stricter legislation. However, the pesticides have certainly improved our lives by being versatile tools in food production and in the combat of insect-borne diseases.

1.3 A great market

1.3.1 The number of chemicals used as pesticides

The Pesticide Manual from 1979 (C. Worthing, 6th edition, British Crop Protection Council) presents 543 active ingredients. Approximately 100 of these are organophosphorus insecticides and 25 are carbamates used against insects. The issue of *The Pesticide Manual* from 2000 (T. Tomlin, 12th edition, British Crop Protection Council, 49 Downing St., Farnham, Surrey GU9 7PH, U.K., www.bcpc.org) describes 812 pesticides and lists 598 that are superseded. Today's 890 synthetical chemicals are approved as pesticides throughout the world and the number of marketed products is estimated to be 20,700. Organophosphorus insecticides are still the biggest group of insecticides with, according to *The Pesticide Manual*, about 67 active ingredients on the market, but the pyrethroids are increasing in importance, with 41 active ingredients. The steroid demethylation inhibitors (DMIs) constitute the main group of fungicides (31). Photosynthesis inhibitors (triazines 16, ureas 17, and other minor groups) and the auxin-mimicking aryloxyalkanoic acids (20) are still very popular as herbicides, but many extremely potent inhibitors of amino acid synthesis (e.g., the sulfonylureas (27)) are becoming more important.

It is very interesting to study lists of pesticides for sale in 1945 or earlier. Lead arsenate, mercury salts, and some organic mercury compounds, zinc arsenate, cyanide salts, nicotine, nitrocresol, and sodium chlorate were sold with few restrictions. Very few of these early pesticides are now regarded as safe. The world had a very strong need for safe and efficient pesticides like DDT. This fantastic new substance started to appear on the lists of approved pesticides under various names (Gesarol, Boxol S, pentachlorodiphenylethane, etc.) at that time.

The herbicide 2,4-D got a similar status as the first real efficient herbicide that made mechanization in agriculture possible. "The discovery of 2,4-D as an herbicide during World War 2 precipitated the greatest single advance in the science of weed control and the most significant in agriculture" (cited in Peterson, 1967).

1.3.2 Amounts of pesticides produced

Successful pesticides are produced in massive quantities. It has been estimated that between 1943 and 1974 the world production of DDT alone reached 2.8×10^9 kg (Woodwell et al., 1971). DDT was the first efficient synthetic pesticide and had all the good properties for an insecticide any person at that time could imagine. It is extremely stable, and only one treatment may suffice for good control of insect pests. It was cheap to produce and had (and still has) a low human toxicity, but is extremely active toward almost all insects. As a tool in antimalarial campaigns, it was extremely efficient. By the end of World War II it was used to combat insect-transmitted diseases and agricultural and household pests like flies and bedbugs. The production reached the maximum in 1963 with 8.13×10^7 kg in the U.S. alone. Bans and restrictions of DDT usage have since reduced the production volume of this first and efficient modern pesticide. Today an international treaty has been signed to restrict its use to very few applications in vector control.

DDT is therefore not very important as a commercial product anymore. There are no patent protections. Because of environmental problems, its usefulness is limited. Furthermore, insect resistance to DDT would in any case have restricted its usefulness.

However, other pesticides are now an integral part of agriculture throughout the world and account for approximately 4.5% of total farm production costs in the U.S. Pesticide use in the U.S. averaged over 0.544×10^9 kg of active ingredients in 1997, exceeding a price of $11.9 billion, whereas the world pesticide consumption in 1995 has been estimated to be 2.6×10^9 kg of active ingredient. The newer superactive pesticides, including herbicides such as glufosinate and glyphosate and insecticides such as the synthetic pyrethroids, can be used at very low volumes.

When measured in dollars, the herbicides dominate the market as shown by the table:

Sales	
Herbicides	47.6%
Insecticides	29.4%
Fungicides	17.4%
Others	5.5%

Herbicides are applied to 92 to 97% of acreage planted with corn, cotton, soybeans, and citrus; three quarters of vegetable acreage; and two thirds of the acreage planted with apples and other fruit.

