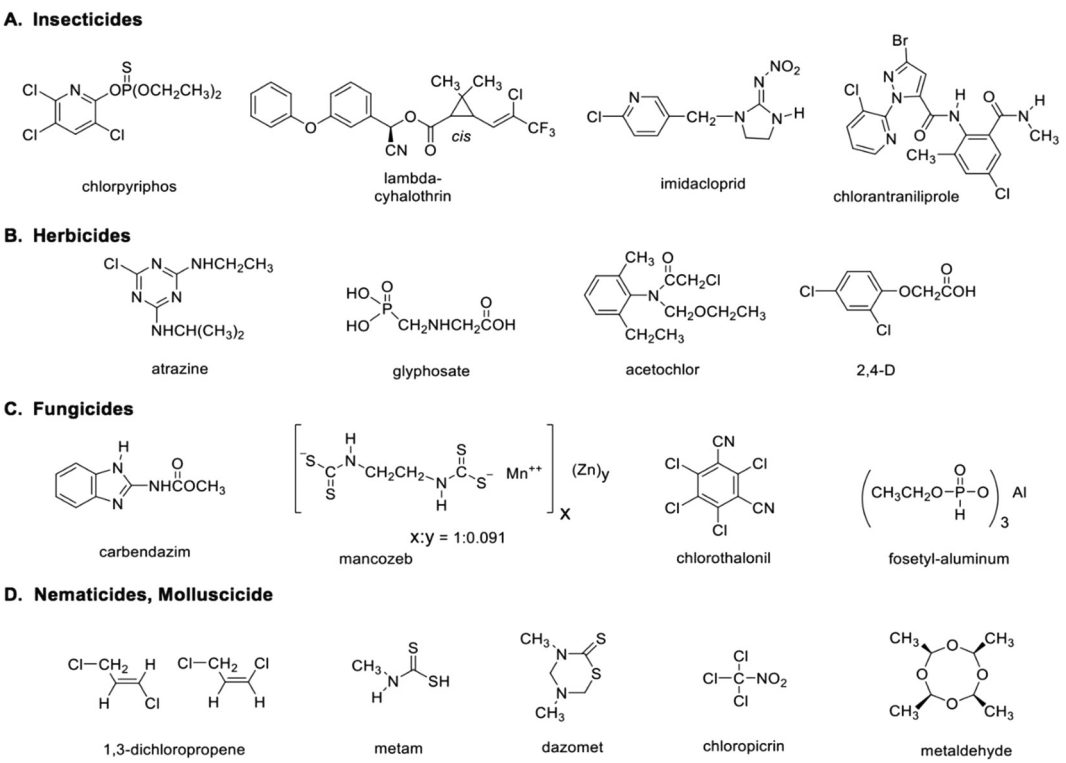

Fig. 2 Structures of the top four insecticides (A), herbicides (B), and fungicides (C), and top five nematicides/molluscicide (D) in 2015 annual amounts.

Table 1 Relative importance of the pesticide types as the 2015 amounts and sales

	Annual millions		Percent of total	
Pesticide type	Amount (m/t)	Sales ($ mn)	Amount	Sales
Insecticides	114 100	2515	5.7	14.7
Herbicides	1 111 900	10 305	55.4	60.2
Fungicides	573 450	3189	28.6	18.6
Others[a]	206 815	1118	10.3	6.5
Total	2 006 265	17 127	100.0	100.0

[a] 1,3-Dichloropropene, metam, chloropicrin, dazomet and metaldehyde.

based on sales were 14.7%, 60.2%, 18.6% and 6.5% respectively (Table 1, Fig. 3A). The amounts and sales favor herbicides followed by fungicides and insecticides. Volume and sales in 2015 were dominated by the herbicide glyphosate with 715 000 m/t or 1.6 billion lbs and sales of 5.56 billion dollars. The newer compounds are generally more potent and expensive so even a few years difference often changes the balance in pesticide amounts and sales.

