Chapter 42

Pesticides

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Contents

42.1 Introduction

Most pesticides are chemicals used in agriculture to control of pests, weeds or plant diseases. Some pesticides are used as vector control agents in public health programs. Pesticides are also used in horticulture, forestry and livestock production. Herbicides, insecticides and fungicides are the major groups (Table 1). Most pesticides used are synthetic products, but some are of biological origin, such as plant extracts or microorganisms. Many pesticides are potentially very hazardous to human health (Table 2) and to other organisms in the environment, and they may cause damage to the ecosystem. Human exposure to pesticides is generally unintentional – dermal, oral or respiratory. Dermal exposure is often the major route through which acute and severe toxic effects are initiated, mainly by the skin's absorption of cholinesterase-inhibiting insecticides (organophosphorus compounds). Contact dermatitis and other adverse skin effects are also important (Table 3). Intentional ingestion during a suicide attempt is often fatal. Acute and chronic health effects of exposure to pesticides constitute a large public health problem in developing countries [57].

Core Message

- Dermal exposure to pesticides may cause systemic toxic effects, dermatitis or other adverse skin effects.

Table 1. Main categories of pesticides

Herbicides and desiccants
Insecticides, acaricides, molluscicides and nematicides
Fungicides
Plant grow regulators
Repellents
Rodenticides
Wood preservatives
Slimicides
Products used against microorganisms in chemical toilets, etc.
Anti-fouling products
Other products
Biological pesticides

Table 2. Health effects of pesticides (based on [57])

Bone-marrow effects
Cancer
Developmental effects
Enzyme induction
Eye lesions
Immunological effects
Neurotoxicity
Reproductive dysfunction
Respiratory effects
Skin lesions (see Table 3)
Systemic poisoning

Table 3. Skin effects of pesticides (based mainly on [1, 8, 18, 28])

Absorption through the skin
Accumulation in skin
Chemical burns
Chloracne
Contact dermatitis: allergic and irritant
Hyper- and hypopigmentation
Nail dystrophy
Photosensitivity
Porphyria cutanea tarda
Sclerodermatous changes
Squamous cell carcinoma

42.2 Use of Pesticides and Limitations of Use

Today, about 750 active ingredients are used as pesticides in 50,000 commercial formulations on the world market, and 25% of the world consumption of pesticides occurs in developing countries [56, 57].

Historically, the use of inorganic chemicals, sulfur and arsenic to control insects dates back to classical Greece and Rome. Paris green, an impure copper arsenite, was introduced in 1867 for crop protection. Iron sulfate was found to be useful for weed control. The first organomercury seed dressing was introduced in 1913 in Germany. DDT was developed in 1940. Since then, a wide range of chemical compounds have been introduced as pesticides.

The use of pesticides is, in large parts of the world, surrounded by regulations concerning the substances allowed, methods, indications and periods of application, education and protective equipment for workers. An increasing number of pesticides have, during the last decades, been banned or severely restricted for use in large parts of Europe and in Northern America, mainly due to their unwanted effects on the environment, and in some cases due to their effects on human health. Examples are DDT and other organochlorine insecticides, many mercury compounds, some phenoxy acid herbicides, and the herbicide paraquat. Many of those pesticides are, however, widely exported to and used in developing countries [9, 10, 52, 57].

DDT and the phenoxy acid herbicide 2,4,5-T are banned in all European Union countries. The producers of paraquat are promoting its use all over the world, stating that it is safe to use according to label instructions. The major markets for paraquat are in Asia, Central and South America, which use ~75% of the paraquat produced. Less than 10% of it is used in Europe [10]. Particularly in developing countries, but also elsewhere, conditions are substandard, resulting in substantial skin exposure. Paraquat is banned in 13 countries. Malaysia was the first developing country to decide (in 2002) to ban paraquat. It has been forbidden in Sweden since 1983. The European Commission decided in 2003 to include paraquat in Annex I of Directive 91/414/EEC, and member countries may allow its use. Sweden has applied to the Court of Justice of the European Communities to annul the decision to authorize paraquat, as it would result in an unacceptably low level of protection (P. Bergkvist, Swedish Chemicals Inspectorate, personal communication).