The Nordic countries have fewer insect pests in agriculture and very few human or veterinary diseases that are transmitted by insects. There are restrictions against the use of aircraft for insecticide spraying in forestry and agriculture. Insecticides are therefore, by volume, much less significant than the herbicides.

Eighty-seven percent of the global pesticide use is in agriculture, and Europe, the U.S., and Japan constitute the biggest market, especially for herbicides, whereas insecticides dominate Asia, Africa, and Latin America. Figure 1.1 shows the approximate amounts of active ingredients in the various regions of the world.

The global chemical–pesticide market of about $31 billion is increasing 1 to 2% per year; the cost for developing a single new pesticide was estimated to be about $80 million in 1999, and the demand for much toxicological research on each single new substance is the most important reason for this

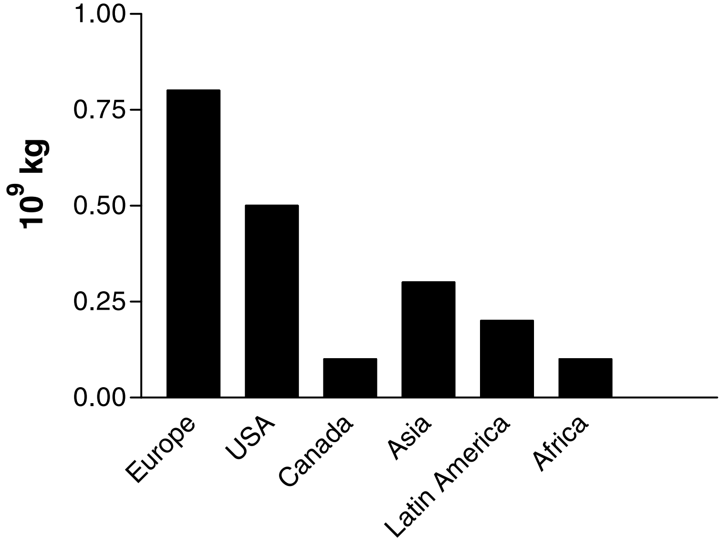


Figure 1.1 Mass of active ingredients from pesticides in different regions of the world. (From data in Board on Agriculture and Natural Resources and Board on Environmental Studies and Toxicology, C.o.L.S. 2000. The Future Role of Pesticides in U.S. Agriculture/Committee on the Future Role of Pesticides in U.S. Agriculture. 301 pp.)

high cost. It is, of course, much cheaper to develop a new pesticide when the mode of action is known. Therefore, it is not surprising that new organophosphorus insecticides and herbicidal urea derivatives are marketed every year. The pyrethroids constitute a new group of similar reputation. The exact mode of action was long not understood, but at Rothamstead Experimental Station and other institutes, basic studies of structure–activity relationships were carried out, making it possible to develop more active compounds.

1.3.3 Marketing

Very few multinational agrochemical companies dominate the market. Due to vertical and horizontal integration, the number of companies becomes fewer every year. For instance, the Swiss companies CIBA and Geigy amalgamated to become CIBA-Geigy, which amalgamated with Sandoz to form Novartis, which merged with AstraZeneca to form Syngenta. AgroEvo has merged with Rhône-Poulenc to form Aventis. The new era of biotechnology that has just started will speed up this process. Companies will try to get hold of the seed market for transgenic crops made resistant to insect pests and diseases or made tolerant to herbicides. It is worth mentioning that many countries like India, Brazil, China, and South Africa have great producers of pesticides. Often they take up the production of older pesticides without patent protection and produce pesticides that for various reasons are no longer approved in the U.S. or Europe. An example is the very toxic organophosphorus insecticide monocrotophos, which was cancelled in the U.S. in 1988 but is produced and used in Asia.

1.3.4 Dirty dozens

The profit rate for a product will decrease over the years because new competing compounds are developed, because resistance may restrict its usefulness, and because new data about ecotoxicological or human health-related toxicity appear. Many organizations engaged in environmental problems try to speed up the process and promote agricultural production without use of pesticides. It is very popular to set up lists of dirty dozens, i.e., compounds that are regarded as very hazardous for health or the environment. Very often, these substances have already been superseded and do not have any patent protection. For instance, the following list produced by the Pesticide Action Network was taken from http://www.pan-uk.org/briefing/SIDA_FIL/Chap1.html at the time of this writing. The year of marketing or patenting has been added. All substances are older than 30 years. Many of them are already in the list of superseded pesticides according to *The Pesticide Manual* (1994 or later) and are therefore of less interest today.