4. Insecticides

Amounts

More than half (16/30) of the top volume insecticides are organophosphates (OPs) or methylcarbamates (MCs) accounting for 59.6% of the total insecticides by amount but 17.2% by sales (Table 2, Fig. 3B), indicating that their cost per pound is less than that of other insecticides. Thus chlorpyriphos is the number one synthetic insecticide by volume (40.8%) but only 2.2% by sales. The pyrethroids (pyrs) account for 5.6% by volume and 12.5% by sales. The four top volume nicotinic acetylcholine receptor (nAChR) agonists total only 12.0% by volume but 43.1% by sales. Other major insecticides by volume are 4 synthetics; the bacteria-derived *Bacillus thuringiensis* (Bt) and an inorganic (cryolite). The more expensive pyrs, neonicotinoids (neonics) and other insecticides reflect their structural complexity and newer status.

Biology

The OPs (IRAC 1B) and MCs (IRAC 1A) as acetylcholinesterase (AChE) inhibitors are limited in effectiveness by cross-resistance in many pest species. Some of the OPs and MCs have high mammalian acute toxicity and three (malathion, omethioate, and carbaryl) have observed long-term effects in

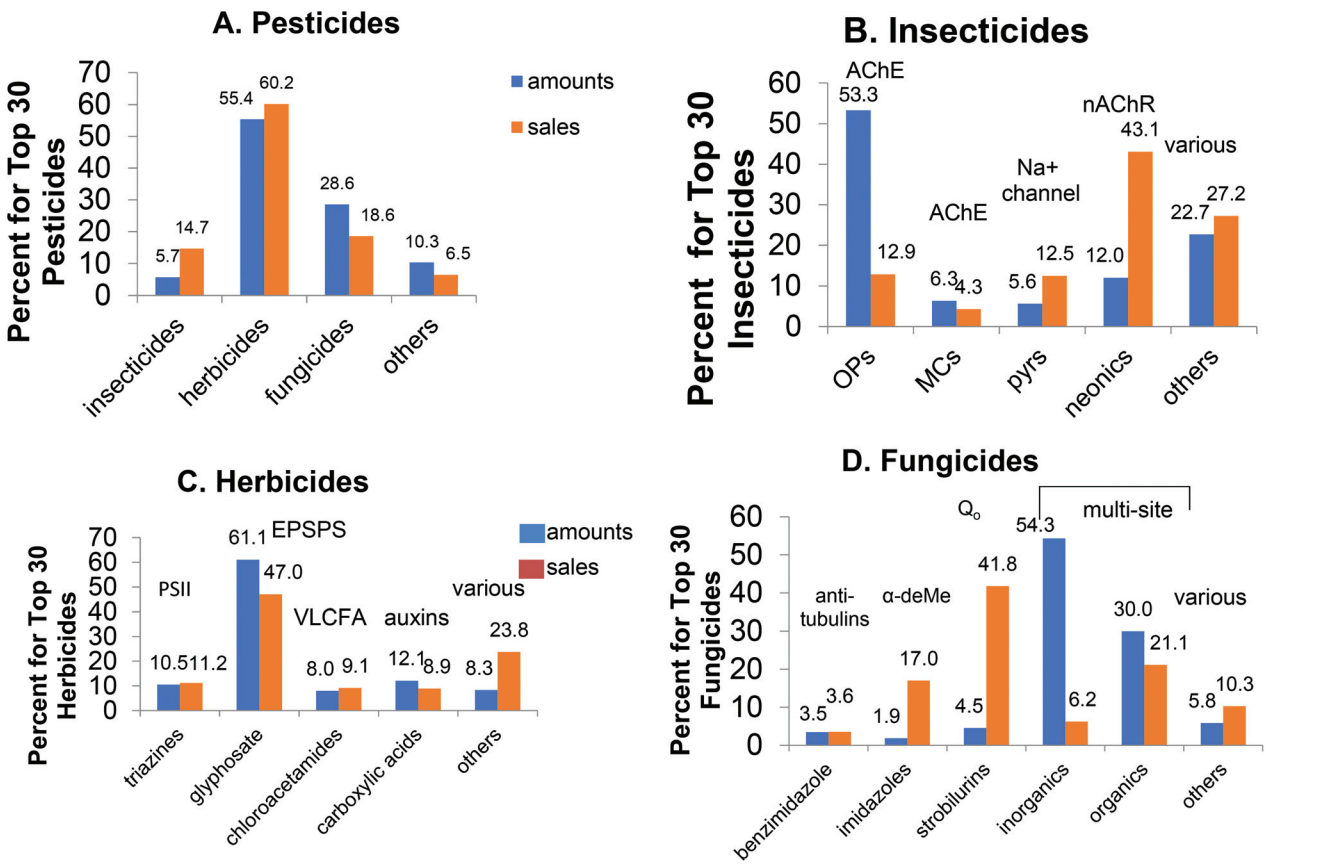

Fig. 3 Major pesticides, insecticides, herbicides, and fungicides in 2015 annual amounts and sales. Panel A considers the top 30 pesticides in amounts and the corresponding sales data for this compound set. Panel B for insecticides, C for herbicides, and D for fungicides are each based on the top 30 compounds of the type in amounts and sales in each case indicating the molecular targets and chemotypes. In Panel C, others include three categories (superoxide-bipyridylium, antitubulin-dinitroanilines, and various others) from Table 3 given later.

Table 2 Thirty major insecticides and their molecular targets, chemotypes, IRAC classifications, 2015 annual amounts and sales and 2016 PAN international hazard ratings

		Annual millions			Hazard ratings[b]	
