Pyrethrum (pyrethrins)

(CAS No: 8003-34-7)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

No. 2000/15OSH/138 The Hague, November 9, 2004

1   Introduction

The present document contains the assessment of the health hazard of pyrethrum (pyrethrins) by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was written by J Krüse, Ph.D., JAGM van Raaij, Ph.D., WK de Raat, Ph.D. (OpdenKamp Registration & Notification, Zeist, the Netherlands).

The evaluation of the toxicity of pyrethrum has been based on reviews published in the monographs 'Handbook of Pesticide Toxicology' (Ray91) and 'Pyrethrum Flowers' (Cas95a) and by the American Conference of Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in December 1998, literature was searched in the on-line databases Toxline, Medline, and Chemical Abstracts, starting from 1965-1966, and Extoxnet, and using the following key words: pyrethrum, pyrethrins, and 8003-34-7. Data from unpublished studies were generally not taken into account. Exceptions were made for studies that were summarised and evaluated by the Food and Agricultural Organization/ World Health Organization (FAO/WHO: Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group - JMPR) (FAO65, FAO71, FAO00). The final literature search was carried out in Toxline and Medline in October 2003.
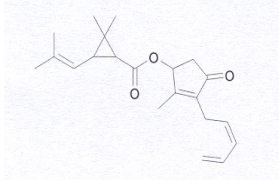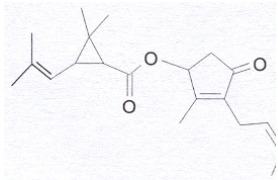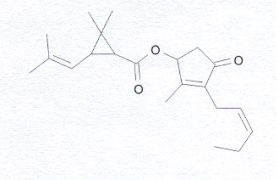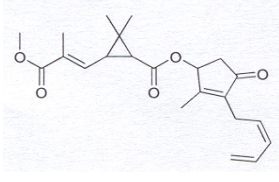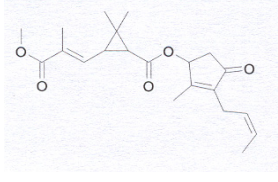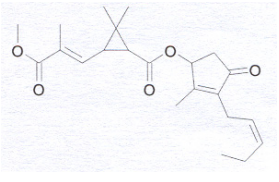
In October 2003, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: A Aalto (Ministry of Social Affairs and Health, Tampere, Finland). These comments were taken into account in deciding on the final version of the document.

2   Identity

Pyrethrum is extracted from the dried flowers of *Chrysanthemum cinerariaefolium*. The extract contains a mixture of 3 naturally occurring, closely related insecticidal esters of chrysanthemic acid (the pyrethrins I) and 3 closely related esters of pyrethric acid (the pyrethrins II). The pyrethrins I comprise pyrethrin I, cinerin I, and jasmolin I, and the pyrethrins II comprise pyrethrin II, cinerin II, and jasmolin II. Pyrethrins is the collective term for these 6 insecticidal ingredients. The first stage of extraction of pyrethrum flowers with low-boiling petroleum solvents results in crude extract or oleoresin ('OR concentrate') containing 30-35% pyrethrins. The most refined commercial grade

pyrethrum ('pale extract') contains about 55-60% total pyrethrins (FAO00, Gri73). A typical pyrethrins I/pyrethrins II ratio is 1.85; the ratio of pyrethrin (I and II), cinerin (I and II) and jasmolin (I and II) in the mixture is 71:21:7 (FAO00, Rob99).

Data on the identity of the 6 constituents of pyrethrum (CAS No: 8003-34-7 are presented below.

name	pyrethrin I	cinerin I	jasmolin I
synonyms	cyclopropanecarboxylic acid, 2,2-dimethyl-3-(2-methyl-1-propenyl)-2-methyl-4-oxo-3-(2,4-pentadienyl)-2-cyclopenten-1-yl ester [1R-[1α[S*(Z)],3β]]; chrysanthemummonocarboxylic acid pyrethrolone ester	cyclopropanecarboxylic acid, 2,2-dimethyl-3-(2-methyl-1-propenyl)-3(2-butenyl)-2-methyl-4-oxo-2-cyclopenten-1-yl ester [1R-[1α[S*(Z)],3β]]	cyclopropanecarboxylic acid, 2,2-dimethyl-3-(2-methyl-1-propenyl)-2-methyl-4-oxo-3-(2-pentenyl)-2-cyclopenten-1-yl ester [1R-[1α[S*(Z)],3β]]; 4',5'-dihydropyrethrin I
molecular formula	$C_{21}H_{28}O_3$	$C_{20}H_{28}O_3$	$C_{21}H_{30}O_3$
structural formula			
CAS number	121-21-1	25402-06-6	4466-14-2

name	pyrethrin II	cinerin II	jasmolin II
synonyms	cyclopropanecarboxylic acid, 3-(3-methoxy-2-methyl-3-oxo-1-propenyl)-2,2-dimethyl-2-methyl-4-oxo-3-(2,4-pentadienyl)-2-cyclopenten-1-yl ester [1R-[1α[S*(Z)],3β] (E)]; chrysanthemumdicarboxylic acid monomethyl ester pyrethrolone ester	cyclopropanecarboxylic acid, 3-(3-methoxy-2-methyl-3-oxo-1-propenyl)-2,2-dimethyl-3-(2-butenyl)-2-methyl-4-oxo-2-cyclopenten-1-yl ester [1R-[1α[S*(Z)],3β] (E)]	cyclopropanecarboxylic acid, 3-(3-methoxy-2-methyl-3-oxo-1-propenyl)-2,2-dimethyl-2-methyl-4-oxo-3-(2-pentenyl)-2-cyclopenten-1-yl ester [1R-[1α[S*(Z)],3β] (E)]; 4',5'-dihydropyrethrin II
molecular formula	$C_{22}H_{28}O_5$	$C_{21}H_{28}O_5$	$C_{22}H_{30}O_5$
structural formula			
CAS number	121-29-9	121-20-0	1172-63-0

3   Physical and chemical properties

	pyrethrum	pyrethrin I	cinerin I	jasmolin I	pyrethrin II	cinerin II	jasmolin II
molecular weight	316-374	328.5	316.4	330.5	372.5	360.4	357.7
boiling point[a]	-	$170°C^{0.013}$	$136\text{-}138°C^{0.001}$	-	$200°C^{0.013}$	$182\text{-}184°C^{0.00013}$	-
melting point	-	-	-	-	-	-	-
flash point	82-88°C (open cup)	-	-	-	-	-	-
vapour pressure	at 20°C: 0	3×10^{-3} Pa[b]			5×10^{-3} Pa[b]		
solubility in water	insoluble	insoluble	insoluble	insoluble	poorly soluble	insoluble	insoluble
log $P_{octanol/water}$[c]		6.28	5.93	6.42	5.33	4.98	5.47
conversion factors	not applicable						

[a]   Number in superscript represents the atmospheric pressure in kPa at which the presented value was determined.
[b]   Temperature not given.
[c]   All estimated values.

Data from ACG99, Bud96, Cas95a, Gri73, Rob99, Tom97, http://www.syrres.com/esc/est_kowdemo.htm.