Core Message

- The use of pesticides in Europe and Northern America is surrounded by regulations for the protection of the environment and human health, while the use of pesticides causes severe problems in developing countries.

42.3 Terminology, Classification, and Formulations

Pesticides are usually categorized according to what they are used against or to protect (Table 1). The active ingredients are often mentioned by their common names or by trivial names, according to the International Organization for Standardization (ISO), which is the terminology used in this chapter as well. Many synonyms occur, and many pesticides are better known by trade names of pesticide products. The WHO classification by degree of acute hazard to humans is widely used: class Ia is extremely hazardous; Ib is highly hazardous; II is moderately hazardous; and III is slightly hazardous.

Pesticides are formulated in different ways – such as solid or liquid concentrates, solutions or emulsions in water or organic solvents, aerosols, granules, powders, or mixed with sand, dusts, and fumigants. It is essential to recall that pesticide products, besides their active ingredients, also contain non-active ingredients and possibly contaminants. Many of the nonactive ingredients and contaminants are toxic substances, and some are known skin irritants or allergens (organic solvents, formaldehyde, isocyanates). The formulants can also act as facilitators for transport into the skin and may therefore worsen a

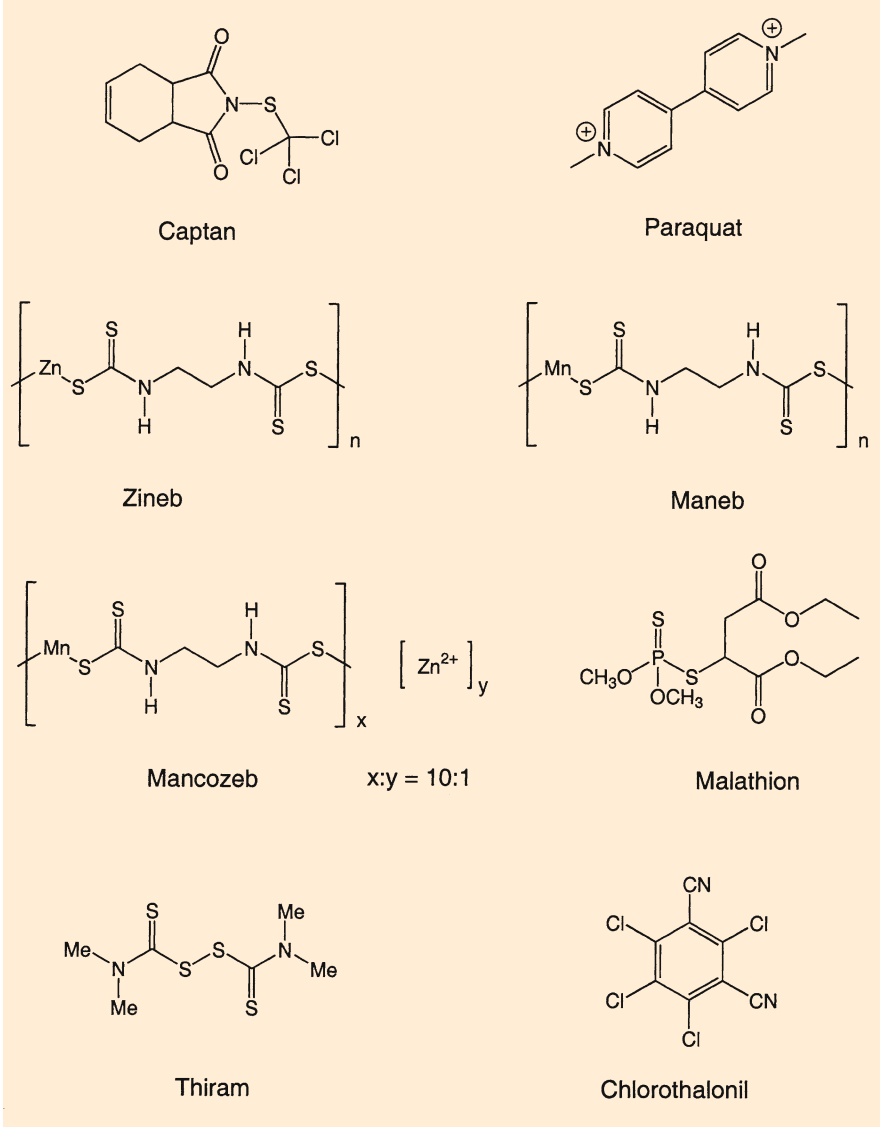

Fig. 1.
Chemical structures of some pesticides

lesion. The chemical structures of some pesticides are shown in Fig. 1.