No. in top 30 insecticides[a]	Name	Amount (m/t)	Sales ($ mn)	IRAC class.	Mammal[c]	Environment[d]
AChE – organophosphates (OPs)						
1	Chlorpyriphos	46 500	543	1B	0/0	1/0/0/0
3	Acephate	14 000	120	1B	0/0	1/0/0/0
4	Dimethoate	11 600	95	1B	0/0	1/0/0/0
6	Malathion	8500	91	1B	0/1	1/0/0/0
9	Phorate	5200	42	1B	1/0	1/0/0/0
14	Triazophos	2425	21	1B	1/0	0/0/0/0
17	Methamidophos	2350	15	1B	1/0	1/0/0/0
18	Terbufos	2235	69	1B	1/0	0/0/0/0
19	Chlorethoxyfos	2200	40	1B	1/0	1/0/0/0
21	Profenofos	2100	46	1B	0/0	1/0/0/0
25	Fosthiazate	2010	78	1B	0/0	1/0/0/0
28	Omethoate	2000	29	1B	1/1	1/0/0/0
AChE – methylcarbamates (MCs)						
7	Carbofuran	6200	215	1A	1/0	1/0/0/0
24	Oxamyl	2050	68	1A	1/0	1/0/0/0
27	Carbaryl	2000	46	1A	0/1	1/0/0/0
30	Methomyl	1775	67	1A	1/0	1/0/0/0
Na^+ channel – pyrethroids (Pyrs)						
11	Lambda-cyhalothrin	3500	605	3A	1/1	1/0/0/0
12	Cypermethrin	2825	187	3A	0/0	1/0/0/0
16	Permethrin	2360	310	3A	0/1	1/0/0/0
26	Fenvalerate	2000	53	3A	0/0	1/0/0/0
nAChR – neonics						
5	Imidacloprid	10 000	1508	4A	0/0	1/0/0/0
8	Acetamiprid	5750	376	4A	—	—
10	Thiamethoxam	4650	1481	4A	0/0	1/0/0/0
15	Clothianidin	2400	612	4A	0/0	1/0/0/0
Others[e]						
2	*Bacillus thuringiensis*	32 000	249	11A	—	—
13	Chlorantraniliprole	2750	1260	28	0/0	0/1/1/0
20	Fipronil	2100	730	2B	0/0	1/0/0/0
22	Cartap hydrochloride	2070	106	14	—	—
23	Buprofezin	2050	160	16	—	—
29	Cryolite	2000	6	8C	—	—

[a] Rankings 1–30 among the insecticides from most to least in annual amounts. [b] Ratings from PAN international list of highly hazardous pesticides (12/2016) as highly hazardous (1) or not (0). Blanks indicate not rated. [c] Acute toxicity/chronic or long term effects (carcinogen, mutagen and reproductive). [d] Sequentially bees/aqueous organisms/persistence/bioaccumulation. [e] Chemotypes: fipronil – phenylpyrazole; cryolite – inorganic; *Bacillus thuringiensis* – microbial; cartap hydrochloride – nereistoxin analogue; buprofezin – thiadiazinone; chlorantraniliprole – diamide.