Pyrethrum is a viscous brown resin or solid (ACG99). Pyrethrins are very unstable in light and air, with loss of insecticidal activity. The preparation of concentrations containing high amounts of pyrethrins (>80%, prepared by extracting OR with nitropyrene) leads to lack of stability, and it is therefore not practised commercially. Pyrethrins I and II must be stored in glass wrapped in metal foil, sealed in polythene, at a temperature of about -25°C (Ray91).

4   Uses

Pyrethrum is a non-systemic insecticide with contact action. It has some acaricidal activity. It is used for the control of a wide range of insects and mites in public health and on domestic and farm animals and for the control of chewing and sucking insects and spider mite on fruit, vegetables, field crops, ornamentals, glasshouse crops, and house plants. It is normally combined with synergists, e.g., piperonyl butoxide, which inhibit detoxification in insects.

Pyrethrins have been used extensively for the control of human body lice, and are still effective for control of head lice (Ray91).

The biological activities of the pyrethrum constituents depend on the structural characteristics of the acid and alcohol components. Pyrethrins I and II are considerably more potent than the cinerins and jasmolins. The chrysanthemates

(pyrethrin I series) are generally more potent killing agents, while the pyrethrates (pyrethrin II series) are more potent knock-down agents (Cas80).

Pyrethrins are often mixed with organophosphates, carbamates, chlorinated pesticides, or rotenone. The following formulation types are in use: fogging concentrate, emulsifiable concentrate, aerosol dispenser, wettable powder, dispersible concentrate, and ultra-low volume liquid. Pyrethrum-containing products can be liquids (sprays, aerosols, shampoos, or lotions), semi-solids (creams and ointments), solids (mosquito coils), powders, and dusts (Tom97). The usual household formulation contains about 0.5% active pyrethrum (Ray91).

According to the database of the Dutch Pesticide Authorisation Board (CTB)*, pyrethrins are at present registered in the Netherlands for use as an active ingredient in insecticides for specified applications. The 'Geneesmiddelen Repertorium', an overview of information on pharmaceutical specialties registered by the Dutch Medicines Evaluation Board, did not list pyrethrum- or pyrethrins-containing products**.

5 Biotransformation and kinetics

The committee did not find quantitative data on the respiratory absorption of pyrethrins in humans or experimental animals.

The *in vivo* dermal absorption of pyrethrin was studied by spreading [^{14}C]pyrethrin to the ventral forearm of 6 male volunteers and washing it off after 30 minutes. The commercial formulation used contained 0.3% pyrethrin. Concentrations applied amounted to 5.5 μg pyrethrin/cm^2. Hardly any radioactivity was detected in the urine samples until day 2. At this day, excretion of radioactivity peaked (ca. 0.4% of the dose applied). Thereafter, excretion levels decreased through day 7 (ca. 0.2%), the end of the experiment. The calculated half-life for urinary ^{14}C excretion was 50 hours. Based on the 7-day cumulatively excreted radioactivity and urinary excretion data from rhesus monkeys injected with [^{14}C]pyrethrin, Wester et al. calculated that 1.9 (±1.2)% of the dose applied was absorbed through the skin (Wes94).

When male Sprague-Dawley rats were given an oral (gavage) dose of 3 mg/kg bw of [^{3}H]-pyrethrin I or [^{3}H]-pyrethrin II (label in the 6'-methyl and the 5'-methylene groups of the cyclopentenolone ring, i.e., the alcohol moiety),

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*	at: http://www.ctb-wageningen.nl.
**	at: http://www.geneesmiddelenrepertorium.nl/nefarma/.

30.2% or 33.0% of the doses were excreted in the urine and 41% or 30.7% in the faeces, respectively, within 100 hours after administration. Most of the radioactivity (74-76%), excreted in the urine within 100 hours was produced during the first 20 hours after administration. When mice or rats received single doses of 1 to 5 mg/kg bw of radiolabelled ^{14}C-pyrethrin I (label in the cyclopropane carboxy group, i.e., the acid moiety), 52 or 46% of the doses were excreted in urine and 1.0 and 0.3% as $^{14}CO_2$, respectively, within 48 hours after administration. With the ^{14}C-label in the methoxy position of pyrethrin II, rats excreted 7% of the label in the urine and 53% as $^{14}CO_2$ within 48 hours after administration. It is concluded that the methoxycarbonyl group of pyrethrin II is largely hydrolysed in rats to a carboxyl group (Cas71, Ell72a).

The metabolism of the pyrethrins I and II in rats, as found in these early studies, is shown in Figure 1 (see Annex I). By oxidation of the 10-methyl group in the acid moiety of pyrethrin I, a carboxylic acid is formed via an alcohol and an aldehyde metabolite. The same metabolite is formed after hydrolysis of the methoxycarbonyl group of pyrethrin II. This carboxylic acid metabolite is further biotransformed by oxidation of the alcohol side chain of pyrethrins I or II, to give a 10',11'-dihydrodiol (14-21% of the dose), which was partly conjugated with glucuronic acid or sulphate (3.9-6.2% of the dose) prior to excretion. In addition, a 8',11'-dihydrodiol was formed (3.3-4.4% of the dose). The identified products all retained the cyclopropane ester linkage. All these metabolites were present in both urine and faeces. The faeces, but not the urine, contained some unmetabolised compound (4-18% of the dose) (Cas71, Ell72a, Ell72b, Rob99).

In a later unpublished study, under the auspices of the Pyrethrin Joint Venture, a consortium of major pyrethrum-manufacturing and -formulating companies, rats were given ^{14}C-labelled pyrethrins I in single oral doses of 10 mg/kg bw (males and females), 50 mg/kg bw (females), or 100 mg/kg bw (males). The peak concentration of radiolabel in blood occurred between 5 and 8 hours after administration. The mean percentage of administered radiolabel excreted in urine, for the various dosing regimens, was 32-47% in males and 50-57% in females, whereas in faeces 55-71% was found in males and 50-52% in females. Radiolabel was found in all tissues analysed, with the highest level found in the fat of females. The elimination half-life of pyrethrins I in the urine was 5-7 hours. Following repeated doses of pyrethrins (10 mg/kg bw/day; number of treatments not given), no accumulation of radioactivity in tissues occurred in animals of each sex. Identification of metabolites confirmed the findings of previous published studies, i.e., oxidation of the double bonds forming diols and of the methyl groups forming carboxylic acids. The major metabolite in urine was chrysanthemum dicarboxylic acid. A second pathway

involved hydrolysis of the ester bond of the methoxycarbonyl group to form the corresponding acid and alcohol (Sel95).