42.4 Skin Exposure and Absorption Through Skin

There is a broad variation in the degree of skin exposure to pesticides at work. Sprayers, mixers, loaders, packers, and mechanics perform work with high risk of direct skin contact with pesticides. Sprayers are also exposed to aerosols, during and after application. Workers may be exposed to pesticide residues on treated flowers, crops, bulbs, and wood. Some pesticides are quickly degraded while others are more or less persistent.

A number of methods of exposure assessment have been used for different pesticides [21] (see also Chap. 25, Allergens Exposure Assessment). Cholinesterase activity in erythrocytes or in plasma should be determined in workers using organophosphorus compounds. Paraquat and some other pesticides or their metabolites can be measured in urine. Skin exposure can be studied by hand-wash techniques, by fluorescent tracer technique, and by analysis of pesticide levels in patches on the skin. The hands are generally the part of the body with the highest exposure, but the arms and face and other unprotected or soaked parts are exposed, and with knapsack sprayers, the back and lower legs are too [4].

Percutaneous absorption of pesticides varies considerably from compound to compound, as shown by

experimental studies on normal skin of human volunteers, and by in vitro studies [2, 39, 54, 55]. The regional variation in pesticide absorption through the skin is large and highest from scrotal skin, head and neck. Occlusion, skin damage, concentration, contact time, area, humidity and temperature are factors that are important for absorption.

Core Message

- Percutaneous absorption of pesticides varies between compounds. Occlusion, skin damage, concentration, contact time and surface area are important factors for absorption. The fluorescent tracer technique and other methods may be used in exposure assessment.

42.4.1 Prevention of Skin Exposure

The most appropriate equipment for protection against exposure to hazardous pesticides depends on the type of work and the properties of the pesticide product. For the most heavily exposed groups, such as applicators, mixers, and producers, the use of coverall, apron, raincoat, gloves, hat, boots, mask and goggles or face shields is often indicated (Fig. 2). For protection it is important that the equipment is used properly, that it is clean and that it is in good shape. The gloves that generally give the best protection are nitrile/butyl rubber gloves or laminate gloves (4H or Barrier). Barrier creams have not been shown to provide effective protection.

Fig. 2. Well-protected pesticide worker (Photo by Birgitta Kolmodin-Hedmen)

In many parts of the world, adequate conditions are not provided for protecting pesticide workers. The reasons for insufficient protection are often a lack of resources and low level of awareness of risks due to skin exposure. It is also uncomfortable to use fully protective equipment in a hot and humid climate. In the poorest developing countries, where many of the most dangerous pesticides are used, workers may have no protection at all. Knapsack sprayers may carry out mixing and spraying dressed in just a T-shirt and shorts (Fig. 3). Spraying by airplane is frequent and people on the ground may be unprotected. This is particularly true for the "flaggers" who are workers in the field guiding the pilot during spraying. Adequate washing conditions for skin, clothes and equipment are often not present.

Skin exposure to pesticides is heavily dependent on how the work is carried out, and on awareness of the risk caused by contamination of the skin. The use of a fluorescent tracer mixed with the pesticide has been introduced for visualization, by UV light, of skin contamination [3, 4, 11]. The method has been very useful for explaining risky techniques and occurrences to workers. Guidelines for personal protection and for field surveys have been published by authorities and organizations such as WHO, US EPA (the U.S. Environmental Protection Agency) and Crop Life International (former GIFAP and GCPF).

Core Message

- Adequate protective equipment and working conditions, and awareness of risks and safe handling, are essential for the prevention of severe health effects due to skin exposure to pesticides.

42.5 Skin Effects of Some Pesticides

The true prevalence and incidence of skin disease due to pesticide exposure is not known. It is likely that many of the pesticides cause more dermatitis

Fig. 3.
Unprotected pesticide worker (Photo by Carola Lidén)

than is reported [8]. Farmers generally do not have easy access to dermatologists; many agricultural workers are temporarily employed and do not seek medical care; and in most developing countries, where skin exposure is expected to be the highest, dermatologists are rare and patch testing is often not done.