Dirty-Dozen List Found on the Internet

Substance	Year of Marketing/Patenting
Aldicarb	1965
Aldrin	1948
Amitrol	1955
Binapacryl	1960
Camphechlor	1947
Chlordane	1945
Chlordimeform	1966
Chlorobenzilate	1952
Chlorpropham	1951
DBCP[1]	1955
DDT	1942
Dieldrin	1948
Dinoseb	1945
EDB[2]	1946
Endrin	1951
Ethylene oxide	1935
Fluoroacetamide	1955
Heptachlor	1951
Hexachlorbenzene	1945
Hexachlorocyclohexane (mixed isomers)	1940
Isobenzan	1957
Lindane	1942
Mercury compounds	?
Methamidophos	1970

Dirty-Dozen List Found on the Internet (continued)

Substance	Year of Marketing/Patenting
Mirex	1955
Monochlorophos	1965
Paraquat	1958
Parathion	1946
Parathion-methyl	1949
Pentachlorphenol	1936
Phosphamidon	1946
Propham	1946
2,4,5-T	1944

Source: http://www.pan-uk.org/briefing/SIDA_FIL/Chap1.html.

[1] 1,2 dibromo-3-chloropropane

[2] ethylenedibromide

The public concern and the pressure groups may speed up the change to better and safer pesticides. The agrochemical companies' shift toward the development of reduced-risk pesticides is encouraged. More efficient approval procedures are an instrument that may be used to speed up the change. From 1993, the U.S. Environmental Protection Agency (EPA) began a program of expedited review of what could be classified as reduced-risk pesticides. Expedited reviews can reduce the time to registration by more than half.

It may be of interest to study the criteria established by the EPA for reduced-risk pesticides because they are important guiding principles in the development of new pesticides:

The pesticide:

- Must have a reduced impact on human health and very low mammalian toxicity
- May have toxicity lower than alternatives
- May displace chemicals that pose potential human health concerns or reduce exposures to mixers, loaders, applicators, and reentry workers
- May reduce effects on nontarget organisms (such as honey bees, birds, and fish)
- May exhibit a lower potential for contamination of groundwater
- May lower or entail fewer applications than alternatives
- May have lower pest resistance potential (have a new mode of action)
- May have a high compatibility with integrated pest management
- Has increased efficacy

About 20 such reduced-risk pesticides are now registered in the U.S., comprising herbicides (5), insecticides (8), fungicides (5), 1 bird repellent, and 1 plant activator. Their mode of action is based on more new principles. Most of them are listed below, together with the year of registration.

Pesticide	Mode of Action	Year of Registration
	Herbicides	
Imazapic	ALS inhibitor (1997)[1]	1997
Imazamox	ALS inhibitor (1997)	1997
Carfentrazone	Inhibits protoporphyrinogen oxidase, giving membrane disruption (1996)	1996
Diflufenzopyr	Inhibits the auxin transport mechanism (1999)	1999
Dimethenamide-P	Cell division inhibitor	1999
	Insecticides	
Diflubenzuron	Chitin synthesis inhibitor	1998
Hexaflumuron	Chitin synthesis inhibitor	1994
Pymetrozine	Feeding arrestant	1999
Tebufenozide	Binding (agonistically) to the ecdysone-binding site	1992
Pyriproxyfen	Inhibits the embryogenesis	1998
Spinosad	Activates the nicotinic acetylcholine receptor	1997
	Fungicides	
Azoxystrobin	Blocks electron transfer between cytochrome b and cytochrome C_1 in the mitochondria	1997
Cyprodinil	Inhibits synthesis of methionine	1994
Fludioxonil	May inhibit phosphorylation of glucose	1993
Metalaxyl-M	Inhibits synthesis of ribosomal RNA in fungi	1996