In a comparative *in vitro* study, the metabolism of all 6 natural pyrethrins was investigated, using both rat and mouse liver microsomes. Pyrethrin I, cinerin I, and jasmolin I were oxidised at the 10-, 10'-, and 11'-methyl groups, the 7'- and 10'-methylene groups, the 7,8- and 8',9'-double bonds, and particularly at the 10',11'-double bond of pyrethrin I. Microsomal oxidases of the rat were more selective than of the mouse in hydroxylating the pyrethrins I at the 10-position versus oxidation at the other sites. Epoxidation of these double bonds yields 7,8-, 8',9'-, and 10',11'-epoxy derivatives. Epoxides from the alcohol moiety metabolites readily form dihydrodiols, i.e., the 8'9'-dihydrodiol from cinerin I-8',9'-epoxy and the 10',11'- and 8',11'-dihydrodiols (which are major metabolites *in vivo*; see above) from pyrethrin I-10',11'-epoxy. In total, 13-18 metabolites were identified. The pyrethrins II have one major metabolite in common with the corresponding pyrethrins I, since oxidation of the 10-methyl group of the pyrethrins I give the same carboxylic acid, formed on hydrolysis of the methoxycarbonyl group of pyrethrins II. The acid moiety of the pyrethrins II is resistant to oxidation, except at a 5- or 6-methyl substituent, whereas the alcohol moieties undergo the oxidation reactions anticipated from the findings on the pyrethrins I. No hydrolysis of the cyclopropane ester bond of any of the 6 pyrethrins has been reported (Cas95b, Cla90).

The toxicity of the pyrethrins is attributable to a combination of the effects of the parent ester and the metabolites generated. The ease of oxidative metabolism of pyrethrins contributes to, or accounts for, their low toxicity to mammals. Hydrolysis of the methoxycarbonyl ester group of the acidic side chain of pyrethrin II to a carboxylic group proceeds faster than oxidation of the 10-methyl group of pyrethrin I, which may explain the higher toxicity of pyrethrin I than pyrethrin II in rats, and also the larger proportion of pyrethrin I excreted unchanged in the faeces (Cas71, Cas95b, Ell72a, Ell72b). The relative rates of microsomal oxidation are similar for pyrethrin I, pyrethrin II, cinerin I, and cinerin II (Sod77).

Human data

Irritation and sensitisation

Allergic dermatitis and asthma are the usual health effects observed in workers exposed to pyrethrum dust or powder. Case reports of adverse respiratory effects attributed to pyrethrins, such as asthma-like attacks and anaphylactic reactions, indicate that these responses often occur in individuals with a history of asthma.

In 2 recent cases, death associated with allergic reactions to dog shampoos containing pyrethrins has been reported. The first case dealt with an 11-year-old asthmatic girl who washed her dog with shampoo containing 0.2% pyrethrin. Within 10 minutes, she suffered a severe asthmatic attack and died within 3 hours, despite medical treatment. The cause of death was listed as 'respiratory arrest secondary to acute asthmatic attack', pathological findings being consistent with the literature on pathological changes in acute asthma (Wag00). In the second case, a 37-year-old female with a 10-year history of mild asthma developed severe shortness of breath within 5 minutes after beginning to wash her dog with a shampoo containing 0.06% pyrethrin. She went into cardiopulmonary arrest and died a short time later, despite efforts to revive her. Post-mortem examination revealed pulmonary findings consistent with reactive airway responses (Wax94). In another report concerning a shampoo containing natural pyrethrins (0.3%), a non-fatal case of a 43-year-old woman with a history of asthma and ragweed allergy, who experienced an anaphylactoid reaction after self-medication for the treatment of head lice was described. Within one hour after application, she had periorbital oedema. The next morning, she also complained of shortness of breath, chest tightness, dysphagia, and numbness in the extremities, and she became unresponsive during transport to the hospital. After 4 days of medical treatment, the patient was discharged (Cul88). No data on exposure or on the purity of pyrethrum extracts (see below) used in the shampoos were reported in either study.

Pulmonary interstitial fibrosis and pneumonia in a 24-year-old woman, who applied approximately 2.5 cans of a pyrethrum-based insecticide every week for 6 months, have been ascribed to pyrethrum hypersensitivity. She complained about increasing fatigue, pain on the chest, cough, and laboured breathing. Furthermore, the serum IgG, IgM, and IgE levels were substantially increased. Skin testing demonstrated type 1 and 3 hypersensitivity reactions. Chest X-ray,

spirometry, and lung biopsy showed symptoms indicative for hypersensitivity lung disease. Cessation of usage of the insecticide resulted in disappearance of the symptoms (Car77). A 24-year-old man presented to an emergency department with stinging sensation on the nasal and upper pharyngeal mucosa, rhinorrhoea, moderate shortness of breath, cough, severe nausea, and diffuse abdominal cramping associated with repeated vomiting, tingling sensation in both hands, dizziness, and fatigue. Thirty minutes prior to the onset of symptoms, he had sprayed his dog and the floor of his enclosed, unventilated bedroom with a flea-killing spray containing 0.15% pyrethrins and rubbed the spray into the dog's fur with ungloved hands. Upon medical treatment, symptoms disappeared within 2 hours with the exception of a feeling of fatigue (Pat88). In an older study, 7 out of 14 patients, who showed adverse reactions to intradermal tests with pyrethrum extracts, developed a mild nose and throat discomfort following inhalation exposure to pyrethrum aerosol. None of the patients developed asthma and there were no delayed reactions (Zuc65). Some of the less purified pyrethrum extracts may contain allergens that cause rhinitis and asthma (Mor82). However, no thorough investigation of the substances responsible for the adverse respiratory responses has been conducted (FAO00).

Reported skin effects in older studies were a mild erythematous, vesicular dermatitis with papules in moist areas and intense pruritus. Oedema and cracking develop in severe cases, particularly of the face, lips, and eyelids. Other effects were rhinitis, asthma, and temporary numbness of the tongue and lips. Hot weather or severe perspirating increase the susceptibility to pyrethrum dermatitis (Cas80, Mar41, McC21, Ram30, Seq36). Ointments that were applied as mosquito repellents, containing 40% colourless concentrate of pyrethrum, caused a high incidence of sensitisation leading to dermatitis in 9.7% of the men and 25.9% of the women who applied the cream on a daily basis (Lor47). A 41-year-old farmer, who used pyrethrin and endosulfan, developed erythematous papular lesions on the face, the dorsum of the hands, and the posterior part of the neck 2 days after use. Histological examination of the skin demonstrated perivascular infiltrates of lymphocytes and necrosis of basal keratinocytes. Patch tests with pyrethrum (2%) were positive (Bra95). Baer demonstrated that 6 out of 200 patients, allergic to ragweed pollen, evaluated for contact dermatitis or other skin diseases, developed contact dermatitis or other skin diseases following exposure to pyrethrum (Bae73).

Several investigations have been undertaken to isolate and characterise the allergen responsible for the dermal reactions. When purified pyrethrum extracts were tested on 106 patients allergic to pyrethrum flowers, only a few subjects

reacted positive. However, all subjects showed positive skin reactions to unrefined pyrethrum (Zuc65). When 200 people (177 woman and 23 men) were patch tested with a 1% water dispersion of pyrethrins, no evidence of primary skin irritancy or of sensitisation was found (FAO71, Gri73). A patient, who was reported to be allergic to pyrethrum flowers, reacted positively in a 48-hour closed patch test with 0.1% w/v pyrethrosin, a sesquiterpene lactone present in pyrethrum powder, and weakly positive to 2% w/v pyrethrin II. Negative responses were obtained with pyrethrin I, cinerin I and II, and jasmolin I and II (Mit72). It is highly unlikely that pyrethrosin, or other allergic impurities, are present in commercial refined pyrethrum extracts (Hea69).