mammals. They are readily biodegradable without major environmental problems other than bee toxicity. The pyrs, as voltage-dependent sodium channel activators (IRAC 3A), initiate hyperactivity alone (Type I) or followed by convulsions (Type II). Cross-resistance is a major problem at a site designated kdr. They are usually very toxic to fish and pollinators. Some pyrs have high mammalian acute and chronic toxicity (lambda-cyhalothrin) but few or no problems of persistence and bioaccumulation. The neonics acting at the nAChR have generally favorable mammalian toxicity. Neonic selectivity for insects *versus* mammals is due in part to differences in the insect and mammalian nAChR binding sites. The neonics are also prone to cross-resistance (IRAC 4A) but the greatest problem is toxicity to pollinators for thiamethoxam, imidacloprid, and clothianidin, which has led to restrictions or bans in many countries. Fipronil is the last remaining major chloride channel blocker with bee toxicity as a problem. The inorganic cryolite is an important component in pest management programs. Bt is present in large amounts in several genetically-modified organism (GMO) crops expressing this insecticide without major toxic problems for mammals or the environment. Cartap acts on the nicotinic receptors and buprofezin on chitin synthesis. The most rapidly growing area is the diamide channel activators[13] exemplified by chlorantraniliprole where mammalian toxicity is very low but some environmental organisms are very sensitive.

Chemistry

The structural complexity of the different insecticide chemotypes is reflected in the cost per pound (sales/volume) increasing for OPs, MCs, neonics, pyrs and anthranilamides (chlorantraniliprole). They are all biodegradable by carboxylesterases, cytochrome P450s (CYPs) or glutathione (GSH) S-transferases (GSTs). Special aspects are the CYP-dependent oxidation/activation of the phosphorothionates and phosphorothiolates and the photodesulfinylation of fipronil as an activation process.

5. Herbicides

Amounts

Herbicides dominate the pesticide market mainly because of glyphosate and its trimesium salt accounting for 61.1% of the worldwide volume and 47.0% of the top 30 herbicide sales in 2015 (Table 3, Fig. 3C). They are followed by phenoxycarboxylic acids (2,4-D and MCPA) and benzoic acids with 12.1% and 8.9% of total herbicide volume and sales, respectively. Other major chemotypes are the 1,3,5-triazines and chloroacetamides, then the bipyridiliums, followed by a great variety of structural types.

Biology

Herbicides must be selective for weeds *versus* crops and systemic for effective control. Resistance is a major limiting factor for every herbicide target. Photosystem II (PS II) inhibitors acting at three different sites [HRAC C1 (the Q_o or plastoquinol binding site), C2 and C3] are among the most important herbicides with atrazine and propanil used in largest amounts in corn and rice, respectively. Mammalian toxicity problems are noted for atrazine, diuron, linuron and bromoxynil. The bipyridyliums paraquat and diquat, acting as superoxide generators, pose acute toxicity problems in mammals (despite relatively high values for LD_{50}s) but few or no environmental problems because of rapid binding in soil. The most important herbicide target is 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), present in the aromatic amino acid biosynthesis pathway in plants but not mammals. The dominance of EPSPS results from the importance of glyphosate and GMOs resistant to glyphosate from expressed bacterial EPSPS of low sensitivity

Table 3 Thirty major herbicides and their molecular targets, HRAC classifications, 2015 annual amounts and sales and 2016 PAN international hazard ratings

		Annual millions			Hazard ratings[b]	
No. in top 30 herbicides[a]	Name	Amount (m/t)	Sales ($ mn)	HRAC class.	Mammal[c]	Environment[d]
PS II – triazines, pyridazinone, phenylcarbamate						
3	Atrazine	59 100	215	C1	0/1	0/0/0/0
19	Phenmedipham	5450	251	C1	—	—
23	Chloridazon	5000	225	C1	—	—
25	Simazine	4400	49	C1	—	—
PS II – anilide, ureas						
8	Propanil	22 600	120	C2	—	—
16	Isoproturon	7150	80	C2	—	—
17	Diuron	6850	79	C2	0/1	0/0/0/0
21	Linuron	5250	53	C2	0/1	0/0/0/0
27	Tebuthiuron	3600	55	C2	—	—
PS II – benzothiadiazinone, hydroxybenzonitrile						
26	Bentazone	4295	188	C3	—	—
28	Bromoxynil	3300	142	C3	1/0	0/0/0/0
Superoxide – bipyridylium						
5	Paraquat-dichloride	38 250	710	D	1/0	0/0/0/0
20	Diquat dibromide	5300	66	D	1/0	0/0/0/0
EPSPS – glycine derivatives						
1	Glyphosate	715 000	5560	G	0/1	0/0/0/0
6	Glyphosate-trimesium	25 000	565	G	—	—
Antitubulin – dinitroanilines						
11	Pendimethalin	16 800	253	K1	0/0	0/0/1/1
13	Trifluralin	9250	101	K1	0/1	0/0/0/1
29	Ethalfluralin	3000	47	K1	—	—
VLCFA – chloroacetamides						
4	Acetochlor	57 550	486	K3	0/1	0/0/0/0
7	S-metolachlor	24 500	516	K3	—	—
14	Metolachlor	9100	123	K3	—	—
18	Butachlor	5760	65	K3	0/1	0/0/0/0
Auxin – carboxylic acids						
2	2,4-DB	106 000	556	O	0/1	0/0/0/0
9	MCPA	17 800	109	O	—	—
10	Dicamba	17 550	345	O	—	—
22	Triclopyr	5200	149	O	—	—
Others[e]						
12	Mesotrione	11 750	870	F2	—	—
24	Clomazone	4600	345	F3	—	—
15	Glufosinate-ammonium	8500	675	H	0/1	0/0/0/0
30	EPTC	3000	27	N	—	—