[1] ALS: Acetolactate synthase

1.4 Nomenclature, definitions, and terminology

1.4.1 Toxicology, ecotoxicology, and environmental toxicology

The Greek word *τοξιχον* (toxicon) was used for poisonous liquids in which arrowheads were dipped. The word *toxicology*, derived from this word, has been used as the name of the science within human medicine that describes the effect of poisons on humans. The definition includes uptake, excretion, and metabolism of poisons (toxicokinetics), as well as the symptoms and how they develop (toxicodynamics). We can say that the toxicodynamics tell us what the toxicants do to the organisms; and toxicokinetics, what the organism does with the substance. Toxicology also includes the legislation enforced to protect the environment and human health, and the risk assessments necessary for this purpose. Today a toxicologist is not exclusively working with the species *Homo sapiens* or model organisms like rats, but all kinds of organisms.

The term *ecotoxicology* is defined as "the science occupied with the action of chemicals and physical agents on organisms, populations, and societies within defined ecosystems. It includes transfer of substances and interactions with the environment" (e.g., Hodgson et al., 1998). Ecotoxicology is sometimes used synonymously with *environmental toxicology*; however, the latter also encompasses the effects of environmental chemicals and other agents on humans. Because the basic chemical and physical processes behind the interaction between biomolecules and chemicals are independent of the type of organism, it is not necessary to have a too rigid division between the various branches of toxicology.

1.4.2 Pesticides, biocides, common names, chemical names, and trade names

Pesticides are chemicals specifically developed and produced for use in the control of agricultural and public health pests, to increase production of food and fiber, and to facilitate modern agricultural methods. Antibiotics to control microorganisms are not included. They are usually classified according to the type of pest (fungicides, algicides, herbicides, insecticides, nematicides, and molluscicides) they are used to control. When the word *pesticide* is used without modification, it implies a material synthesized by humans. *Plant pesticide* is a substance produced naturally by plants that defends against insects and pathogenic microbes — and the genetic material required for production.

The term *biocide* is not used much in the scientific literature. It may be used for a substance that is toxic and kills several different life-forms. Mercury salts (Hg^{++}) may be called biocides because they are toxic for microorganisms, animals, and many other organisms, whereas DDT is not a biocide because of its specificity toward organisms with a nervous system (animals).

The word is also sometimes used as a collective term for substances intentionally developed for use against harmful organisms. In a directive from the European Community (EU Biocidal Products Directive 98/8/EC), we find the following definition:

> The new Directive describes biocides as chemical preparations containing one or more active substances that are intended to control harmful organisms by either chemical or biological, but by implication, not physical means. The classification of biocides is broken down into four main groups — disinfectants and general biocides, preservatives, pest control and other biocides and these are further broken down into 23 separate categories.

Pesticides have one or more *standard name(s)* and one or more *chemical name(s)*. The different companies make products with registered *trade names.* They should be different from the standard names, but also have to be approved. The chemical industry also frequently uses a code number for its products. In Germany, for instance, old farmers still know parathion by the number E-605, which was used by Bayer Chemie before a standard name and a trade name were given to O,O'-diethyl paranitrophenyl phosphorothioate. The chemical name is often very complicated and even difficult to interpret for a chemist. The chemical formula, however, is often much simpler and may tell something about the property of the compound even to a person with moderate knowledge of chemistry.

One or more national standardization organizations and the International Organization of Standardization approve standard names. The chemical names are either according to the rules of the International Union of Pure and Applied Chemistry or according to Chemical Abstracts. The so-called Chemical Abstracts Services Registry Number (CAS-RN) is a number that makes it easy to find the product or chemical in databases from Chemical Abstracts. The standard names are regarded as ordinary nouns, but the pesticide products are sold under a trade name that is treated as a proper name with a capital initial letter. We use the various names of a fungicide as an example:

Common Names

British Standards Institution	Captan
International Organization for Standardization (French spelling)	Captan
Japanese Ministry for Agriculture, Forestry and Fishery	Captan
South Africa	Captan
Norsk språkråd (Norwegian standard)	Kaptan