The committee concludes that the refined pyrethrum extracts do not induce skin allergies when tested on sensitive subjects, and that the dermal effects in the early literature are not relevant to an assessment of refined pyrethrins.

Acute toxicity

Apart from the data on allergic dermatitis and asthma presented above, the committee found only very little information on effects following acute accidental or incidental exposure of humans to pyrethrins. This information is limited to 2 cases both reported at the end of the 19th century. One case concerned a 2-year-old child dying after eating about 15 grams ('half an ounce') of an insect powder. The other case was an 11-month-old infant whose mouth, nostrils, and entire face were accidentally covered with pyrethrum powder. This infant immediately showed pallor, intermittent convulsions, vomiting, collapse, redness by pain when pulled up by the hands, refusal to nurse, feeble and slow heart sounds, and laboured respiration. After carefully washing the face and mucous membranes and abundant vomiting, induced by an emetic, the infant essentially recovered within 1.5 hours, except for a slight inflammation of the conjunctivae and extreme redness of the lips and the tongue (Ray91). When pyrethrins were used as an anthelmintic, the recommended dose was 20 mg for adults given daily for 3 days, with no apparent adverse effects (Ray91). The acute human oral lethal dose has been estimated to be between 700 and 2100 mg/kg bw (Gos84, Leh39).

Interaction with the endocrine system

A purified pyrethrum extract with a total pyrethrin content of 20% was tested *in vitro* for its ability to interact with androgen binding sites in human genital skin fibroblasts and with sex hormone binding globulin (SHBG) in human plasma.

Pyrethrins showed competitive binding to the human androgen receptor and to SHBG, indicating potential androgenic or anti-androgenic activity. Though the activity of natural pyrethrins was higher than that of synthetic pyrethroids, the hormonal activity was relatively weak. According to the authors, huge amounts would be required to induce an effect *in vivo* (Eil90).

Animal data

Irritation and sensitisation

Application of pyrethrins to the skin of albino rabbits produced only minimal skin irritation (Rom91a, Sch95). Undiluted pyrethrum extract produced mild conjunctival irritation to the eyes of albino rabbits during the first 48 hours after application. The irritation disappeared within 72 hours after application. No corneal opacity or iritis was observed (Bie91, Sch95). In older studies, various pyrethrum grades were found to be slightly irritating to the skin and eyes of rabbits (Car50, Mal68). Pyrethrins (purity: 86%) did not cause local reactions, when rubbed into the skin of rats in amounts of 50 mg daily for 30 days (Amb51).

Pyrethrins were not sensitising to the skin of guinea pigs, with a modified Buehler test (Rom91b, Sch95). Other studies in female guinea pigs demonstrated that a refined pyrethrum extract, used in aerosol fly killers, did not evoke an allergic response. Pyrethrins I and II were also negative in these studies (Ric72, Ric73).

Acute toxicity

The results of acute lethal toxicity tests, using 'pale' or 'nitropyrene' pyrethrum extracts are summarised in Table 1. Results are expressed in mg total pyrethrins per kg body weight.

Table 1 Summary of acute lethal toxicity studies for pyrethrum extracts in mammals.

exposure route (duration)		species (sex)	purity (% pyrethrins)	grade	LC_{50}/ LD_{50}	reference
inhalation	(4 h)	rat (males, females)	57.6%	not specified	3400 mg/m^3	Hof91, Sch95
	(1 h)	rat	not specified	not specified	>20 mg/m^3	Gri73
	(30 min)	rat (females)	not specified	not specified	>6200 mg/m^3	Car50
dermal		rabbit	57.6%	not specified	>2000 mg/kg bw	Gab91, Sch95
		rabbit	ca. 20%	'pale'	>5000 mg/kg bw	Mal68
		rabbit	ca. 80%	'nitropyrene'	>19800 mg/kg bw	Mal68
		rat	ca. 20%	'pale'	>1500 mg/kg bw	Mal68
		rat	ca. 80%	'nitropyrene'	>5400 mg/kg bw	Mal68
oral		rat (males)	57.6%	not specified	2370 mg/kg bw	Gab92, Sch95
		rat (females)	57.6%	not specified	1030 mg/kg bw	Gab92, Sch95
		rat	ca. 20%	'pale'	584 mg/kg bw	Mal68
		rat	ca. 60%	'pale'	710 mg/kg bw	Gri73
		rat	ca. 60%	'pale'	1440 mg/kg bw	Bon73
		rat	ca. 80%	'nitropyrene'	715-900 mg/kg bw	Mal68
		rat	ca. 80%	'nitropyrene'	>1400 mg/kg bw	Ver72
		mouse	ca. 20%	'pale'	796 mg/kg bw	Mal68
		mouse	ca. 80%	'nitropyrene'	285-308 mg/kg bw	Mal68
		mouse	ca. 80%	'nitropyrene'	786 mg/kg bw	Mal68
intraperitoneal		rat	ca. 20%	'pale'	189 mg/kg bw	Mal68
		rat	ca. 80%	'nitropyrene'	208-798 mg/kg bw	Mal68
		mouse	ca. 20%	'pale'	185 mg/kg bw	Mal68
		mouse	ca. 80%	'nitropyrene'	160-452 mg/kg bw	Mal68
intravenous		rat	ca. 80%	'nitropyrene'	5 mg/kg bw	Ver72

In summary, the inhalation 4-hour LC_{50} was 3400 mg/m^3 for rats, the dermal LD_{50} values were greater than 1500 and 5000 mg/kg bw for rat and rabbits, respectively, and the oral LD_{50} values varied from 584 to 2400 mg/kg bw for rats, and from 285 to 796 mg/kg bw for mice. Variations in LD_{50} values are suggested to be due to variations in the components in the extracts and the concentrations of pyrethrum in the dosing solutions (Ray91). Female rats are more sensitive to the acute effects of pyrethrum extracts than male rats (Cas95a, Gab92). Administration via the intravenous route is by far the most toxic, probably because the target organ (nerve synapses) is reached before metabolism occurs (Gri73).

After acute inhalation, oral, or parenteral exposure, signs of intoxication were hyperactivity, increased respiratory rate, muscular tremors, ataxia, incoordination, and convulsions (Car50, Mal68, Sch95). No-effect levels for clinical signs following acute oral dosing were 710 and 320 mg/kg bw for males and females, respectively. The inhalation no-effect level was 690 mg/m^3 (Sch95).

Microscopic and macroscopic examination of rats exposed by inhalation revealed moderate congestion of lung tissue at approximately 6200 mg/m^3 for 30 minutes(Car50) and discoloured and oedematous respiratory tissues at 3400 mg/m^3 for 4 hours (Hof91). Following dermal application, rabbits showed slight erythema and very slight oedema (Gab91). Oral administration caused haemorrhagic lungs, tan to yellow fluid in the lower gastro-intestinal tract, and muzzle and genital staining (Gab92).