Irritant contact dermatitis due to pesticide exposure is believed to be more frequent than allergic contact dermatitis. The most frequently reported cases of allergic contact dermatitis have been related to fungicides and insecticides. The most important fatal effects of skin exposure to pesticides are acute toxic reactions due to skin absorption of organophosphorus compounds. Pesticides are also known to cause other skin effects (Table 3).

The following examples may illustrate how the situation varies globally. In California, adverse health effects due to pesticide exposure have attracted much attention. The agricultural sector has had the highest rate of occupational skin disease of any industry, and epidemics of contact dermatitis have been reported. One third of the illnesses and injuries due to pesticides have been reported to involve the skin [28]. In Japan, contact dermatitis was reported in 27% of 815 patients diagnosed with and treated for pesticide poisoning. The principal pesticides reported to be responsible for the dermatitis cases were fungicides and insecticides, and spraying operations were reported in 78% of cases. Results from patch testing were not given [35]. In Denmark, clinical examination and patch testing was carried out on 253 gardeners and greenhouse workers with occupational skin symptoms identified by a questionnaire. Contact allergies to the fungicides captan (ten cases) and maneb (three cases) were recorded. The relatively low prevalence of contact allergy to fungicides was thought to reflect the effect of protective measures [41].

Detailed reviews on occupational skin disease related to pesticides, covering large numbers of case reports, as well as more conclusive studies, have been published [1, 8, 18, 28, 47]. The results from the predictive testing of 23 pesticides in guinea-pigs are presented in a review [51]. Some of the most relevant information on the skin effects of commonly used pesticides is summarized below.

Core Message

- Irritant and allergic contact dermatitis and other skin effects are caused by pesticide exposure. Fungicides and insecticides are the most frequently reported causes of allergic contact dermatitis. Skin absorption of organophosphorus compounds and paraquat cause severe toxic effects.

42.5.1 Herbicides and Desiccants

Glyphosate (Roundup and other trade names) is the largest selling non-selective herbicide applied in agriculture, public areas and for home use. It has been associated with skin disease [40]. Human experimental assays, however, showed no evidence for induction of photo-irritation, allergic or photo-allergic contact dermatitis, and it was a mild irritant [27].

Paraquat (Gramaxone and other trade names) is a nonselective contact herbicide and desiccant. It is one of the most widely used pesticides for weed control. Paraquat is highly toxic when ingested, causing multiple organ failure, and there is no antidote. Irritant contact dermatitis, occupational keratoses, nail lesions with discoloration, deformity and onycholysis, necrotic ulcers and also fatalities have been reported after skin exposure [28]. Fifteen fatal cases of occupational exposure to paraquat in Costa Rica were described, and five were explained by dermal exposure [53]. Considerable amounts may be absorbed through damaged skin and under occlusion, while absorption through intact skin is limited [14].

2,4-D and 2,4,5-T are phenoxy acid herbicides [17, 21]. They are selective against broad-leaved plants and used as defoliants, and are produced in enormous quantities. They may contain TCDD (dioxin), which is often formed during production. This is the explanation for several outbreaks of chloracne and porphyria cutanea tarda among workers in pesticide production, and for the disaster in Seveso, Italy, in 1976. Severe contact dermatitis from a mixture of 2,4-D and 2,4,5-T has been reported. 2,4-D and 2,4,5-T were components of "Agent Orange", used by the United States army to defoliate jungle areas in South Vietnam. "Agent Orange" was contaminated by dioxins and dibenzofurans related to 2,4,5-T.

42.5.2 Insecticides

Many insecticides are very toxic on skin contact, resulting in systemic toxicity; some are skin irritants and some are identified as clinically relevant contact allergens. A substantial number of case reports have been published on different types of skin reaction to several insecticides. Reference is given to reviews [1, 8, 18, 28]. Some illustrative examples are given below.

Pyrethrins are botanical pesticides, and plant extracts. The pyrethrins are obtained from *Chrysanthemum cinerariaefolium* and they are moderately potent allergens. Pyrethroids are synthetic compounds with a longer duration of activity against insects than that of pyrethrum, and less toxicity to mammals than organophosphorus compounds. Paresthesias following skin exposure has been described, but allergic contact dermatitis due to pyrethroids has not been reported [24, 28].