[a] Rankings 1–30 among the herbicides from most to least in annual amounts. [b] Ratings from PAN international list of highly hazardous pesticides (12/2016) as highly hazardous (1) or not (0). Blanks indicate not rated. [c] Acute toxicity/chronic or long term effects (carcinogen, mutagen and reproductive). [d] Sequentially bees/aqueous organisms/persistence/bioaccumulation. [e] Chemotypes: mesotrione – triketone; clomazone – isoxazolidinone; glufosinate-ammonium – phosphinic acid; EPTC – thiocarbamate.

and expressed bacterial glyphosate oxidase to detoxify before toxic effects in maize. A major debate continues on classification of glyphosate as a probable human carcinogen. Glyphosate resistance in many weeds has resulted in increased dosages and even more questions on safety. The dinitroaniline antitubulins have some long-term toxicological effects in mammals and questions on persistence and bioaccumulation. The chloroacetamides acetochlor and its analogs block very long chain fatty acid (VLCFA) biosynthesis and generate reactive quinoneimine metabolites. The auxin-targeting carboxylic acids of the 2,4-D type continue as major compounds with carcinogenesis questions on 2,4-D. Herbicides in major amounts acting on other targets are mesotrione on 4-hydroxyphenylpyruvate dioxygenase (HPPD), clomazone on carotenoid biosynthesis and glufosinate on glutamine synthetase and *N*-methyl-D-aspartate receptors with long-term mammalian toxicity effects for the latter compound. Herbicides lacking crop selectivity are sometimes safened by dichloroacetamides and other inducers of plant GSH and GST synthesis.

Chemistry

Each chemotype has its own characteristic metabolic reactions, *e.g.* GST/weed-crop selectivity for triazines and toxic quinoneimine formation for chloroacetamides. The 2,3,7,8-tetrachlorodibenzodioxin highly toxic impurity in 2,4,5-T (triclopyr) manufacture is mostly removed to meet the high purity standards.

Table 4 Thirty major fungicides and their molecular targets, FRAC classifications, 2015 annual amounts and sales and 2016 PAN international hazard ratings