Oral LD$_{50}$ values of pyrethrin I and II in rats were between 260 and 420 mg/kg bw and greater than 600 mg/kg bw, respectively (Cas71). This difference is due to the differences in the metabolism of pyrethrins I and II (see Chapter 5). The intravenous LD$_{50}$ of pyrethrin I in rats was 5 mg/kg bw (Ver72).

In an unpublished acute neurotoxicity study, under auspices of the Kenya Pyrethrum Information Centre, Sprague-Dawley rats (n=15/sex/group) received single oral doses of pyrethrum extract (purity: 57.6% total pyrethrins) by gavage, at doses of 0, 40, 125, or 400 mg/kg bw for males and 0, 20, 63, or 200 mg/kg bw/day for females. Mortality was observed in 5 males and 2 females of the high-dose group. At this dose, neurological signs of toxicity were tremors, wetness of the urogenital area, salivation, perinasal encrustation, exaggerated startle response, decreased grip strength, hind-leg splay, and increased body temperature. Tremors were also seen in females at 63 mg/kg bw. Behavioural effects (increased motor activity and decreased rearing and ambulation) were observed at the high- and mid-dose levels in males and at the top dose in females. Microscopic examination of the sciatic nerve revealed not dose-related scattered degenerating nerve fibres or myelin sheets in a few animals. The NOAEL was 20 mg/kg bw/day (Her93).

Short-term toxicity

Sherman strain rats (12 males, 15 females) received 85 inhalation exposures to pyrethrum extract at an aerosol concentration of approximately 23 mg pyrethrins/m^3 for 41 days. One 30-minute exposure/day was given during the first week and 2 daily 30-minute exposures thereafter. Mortality, body weight gain, and relative liver and kidney weights were not different from the control group. No treatment-related macroscopic or microscopic changes were observed (Car 50). In a similar experiment conducted by the same authors, in which rats received 42 exposures within 31 days, 30 minutes/day, effects were a significant decrease in number of neutrophils, accompanied by a significant increase in

number of lymphocytes, and a significant decrease in relative kidney weights. No treatment-related macroscopic or microscopic changes were observed (Car50).

In an unpublished inhalation study, under the auspices of the Pyrethrin Joint Venture, groups of 15 Charles River rats of each sex were exposed to a liquid aerosol of pyrethrum extract (purity: 57.6% total pyrethrins) at concentrations of 0, 38, 68, 230, or 830 mg pyrethrins/m^3, 6 hours/day, 5 days/week, for 13 weeks. The average mass median aerodynamic diameter (MMAD) of the aerosol particles was 2.7 μm. One death, potentially related with exposure, was observed in the high-concentration group. Signs of toxicity were laboured breathing, hyperactivity, excess lachrymation, and tremors. Irritation of the respiratory tract was observed at 68 mg/m^3 and above. Body weights, body weight gains, and food consumption were decreased in both males and females exposed to 230 and 830 mg/m^3. Anaemia was observed in males at the 3 highest and in females at the highest exposure level, with significant decreases in haemoglobin levels, haematocrit, and erythrocyte counts. Other effects at the high exposure level were an increase in white blood cell counts in females, and decreased total protein and globulin concentrations in the serum of male animals. Liver weights were increased at 830 mg/m^3. Microscopic examination revealed treatment-related changes in the larynx, nasoturbinates, nasopharynx, and lungs. They were observed in all groups, including the control group, but were more pronounced in the pyrethrin-exposed groups, especially in the high-concentration group (New92, Sch95). Based on anaemia in male animals, the committee concludes that 38 mg/m^3 is a NOAEL for systemic effects, while this level might have induced local effects in the respiratory tract.

When dogs (n=5) were fogged with a 1 L pyrethrum extract (0.25%) in kerosine, producing an aerosol concentration of 562 mg pyrethrins/m^3, 20 minutes/day, for 4 consecutive days (4 exposure periods of 5 minutes, with a 7-10 minute pause between each period), effects were a significant increased number of reticulocytes and a reduced haematocrit at 7 days after the beginning of exposure. White blood cell and platelet counts remained unaffected. However, additional to these effects, splenectomised dogs also showed erythroid hyperplasia in the bone marrow, with a reversal of myeloid:erythroid ratio and a reduction in platelet counts (Lor72). Griffin calculated that the applied concentration was 11,000 times higher than that received by someone spraying a room (Gri73).

In another study, 3 dogs were given 40 30-minute aerosol exposures of approximately 23 mg pyrethrins/m^3 during 26 days. No significant changes were observed in body weight gain or haematological tests. Two pyrethrin-exposed

dogs developed minor congestion of the lungs, but this effect was unlikely related to pyrethrin exposure, as it also ocurred in one control animal (Car50).

Rabbits (n=15) received a dermal application of 0 or 10 mg pyrethrins/kg bw for 15 days, with a 2-day rest after the 5th and the 10th administration. The occluded skin was exposed for 6-8 hours, after which the gauze was removed and the exposed area washed. No treatment-related effects were observed (Gri73).

In an unpublished dermal study, under the auspices of the Kenya Pyrethrum Information Centre, a 25% (w/v) mixture of pyrethrum extract (purity: 57.6% total pyrethrins) in corn oil was administered to the skin of New Zealand rabbits (n=5/sex/dose level), at doses of total pyrethrins of 0, 100, 300, or 1000 mg/kg bw/day, 5 days/week, for 3 weeks. The application sites were occluded during the 6-8-hour exposure. Several animals in the treated groups showed very slight to well-defined erythema of the skin at the application site, but this effect was not dose-related. Microscopic examination of organs and tissues did not show treatment-related abnormalities. The NOAEL for systemic effects was 1000 mg/kg bw/day, the highest dose tested (Gol92, Sch95).

Sherman strain rats (n=6) received pyrethrum extract (20% total pyrethrins) via the diet at a dose level equivalent to 50 mg pyrethrins/kg bw/day, for 14 days. Mean body weight gain was significantly decreased and mean absolute and relative liver weights were significantly increased, compared with control animals. Microscopic examination revealed occasional enlarged hepatocytes, occasional vacuolated cytoplasm, and occasional cytoplasmic inclusions. These changes were intensified when rats received doses of combined pyrethrins and piperonyl butoxide (Kim68).

When male Sprague-Dawley rats (n=4/group) were given pyrethrum extract (20%) at doses equivalent to 85, 200, or 500 mg pyrethrins/kg bw/day by gavage for 15 days, a statistical significant dose-related increase in relative liver weight was observed at the 2 higher levels and a statistical significant increase in the activity of several drug metabolising enzymes at all dose levels. Treatment at 500 mg/kg bw/day for 4 days resulted in increased activities of cytochrome P450 and NADPH-dependent cytochrome c reductase to 141% and 197% of control levels. When animals were treated with 500 mg/kg bw/day for 4, 7, or 17 days, the increases in relative liver weight and in activities of drug metabolising enzymes reached already a plateau at day 4. Liver weights and enzyme activities returned to normal within 7 days after cessation of treatment. The LOAEL was 85 mg/kg bw/day, based on hepatic enzyme induction (Spr73).