Malathion, parathion, naled and dichlorvos are examples of organophosphorus pesticides [28]. Parathion is extremely toxic to man and animals, and its use in Europe and Northern America is heavily restricted. Malathion, which is degraded rapidly in the body, is less dangerous. Malathion is a moderate sensitizer according to predictive testing in man and guinea pig ([37], review by [51]). Dichlorvos has been reported to cause irritant contact dermatitis in impregnated flea collars. Allergic contact dermatitis caused by naled, which has a toxicity level between that of malathion and parathion, has been reported in a few cases. Sclerodermatous changes without internal involvement have occurred in workers handling malathion, parathion, DDT and some other pesticides [19].

DDT and lindane are chlorinated hydrocarbons. The use of DDT is banned in the European Union. Allergic contact dermatitis has not been convincingly reported. Lindane is widely used and is a skin irritant, but allergic contact dermatitis is rare [28].

42.5.3 Fungicides

Benomyl, captan, chlorothalonil, difolatan, fluazinam, mancozeb, maneb, zineb, and thiram are some of the fungicides that are most frequently, or convincingly, reported to cause allergic contact dermatitis (reviewed in [1, 8, 18, 28]). Several other fungicides are reported to have caused allergic contact dermatitis in single cases. Some illustrative examples of contact allergy to fungicides are given below.

Benomyl is used for fruits, nuts, vegetables, crops and ornamentals. Several cases of allergic contact dermatitis from exposure to benomyl have been reported. Picking plants containing residues was found to be an important source of sensitization [12, 50].

Mancozeb, maneb, zineb, thiram, and other thiurams are members of the dithiocarbamate group. Cross-reactivity may be present in persons sensitive to these pesticides or chemically related rubber chemicals.

Chlorothalonil (Bravo, Daconil and other trade names) is a broad-spectrum fungicide used on vegetables, fruits, flowers, trees and bananas. Chlorothalonil is also used as a wood preservative and as a fungicide in paints. Allergic contact dermatitis in workers exposed to chlorothalonil in floriculture, banana fields, wood preservation and paints has been described [5, 20, 23, 36, 42, 44, 46]. Chlorothalonil has al-

so been described as a possible cause of skin pigmentation (ashy dermatitis) in 39 banana field workers, of whom 34 were patch test positive [43].

Fluazinam caused outbreaks of contact dermatitis on the arms and face at a tulip processing company and among farmers shortly after it had been introduced. Exposed workers were patch test positive and control persons patch test negative [7, 49].

Predictive testing in animals by the guinea-pig maximization test has shown that benomyl, captan, chlorothalonil, mancozeb, maneb, and zineb are extremely potent sensitizers (reviewed in [51]). The high sensitizing potential of chlorothalonil was further confirmed by testing in mice, using the local lymph node assay, and in the guinea pig, using the cumulative contact enhancement test [5].

42.5.4 Repellents

N,*N*-Diethyl-*m*-toluamide (DEET) is considered to be the most effective insect repellent against mosquitoes. It has been reported to cause antecubital erythema, progressing to bullae and permanent scarring in American soldiers. It has also been reported to exacerbate seborrhea and acne, and to produce allergic contact dermatitis and contact urticaria [28].

42.5.5 Rodenticides

Warfarin is and antu has been frequently used rodenticides, substances used to kill rats and mice. Only single cases of occupational contact dermatitis due to exposure to Warfarin and antu have been reported [28].

42.5.6 Wood Preservatives, Slimicides, and Anti-fouling Products

Besides its use as a fungicide in agriculture, chlorothalonil is also used as a wood preservative. There are a number of publications concerning allergic contact dermatitis (see Sect. 42.5.3, "Fungicides").

Glutaraldehyde is used as a slimicide and is added to wood pulp slurry in the production of paper. Glutaraldehyde is a known contact allergen and is described in other chapters.

5-Chloro-2-methylisothiazol-3-one/2-methylisothiazol-3-one (MCI/MI) is used together with arsenic, chromium, and copper compounds in wood preservation. MCI/MI is also used as a slimicide in the production of paper, added to the wood pulp slurry, and at printing. Contact allergy to MCI/MI (Kathon CG and other trade names), is covered in other chapters.