		Annual millions			Hazard ratings[b]	
No. in top 30 fungicides[a]	Name	Amount (m/t)	Sales ($ mn)	FRAC class.	Mammal[c]	Environment[d]
Antitubulin – benzimidazole						
6	Carbendazim	16 750	158	1, B1, MBC	0/1	0/0/0/0
13	Thiophanate-methyl	6400	235	1, B1, MBC	0/1	0/0/0/0
14α-Demethylase – imidazoles and triazoles						
17	Prochloraz	3510	106	3, G1	—	—
20	Prothioconazole	3100	764	3, G1	—	—
22	Epoxiconazole	2925	496	3, G1	0/1	0/0/0/0
23	Tebuconazole	2900	517	3, G1	—	—
Q_o – strobilurin type						
9	Azoxystrobin	9350	1740	11, C3	—	—
11	Pyraclostrobin	9000	1405	11, C3	—	—
14	Trifloxystrobin	6225	1085	11, C3	—	—
18	Famoxadone	3425	105	11, C3	—	—
29	Kresoxim-methyl	2300	290	11, C3	0/1	0/0/0/0
Multisites – inorganics						
1	Sulphur	286 000	387	M2	—	—
3	Copper salts	74 000	295	M1, M	1/0	0/1/1/0
21	Bordeaux mixture	3000	7	M1, M	—	—
Multisites – dithiocarbamates						
2	Mancozeb	108 000	1185	M3, M	0/1	0/0/0/0
8	Maneb	11 400	38	M3, M	0/1	0/0/0/0
12	Propineb	6560	80	M3, M	—	—
19	Ziram	3400	26	M3, M	1/0	0/0/0/0
30	Metiram	2230	16	M3, M	0/1	0/0/0/0
Multisites – others[e]						
4	Chlorothalonil	43 500	800	M5, M	1/1	0/0/0/0
7	Captan	16 000	96	M4, M	—	—
10	Folpet	9250	98	M4, M	0/1	0/0/0/0
Others[f]						
5	Fosetyl-aluminum	17 800	230	33, U	—	—
15	Tricyclazole	4400	99	16.1, I1	—	—
16	Iprodione	3775	132	2, E3	0/1	0/0/0/0
24	Cymoxanil	2800	155	27, O	—	—
25	Probenazole	2800	138	P, P2	—	—
26	Dimethomorph	2710	142	40, H5	—	—
27	Pyrimethanil	2500	66	9, D1	—	—
28	Metalaxyl	2340	177	4, A1	—	—

[a] Rankings 1–30 among the fungicides from most to least in annual amounts. [b] Ratings from PAN international list of highly hazardous pesticides (12/2016) as highly hazardous (1) or not (0). Blanks indicate not rated. [c] Acute toxicity/chronic or long term effects (carcinogen, mutagen and reproductive). [d] Sequentially bees/aqueous organisms/persistence/bioaccumulation. [e] Chemotypes: captan, folpet – phthalimide; chlorothalonil – chloronitrile. [f] Chemotypes: fosetyl-aluminum – phosphonate; tricyclazole – triazolobenzothiazole; iprodione – dicarboximide; cymoxanil – cyanoacetamide oxime; probenazole – benzoisothiazole, dimethomorph – cinnamic acid amide; pyrimethanil – anilinopyrimidine; metalaxyl – phenylamide or acylalanine.

6. Fungicides

Amounts

The amounts and sales of fungicides fall between herbicides and insecticides with the highest proportionate use in Europe and the Far East (Fig. 3D). The multisite fungicides are largest in volume including the inorganics sulfur, the copper salts and Bordeaux mixture (Table 4). The dithiocarbamates and particularly mancozeb continue as major compounds with the thiol-reactive captan, folpet and chlorothalonil also used in large amounts. These multisite (multiple target site) fungicides are the least likely to undergo selection for resistance. A variety of specific molecular targets account for the rest of the top 30 fungicides in volume (Table 4).

Biology

Fungicides are particularly known for their diversity of biochemical targets in order to minimize selection of resistant strains. There are three specific targets for major fungicides (Table 4, Fig. 3D). The benzimidazoles thiophanate-methyl and its activation product, carbendazim, are antitubulins effective on many types of fungi. The imidazole and triazole ergosterol biosynthesis inhibitiors acting as 14α-demethylase (α-deMe) inhibitors are specific for a biochemical step not involved in cholesterol biosynthesis in mammals thereby conferring a high level of selectivity. The newer strobilurin-type Q_o inhibitors based on the mushroom-derived azoxystrobin are the highest in sales and used in large amounts but already with some loss in effectiveness from resistant strains. Fosetyl-aluminum is a phosphonic acid precursor effective on many fungal diseases without major resistance problems. Several fungicides have long-term effects in mammals and a few (copper salts, ziram, and chlorothalonil) have acute toxicity. Copper salts also have potential environmental problems.

Chemistry

Diversity is the key to fungicide chemistry (Fig. 2 and 4). Reactivity is a second feature for the multisite fungicides. Residues are minimal because of this reactivity.

7. Others

Three nematicides (1,3-dichloropropene, metam and chloropicrin) are or yield volatile toxicants for soil fumigation (Fig. 2). Large amounts are used but at relatively low cost (Table 5). They are bioactivated by CYPs or GSTs. Metaldehyde is the most important molluscicide in this relatively small market. Rodenticides and still other pesticide types are not considered here although their action as vitamin K antagonists, anticoagulants, and at other targets has contributed greatly to toxicology in general.