Female or male rats (n=5/sex) were fed 'pale' pyrethrum extract via the diet, at dose levels equivalent to of 911 or 704 mg pyrethrins/kg bw/day, respectively, for 5 weeks. No clinical signs of toxicity were reported. Macroscopic examination revealed prominent Peyer's patches in the ileum of one male and one female. No further details were provided (Hun72).

In an unpublished oral study, under the auspices of the Pyrethrum Joint Venture, Charles River CD rats (n=15/sex/group) received pyrethrum extract (purity: 57.6% total pyrethrins) via the diet at dose levels equivalent to 0, 17, 57, 170, 590, or 1200 mg pyrethrins/kg bw/day for males and 0, 22, 74, 220, 710, or 1400 mg/kg bw/day for females, for 13 weeks. In the high-dose group, 1 male and 12 females died during the first week of the study. Signs of toxicity were tremors, hyperactivity, increased respiration rate, convulsions, and decreased defecation. Most signs were seen only during the first 2 weeks of the study. Other effects at the 170 mg/kg bw/day were decreased body weight gains, food consumption, haemoglobin levels, haematocrit, and erythrocyte count and increased liver and kidney weights. Macroscopic examination showed a dose-related enlargement and congestion of the liver in both sexes at the 2 highest doses. Microscopic examination revealed treatment-related small focal or multifocal areas of tubular degeneration and regeneration in the renal cortex in animals at 170 (males) or 220 mg/kg bw/day (females) and above. The NOAEL was 57 mg/kg bw/day, based on effects on liver, kidney, and erythrocytes at higher dose levels (Gol88a, Sch95).

In an unpublished oral study, under the auspices of the Pyrethrum Joint Venture, Charles River CD-1 mice (n=15/sex/group) received pyrethrum extract (purity: 57.6% total pyrethrins) via the diet at dose levels equivalent to 0, 47, 160, 460, or 1600 mg pyrethrins/kg bw/day for males, and 0, 56, 200, 580, or 1800 mg/kg bw/day for females, for 13 weeks. In the high-dose group, 4 males and 2 females died on day 2. Signs of toxicity included tremors, dilated pupils, altered activity, laboured breathing, and cold to touch. No treatment-related clinical signs were observed in the other groups. Body weights and food consumption remained unaltered. At the 2 highest dose levels, absolute and relative liver weights were significantly increased in both sexes, and congestion of the liver was observed. Microscopic examination showed hepatocellular hypertrophy at the 3 highest dose levels. The NOAEL was 47 mg/kg bw/day, based on effects on the liver (Gol88b, Sch95).

Beagle dogs (n=6) were fed pyrethrum extract (purity not given) at a dose level equivalent to approximately 165 mg pyrethrins/kg bw, for 90 days. Signs of toxicity were tremors, ataxia, laboured respiration, and salivation, mainly in the 1st month of the experiment. Appetite was poor during the first week, but

improved thereafter. Slight body weight loss was observed, but results of haematological, biochemical, and urine tests were comparable to controls. No treatment-related microscopic changes were seen, apart from slight centrolobular vacuolation in the liver (Gri73).

In an unpublished oral study, under the auspices of the Pyrethrum Joint Venture, beagle dogs (n=2/sex/group) received pyrethrum extract (purity: 57.6% total pyrethrins) via the diet at dose levels equivalent to 0, 18, 30, 86, or 170 mg/kg bw/day for males and 0, 19, 29, 94, or 200 mg/kg bw/day for females, for 8 weeks. At the high dose, 1 male and both females died. Clinical signs observed at the 2 highest dose levels included inappetence, ataxia, tremors, and impaired limb function. Animals in the high-dose group had decreased body weight gains and food consumption, anaemia, alterations in electrolytes, and increased liver enzyme (ALAT and ASAT) activities. At 86 mg/kg bw/day, males showed decreased haemoglobin, haematocrit, and erythrocyte values compared to the controls. Liver weight increases occurred in both males and females at 30 mg/kg bw/day and higher and 29 mg/kg bw/day and higher, respectively. There were no treatment-related microscopic or macroscopic lesions at any dose level. The NOAEL was 18 mg/kg bw/day (Gol88c, Sch95).

In another unpublished dog study, under the auspices of the Pyrethrum Joint Venture, beagles (n=4/sex/dose level) received pyrethrum extract (purity: 57.6% total pyrethrins) via the diet at dose levels equivalent to 0, 2.6, 14, or 66 mg pyrethrins/kg bw/day for males and 0, 2.8, 14, or 75 mg/kg bw/day for females for 52 weeks. No mortality was reported and no signs of toxicity observed in any dog at any dose level. Mean body weights of treated animals were similar to those of controls. Food consumption was lower in animals of the high- and mid-dose groups during the first 2 week only. Effects in the high-dose females were increased white blood cell counts, segmented neutrophil counts, and serum alanine aminotransferase (ALAT). In high-dose males, haemoglobin concentration, haematocrit, and erythrocyte counts were decreased and absolute and relative liver weights increased. Macroscopic and microscopic examination did not reveal treatment-related abnormalities. The NOAEL was 14 mg/kg bw/day, based on haematological and liver effects (Gol90a, Sch95).

A summary of short-term toxicity studies with pyrethrum is shown in Table 2.

Table 2 Summary of short-term toxicity studies for pyrethrum.

exposure route	species (strain, number, sex)	dose levels	exposure duration	critical effect	NOAEL	reference
inhalation	rat (Sherman; 12 males, 15 females)	0, 23 mg/m^3	31-41 d, 30-60 min/d	effects on white blood cells, kidney	LOAEL: 23 mg/m^3	Car50
	rat (Charles River ; n=15/sex/group)	0, 38, 68, 230, 830 mg/m^3	13 w, 5 d/w	anaemia effects on upper respiratory tract, lungs	38 mg/m^3 LOAEL: 38 mg/m^3	New92, Sch95
	dog (n=5)	0, 562 mg/m^3	4 d, 20 min/d	anaemia	LOAEL: 562 mg/m^3	Lor72
	dog (n=3)	0, 23 mg/m^3	26 d, 30-60 min/d	none identified	23 mg/m^3	Car50
dermal	rabbit (n=15)	0, 10 mg/kg bw	15 d	none identified	10 mg/kg bw	Gri73
	rabbit (New Zealand; n=5/sex/group)	0, 100, 300, 1000 mg/kg bw	21 d	none identified	1000 mg/kg bw	Gol92, Sch95
oral	rat (Sherman; n=6/group)	0, 50 mg/kg bw	14 d	liver enlargement	LOAEL: 50 mg/kg bw	Kim68
	rat (Sprague-Dawley; n=4/group)	0, 85, 200, 500 mg/kg bw	3 w	liver enlargement enzyme induction	NOAEL: 200 mg/kg bw LOEL: 85 mg/kg bw	Spr73
	rat	0 ,704 (males), 911 (females) mg/kg bw	5 w	effects on ileum	LOAEL: 704 mg/kg bw	Hun72
	rat (Charles River CD; n=15/sex/group)	0, 1200 (males), 1400 (females) mg/kg bw	13 w	effects on liver, kidneys, erythrocytes	57 mg/kg bw	Gol88a, Sch95
	mouse (Charles River CD-1; n=15/sex/group)	0, 1600 (males), 1800 (females) mg/kg bw	13 w	effects on liver	47 mg/kg bw	Gol88b, Sch95
	dog (beagle; n=6)	0, 165 mg/kg bw	90 d	clinical signs	LOAEL: 165 mg/kg bw	Gri73
	dog (beagle; n=2/sex/group)	0, 170 (males), 200 (females) mg/kg bw	8 w	increased absolute liver weight	NOAEL: 18 mg/kg bw	Gol88c, Sch95
	dog (beagle; n=4/sex/group)	0, 66 (males), 75 (females) mg/kg bw	52 w	effects on liver, white blood cells; anaemia	14 mg/kg bw	Gol90a, Sch95