Tributyltin oxide (TBTO) is used as a wood preservative and in anti-fouling paints. TBTO is a skin irritant and has caused chemical burns, but it is not a skin sensitizer [13, 22].

42.6 Patch Testing

It may be difficult to acquire adequate information concerning possible exposure to pesticide products. It is often even more difficult to obtain detailed information concerning the composition of the actual products, and to achieve access to the active ingredients for patch testing. It is also important to recall that pesticide products, in addition to the active ingredient and possible contaminants, contain other ingredients which may be toxic, irritants or allergens, and that they are often dissolved or mixed in organic solvents or water.

At present, no commercial pesticide patch test series is available. Some patch test clinics have their own pesticides series, composed to correspond to the use of pesticides in their geographical region. As the use of pesticides changes over time and in different areas of application, it is not possible to give definite recommendations.

Patch testing should ideally be carried out with the active ingredients and with other ingredients of the pesticides that the patient is exposed to. It may, however, be extremely difficult to obtain the ingredients. A practical approach is then to patch test with appropriate dilutions of the pesticide product. For many pesticide products, but not all, testing with 1% and 0.3%, and possibly 0.1% of the product in water or petrolatum is possible (D. Bruynzeel, personal communication). It must be stressed, however, that the active ingredient or possibly other ingredients may need further dilution. Positive reactions should be validated by testing on control persons.

Before patch testing, previous experience of testing with the pesticide product or ingredients should be checked in recent reports and reviews. Some of the most well-documented pesticide patch test preparations are listed in Table 4.

Safety is important when testing such potentially hazardous compounds. The recommended amounts applied at patch testing, however, are so small that they are regarded as safe, with no risk of systemic toxicity.

Table 4. Recommended patch test concentrations for some pesticides (based mainly on [1, 8, 18, 28]). (Vehicles: *acet.* Acetone, *aq.* water, *pet.* petrolatum; types of pesticides: *acaricides* Molluscicides and nematicides, *alg* algicides, *fung* fungicides, *herb* herbicides and desiccants, *insect* insecticides, *other* other products, *rod* rodenticides, *slim* slimicides, *wood* wood preservatives)

Active ingredient (CAS number)	Type	Patch test concentration
2,4-DNCB (97–00–7)	Alg	0.01–0.1% aq. or acet.
2-Methyl-4-isothiazolin-3-one (MI) (2682–20–4)	Slim, wood	MI/MCI: 0.01–0.02% aq.
5-Chloro-2-methyl-4-isothiazolin-3-one (MCI) (26172–55–4)	Slim, wood	MI/MCI: 0.01–0.02% aq.
Antu (86–88–4)	Rod	1% pet.
Benomyl (17804–35–2)	Fung	0.1–1% pet.
Captan (133–06–2)	Fung	0.5% aq. or pet.
Chlorothalonil (1897–45–6)	Fung, wood	0.001–0.01% acet.
Dazomet (533–74–4)	Fung, herb, insect	0.1% pet.
DDT (50–29–3)	Insect	1% pet. or acet.
Difolatan (2425–06–1)	Fung	0.1% pet.
Fluazinam (79622–59–6)	Fung	0.5% pet.
Folpet (133–07–3)	Fung	0.1% pet.
Glutaraldehyde (111–30–8)	Slim	0.2–0.3% pet.
Glyphosate (34494–03–6; 38641–94–0; 81591–81–3)	Herb	1–10% aq.
Lindane (58–89–9)	Insect	1% pet.
Malathion (121–75–5)	Insect	0.5% pet.
Maneb (12427–38–2)	Fung	0.5–1% pet.
Paraquat (1910–42–5)	Herb	0.1% pet.
Pentachloronitrobenzene (82–68–8)	Fung	1% pet.
Pyrethrum (several CAS-numbers)	Insect	1% pet.
Thiram (137–26–8)	Fung	1% pet.
Warfarin (81–81–2; 129–06–6)	Rod	0.5% pet.
Zineb (12122–67–7)	Fung	1% pet.
Ziram (137–30–4)	Fung	1% pet.

Core Message

- Patch testing may be performed with appropriate concentrations of the pesticide product or the active ingredient and other ingredients. Consult the literature for safe handling.

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