Chemical Names

Chemical Abstracts (CA)
3a,4,7,7a-tetrahydro-2-[(trichloromethyl)thio]-1*H*-isoindole-1,3(2*H)*-dione
International Union of Pure and Applied Chemistry (IUPAC)
N-(trichloromethylthio)cyclohex-4-ene-1,2-dicarboximide

Trade Names

Captan, Captec, Merpan, Orthocide, Phytocape, etc.
(as many as 38 different trade names and chemical names have been recorded for this substance alone)

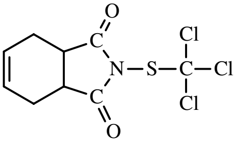
Chemical Abstracts Services Registry Number (CAS-RN)

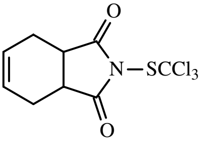
133-06-2

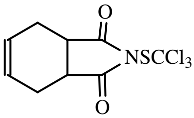
Various Codes

SR 406, ENT 26538

Chemical Structure



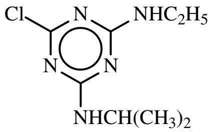




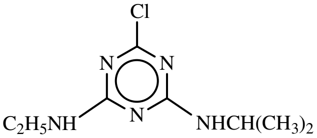
1.4.3 Chemical structures are versatile

The chemical structures are the most versatile way, even for nonchemists, to define a chemical. The chemical structure hides or, better, displays all the properties of the compound. The chemical structures may also be written in several ways. It is therefore not a waste of time to learn some examples of chemical formulas for the more important groups of pesticides.

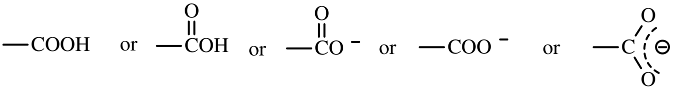
There are some conventions about how the structures are depicted, but in this book, the structure is drawn to make clear the important points. For instance, the structure for atrazine should be written with this orientation, with the number 1 ring — nitrogen — upward.



It is easier to remember and to see the symmetry when written in this direction:

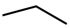
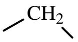


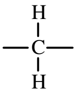
Remember that the same structural elements may be written quite differently. Carboxyl groups (organic acids) may be drawn in two ways, or in the anionic form, without the hydrogen:



$$-\text{COOH} \quad \text{or} \quad -\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{OH} \quad \text{or} \quad -\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{O}^- \quad \text{or} \quad -\text{COO}^- \quad \text{or}$$

A methylene bridge can be written in at least three different ways:



Remember also that the paper in this book is flat, but molecules are three-dimensional and their true shape cannot easily be drawn in two dimensions.

By looking at the formula, it may be possible to get a qualified opinion about such important features as:

- Water and fat solubility
- Soil sorption property

- Stability toward oxidation, UV light, biotransformation, etc.
- Classification and mode of action
- Stereoisomeri — carbon (or phosphorus) atoms that are connected to four different groups will give stereoisomeric compounds that are biologically different from each other
- Composition and possible xenobiotic character — what elements does the compound contain besides carbon and hydrogen (sulfur, halogen, nitrogen, some odd metals, silicium, etc).

This can be done without much theoretical knowledge of chemistry. Unfortunately, the current knowledge in toxicology is not sufficient to make it possible to deduce all the properties of a chemical just by looking at the structure, but a lot can be said, or at least presumed.

Helpful reading

There is an extensive literature cited section at the end of the book. The following books are useful as general texts.

Biochemistry and cell biology

Alberts, B., Bray, D., Johnson, A., Lewis, J., Raff, M., Roberts, K., and Walter P. 1998. *Essential Cell Biology: An Introduction to the Molecular Biology of the Cell.* Garland Pub., New York. 630 pp.

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Wilkinson, C.F. 1976. *Insecticide Biochemistry and Physiology*, Vol. XXII. Plenum Press, New York. 768 pp.

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The current Web address of the British Crop Protection Council is www.bcpcorg. It is useful for ordering the current issue of *The Pesticide Manual* and for updating the knowledge of pesticides.

Side effects of pesticides

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