Long-term toxicity and carcinogenicity

Rats (n=12/sex/group) were fed pyrethrum extract via the diet at doses equivalent to 10, 50, and 250 mg total pyrethrins/kg bw/day for 2 years. No treatment-related effects were observed on mortality or growth of the animals. Microscopic examination revealed slight liver damage, characterised by bile duct proliferation and focal necrosis at the 2 highest dose levels. There was no evidence for the induction of treatment-related tumours. No further information was given. The NOAEL was 10 mg/kg bw (Cas80, FAO65, Leh65).

In an unpublished toxicity and carcinogenicity study, under the auspices of the Pyrethrum Joint Venture, Charles River CD rats (n=60/sex/group) received diets containing pyrethrum extract (purity: 57.6% total pyrethrins) at dose levels equivalent to 0, 4, 43, or 130 mg pyrethrins/kg bw/day for males and 0, 5, 56, or 170 mg/kg bw/day for females, for 104 weeks. No treatment-related mortality or signs of toxicity were observed. Animals in the high-dose group showed decreased body weights (7-10%) during the first 78 weeks of the study, together with a slight decrease in food consumption. No treatment-related ophthalmological abnormalities or changes in organ weights and haematology or urinanalysis parameters were found. Males in the high-dose group had substantially increased serum transaminase levels during the study. At the high-dose, the incidence of hepatocellular adenomas was statistically significantly increased in females, but no increased incidence of hepatocellular carcinomas was found. The incidence of hyperplasia of the thyroid was found to be enhanced in a dose-related fashion, but the increase was not statistically significant. At the 2 highest dose levels, the incidences of follicular adenomas of the thyroid in males and females were higher than the upper range seen in historical controls. A statistically significantly increased incidence, compared with control animals, was only observed in high-dose females. No statistically significantly increased incidence of follicular carcinomas was observed at any dose level, compared with controls. Macroscopic examination of the skin showed a slight, dose-related, increased incidence of cystic lesions in males, which was not statistically significant. Microscopic examination revealed a statistically significantly higher incidence of keratoacanthomas in males at the high dose. The authors concluded that the increased incidences of liver and thyroid tumours and of keratoacanthomas of the skin were treatment-related effects, but threshold phenomena. Macroscopic or microscopic results of non-neoplastic lesions were not reported. The NOEL was 4 mg/kg bw/day, based on an increased incidence of follicular adenomas of the thyroid at higher dose levels (Gol90b, Sch95).

In another unpublished carcinogenicity study, under the auspices of the Pyrethrum Joint Venture, Charles River CD-1 mice (n=60/sex/group) received diets containing pyrethrum extract (purity: 57.6% total pyrethrins) at dose levels equivalent to 0, 14, 350, or 690 mg pyrethrins/kg bw/day for males and 0, 17, 410, or 830 mg/kg bw/day for females, for 18 months. At the high dose, 1 male and 1 female animal died during the first week. No other treatment-related mortality occurred, and survival was similar in the control and treated groups. Animals in the high-dose group exhibited hyperactivity during the first week of the study only. No treatment-related effects on body weight or food consumption were found. Macroscopic examination showed increased absolute and relative liver weights and discoloured dark livers at the 2 highest dose levels. Microscopic examination revealed vacuolar fatty change in the livers at these doses. The incidence of nodules and masses in the lungs appeared to be slightly increased in high-dose animals. Microscopic examination showed statistically significantly increased incidences of alveolar bronchiolar adenomas in females at the high dose and of alveolar bronchiolar carcinomas in males at the mid- and high-dose levels, compared with control animals. The authors concluded that these tumours had a threshold exposure level and that the NOAEL of the study was 14 mg/kg bw/day (Gol90c, Sch95).

Mutagenicity and genotoxicity

In vitro tests:
- Gene mutation assays. Pyrethrins did not induce reverse mutations in *E. coli* WP2 Try⁻, in a test without metabolic activation. Concentrations of pyrethrins tested were not given (Ash72). Tests for inverse mutations were negative in various *S. typhimurium* strains (TA98, TA100, TA1535, TA1537, TA1538) and in *E. coli* WP2*hcr*, in the presence or absence of metabolic activation by a rat liver microsomal S9 preparation (Mor83). In a later unpublished study, under auspices of the Pyrethrum Joint Venture, tests for reverse mutations in *S. typhimurum* TA98, TA100, TA1535, T1537, and TA1538 were negative at concentrations up to 8772 μg/plate (as total pyrethrum extract, containing 57.6% total pyrethrins), with and without metabolic activation (San89, Sch95).
- Cytogenicity assays. In an unpublished study, under auspices of the Pyrethrum Joint Venture, pyrethrum extract (purity: 57.6% total pyrethrins) did not induce an increased incidence in the frequency of chromosomal aberrations in Chinese hamster ovary cells, in the presence or absence or

metabolic activation, at concentrations ranging from 0.005 to 0.32 μL/mL (Put89, Sch95).
- Other mutagenicity assays. In an unpublished study, under auspices of the Pyrethrum Joint Venture, pyrethrum extract (purity: 57.6% total pyrethrins) did not increase unscheduled DNA synthesis in rat primary hepatocytes at concentrations between 0.03 and 1μL/mL (Cur89, Sch95).

The committee did not find data from *in vivo* genotoxicity tests on pyrethrum.

Reproduction toxicity

In a 2-generation reproduction toxicity study, rats (n=18) were given pyrethrum extract via the diet at a dose level equivalent to approximately 250 mg pyrethrins/kg bw/day, starting 3 weeks prior to first mating. After weaning the first litter, they were mated again. The only reported effect was significantly reduced body weights of F1 and F2 weanlings. This treatment did not result in effects on the reproductive performance of the parents (Wei66).

In an unpublished 2-generation reproduction toxicity study, under auspices of the Pyrethrum Joint Venture, groups of 28 male and 28 female Charles River rats received diets containing pyrethrum extract (purity: 57.6% total pyrethrins) at doses equivalent to 0, 10, 100, or 300 mg pyrethrins/kg bw/day, for a minimum of 77 days before mating. The same number of weanlings from the F1b litters was treated for a minimum of 95 days before mating. For both parental groups, treatment was continued through gestation and lactation. No signs of toxicity or effects on body weight or food consumption were observed in parental animals of the F0 generation. However, parental animals of the F1 generation showed reduced body weights and reduced food consumption at the 2 highest doses. At these levels, body weights were also significantly reduced at birth and during lactation for F1 and F2 offspring of each sex. No other reproductive effects were observed. No treatment-related effects were observed on male and female fertility indices, gestation lengths, litter size, numbers of viable and stillborn pups, and pup survival and growth during lactation. The NOAEL for parental and reproductive toxicity was 10 mg/kg bw/day (Sch89, Sch95).