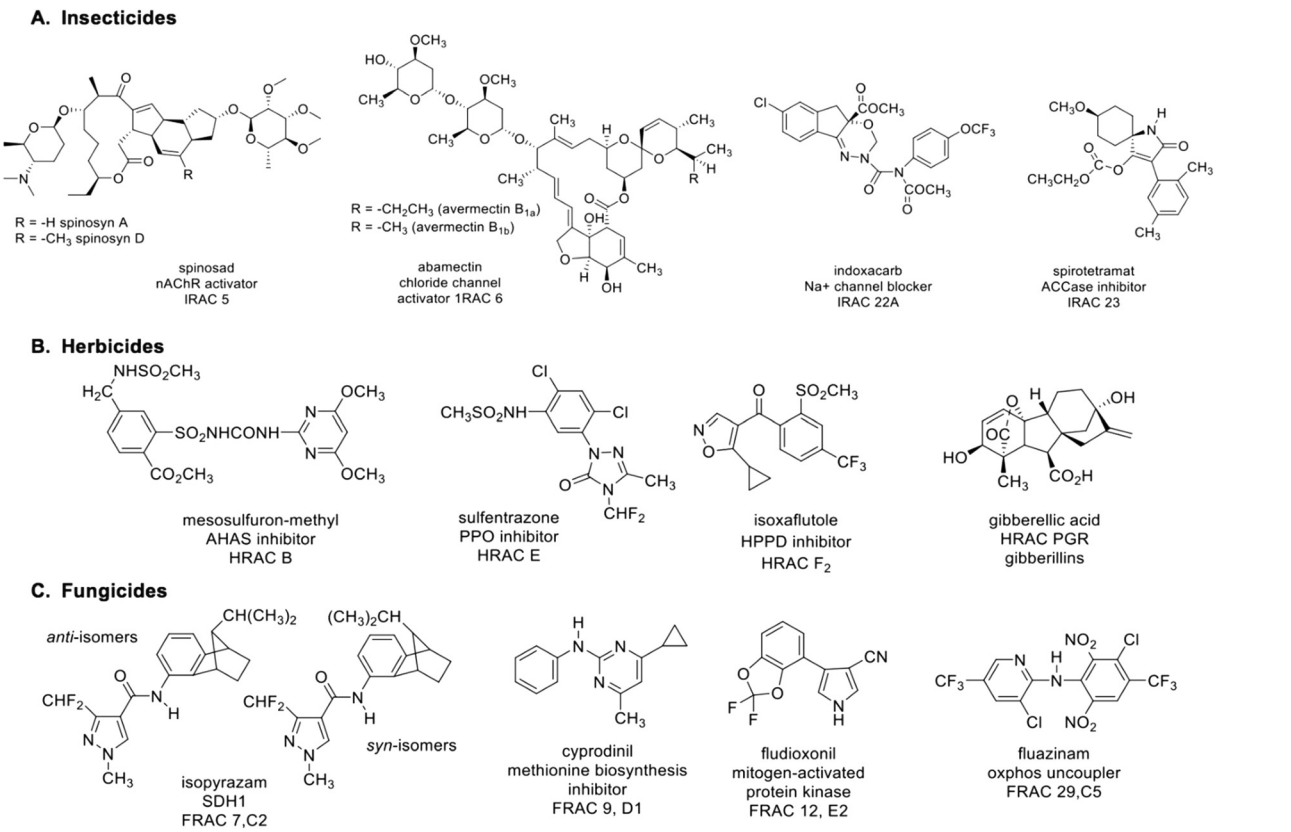

Fig. 4 Other major insecticides, herbicides, and fungicides in 2015 annual sales but not amounts and their target and resistance classifications.

Table 5 Four nematicides and a molluscicide and their 2015 annual amounts and sales relative to the top 30 pesticides and 2016 PAN international hazard ratings

		Annual millions		Hazard ratings[b]	
No. in top 30 pesticides[a]	Name and IRAC/HRAC class.	Amount (m/t)	Sales ($ mn)	Mammal[c]	Environment[d]
5	1,3-Dichloropropene	87 000	286	0/1	0/0/0/0
9	Metam (HRAC Z)[e]	52 500	109	0/1	0/0/0/0
13	Chloropicrin (IRAC 8B)[e]	32 000	261	1/0	0/0/0/0
18	Dazomet (HRAC Z)[e]	21 350	181	—	—
26	Metaldehyde	13 965	281	—	—

[a] Rankings 1–30 relative to the top 30 pesticides from most to least in annual amounts. [b] Ratings from PAN international list of highly hazardous pesticides (12/2016) as highly hazardous (1) or not (0). Blanks indicate not rated. [c] Acute toxicity/chronic or long term effects (carcinogen, mutagen and reproductive). [d] Sequentially bees/aqueous organisms/persistence/bioaccumulation. [e] Amounts, sales and hazard ratings are given for other insecticides in Table 2 and herbicides in Table 3.

8. Concluding comments

The selection of resistant strains is the driving force in pesticide evolution. The need for replacement pesticides to maintain pest control on the "pesticide treadmill" guarantees a major market for any new highly effective, safe, and moderate cost discovery. The compounds are generally increasingly complex (*e.g.* more fluorine atoms per molecule) and potent (to reduce the dose and increase the selectivity). Pesticide research is remarkably effective in finding new chemical pathways and coupled systems due to the variety of systems and organisms tested with designed or random libraries of compounds.

This review considers only certain areas of pesticide toxicology research with emphasis on the following three aspects. First, it is based on current high volume pesticides. Other highly effective pesticides may not reach the high volume because of potency or high cost as illustrated by 13 compounds in Fig. 4. Two of the four insecticides are modified or reconstructed natural products to achieve higher stability and potency. Others are relatively new compounds with an expanding market. Second, it is restricted to synthetic organics and does not consider RNA/DNA modifiers. The use of omic technologies will continue to facilitate mechanism studies and expanding knowledge in comparative biochemistry and biophysics will help create selective compounds. Third, it recognizes the importance of Bt as a biological agent but does not consider GMOs, which are a major factor in the dominance of glyphosate as a broad-spectrum herbicide used on multiple genetically engineered herbicide-resistant crops.

The competition of pests and people for food, fiber, environmental niches, and health will continue to provide a role for pesticide toxicology to establish and insure a firm scientific base for developments. Creative approaches and careful applications will assure effective pest control essential for human and environmental health.

In summary, pesticide toxicology research involves inventors, developers, and regulators considering amounts, biology, and chemistry with the common goal of creating and maintaining safe and effective pesticides. The potency should be high so only small amounts are used. The molecular target or mode of action should allow high selectivity for pests *versus* nontarget species and with little or no cross-resistance with other compounds. The chemical must be adequately stable to control the pest yet biodegradable so that there are little or no food residues or environmental contaminants. These relationships must be thoroughly evaluated for each compound and the results made available for everyone to evaluate and judge the degree of safety. Therein lies the challenges and multidisciplinary adventures of pesticide toxicology research.

Abbreviations

2,4,5-T	2,4,5-Trichlorophenoxyacetic acid
2,4-D	2,4-Dichlorophenoxyacetic acid
ABCs	Amounts, biology, chemistry
AChE	Acetylcholinesterase
Bt	*Bacillus thuringiensis*
CYPs	Cytochromes P450
EPA	Environmental protection agency
EPSPS	5-Enolpyruvylshikimate-3-phosphate synthase
FRAC	Fungicide resistance action committee
GMO	Genetically modified organism
GSH	Glutathione
GSTs	Glutathione S-transferases
HPPD	4-Hydroxyphenylpyruvate dioxygenase
HRAC	Herbicide resistance action committee
IRAC	Insecticide resistance action committee
kdr	Site for cross-resistance of pyrs
MCPA	2-Methyl-4-chlorophenoxyacetic acid
MCs	Methylcarbamates
nAChR	Nicotinic acetylcholine receptor
Neonics	Neonicotinoids
OPs	Organophosphates
PAN	Pesticide action network
PS II	Photosystem II
Pyrs	Pyrethroids
Q_o	Plastoquinol binding site of PS II
VLCFA	Very long chain fatty acid
α-deMe	14α-Demethylase

Author contributions

The data for pesticide amounts and sales were complied by Robert Bryant and the remaining portion was written by John Casida.

Conflicts of interest

There are no conflicts of interest to declare.

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