In a developmental toxicity study, pregnant Wistar rats (n=20/group) received pyrethrum (purity: 20% total pyrethrins) in corn oil by gavage at doses of 10, 20, or 30 mg pyrethrins/kg bw/day, on days 6-15 of gestation. On day 22 of pregnancy, the dams were killed and subjected to macroscopic examination. Fetuses were weighed and examined for viability and for external, visceral, and

skeletal abnormalities. No mortality or signs of toxicity were noted. Maternal body weight gain did not significantly differ among treated and control groups. There was a statistically significant increase in the proportion of resorptions in all dose groups, without any significant difference in the mean number of corpora lutea, total implants, live fetuses per dam, or fetal weight. According to the authors, this difference was due to the unusual low incidence of resorptions in the control group (3% vs. 6% normal). The proportion of fetuses with skeletal abnormalities was significantly increased in the mid- and high-dose groups, but no difference was seen in the incidence of skeletal defects such as extra ribs, missing or fused sternebrae, or delayed ossification of sternebrae. The incidence of external or visceral defects in the treated groups was not significantly greater than in the control group. In this study, 30 mg/kg bw, the highest dose tested, was a NOAEL for maternal and developmental toxicity (Khe82).

In another, unpublished, developmental toxicity study, under auspices of the Pyrethrum Joint Venture, pregnant Charles River rats (n=25/group) received pyrethrum extract (purity: 57.6% total pyrethrins) at doses of 0, 5, 25, or 75 mg pyrethrins/kg bw/day by gavage, on days 6-15 of gestation. On day 20 of gestation, fetuses were removed by Caesarean section. No mortality, treatment-related signs of toxicity, or changes in body weight gains were observed in any of the animals in any of the groups. Maternal ovarian and uterine examination did not show abnormalities, and no treatment-related changes were observed in fetal external examination and in fetal internal soft tissue and skeletal examinations at any dose tested. The NOAEL for both maternal and developmental toxicity was 75 mg/kg bw/day, the highest level tested (Cas95a, Sch87a).

In a developmental study, pregnant rabbits (n=9/group) were given daily oral doses of pyrethrum extract at doses of 0 and 90 mg pyrethrins/kg bw/day, on days 8-16 of gestation. Of 4 rabbits per dose level, pups were delivered by Caesarean section on day 30, and the remainder were delivered by normal parturition. No effects were noted on the number and weight of fetuses, implantation sites, or on gross external and internal examination. Two control pups and 1 treated pup had a deformed front paw, and 1 treated pup had a missing caudal vertebrae. It was concluded that pyrethrum did not induce teratogenic effects in rabbits (Wei66).

In an unpublished developmental study, under auspices of the Pyrethrum Joint Venture, pregnant New Zealand rabbits (n=16/group) were given pyrethrum extract (purity: 57.6% total pyrethrins) at doses of 0, 25, 100, or 250 mg pyrethrins/kg bw/day by gavage, on days 7-19 of gestation. On day 29 of gestation, fetuses were removed by Caesarean section. One doe at the high dose aborted on day 28 of gestation. Signs of toxicity included excessive salivation,

arched head, and laboured breathing at the high dose on days 18 and 19 of gestation. Reduced body weights were observed in does at the 2 highest dose levels. Macroscopic and microscopic examination did not show changes related to treatment in any of the animals in any of the groups. No abnormalities were found in mean numbers of total implantations, post-implantation losses, and viable fetuses, and in fetal body weights or sex distribution. No treatment-related fetal malformations were observed. The NOAEL for maternal toxicity was 25 mg/kg bw/day, and the NOAEL for developmental toxicity was 250 mg/kg bw/day, the highest dose tested (Sch87b, Sch95).

7   Existing exposure limits

The current administrative occupational exposure limit (MAC) for pyrethrum in the Netherlands is 5 mg/m^3, 8-hour TWA.

Existing occupational exposure limits for pyrethrum in some European countries and in the USA are summarised in
Annex II.

8   Assessment of health hazard

The health hazard assessment of pyrethrum is based to a large extent on a toxicology review issued by the FAO/WHO Joint Meeting on Pesticide Residues for recommendation of an acceptable daily intake (ADI) and a toxicology review published in 'Pyrethrum Flowers' (Cas95a). Toxicity data presented in these reviews are obtained mainly from unpublished studies, conducted for registration purposes and sponsored by a consortium of companies, manufacturing or marketing the product.

The most likely routes of exposure of workers to pyrethrum are inhalation of aerosols or direct contact with the pyrethrum extract or a formulation. No data is available of the percentage of uptake of the compound through the lungs or through the skin. In view of the low acute and short-term dermal toxicity, the committee concludes that skin penetration is low. This is in accordance with the negligible absorption of the synthetic pyrethroid cypermethrin, following application on the skin of a human volunteer (Ead88). Following oral administration, the extent of absorption of pyrethrins I and II ranges from 70 to close to 100%. Peak levels of pyrethrins or metabolites in blood were reached between 5 and 8 hours after administration, and the half-life of elimination was approximately 6 hours. Pyrethrins are rapidly and extensively metabolised by rat and mouse liver microsomes. Major metabolic pathways involve oxidation of the

double bond and/or methyl groups, resulting in about 63 metabolites for pyrethrins I and II. Hydrolysis of the cyclopropane ester bond, found with synthetic pyrethroids, has not been demonstrated. There is no evidence of accumulation of the compound in any of the tissues.

Most reported human health effects associated with exposure to pyrethrum were allergic dermatitis and asthma. These allergic reactions are believed to be due to impurities no longer present in the currently purified extracts. However, recently, death has been reported in 2 asthmatic female subjects, allegedly exposed to pyrethrum extracts of unknown purity in dog shampoo. No cases of inadvertent acute poisoning of spray-men or factory workers have been documented. Accidental oral or dermal exposure to high doses of pyrethrins can cause a temporary numbness of the tongue and lips.

In experimental animals, pyrethrum extract was only minimally irritating to the skin and eyes and showed no potential for skin sensitisation. Based on the acute lethal toxicity studies with purified pyrethrum extract (57.6% total pyrethrins), the committee considers the extract as unlikely to present an acute health hazard. On the basis of signs of poisoning in mammals, the nervous system is the critical organ following acute exposure. The oral NOAEL for acute neurological disorders and behavioural effects was 20 mg/kg bw.

In a 13-week inhalation toxicity study in rats, critical effects of exposure to a liquid aerosol of pyrethrum extract (57.6% pyrethrins) were anaemia and microscopic abnormalities in the upper respiratory tract and the lungs. The NOAELs for systemic and local effects were 38 mg/m^3 and (possibly) <38 mg/m^3, respectively.

Dermal application of pyrethrum extract (57.6% total pyrethrins) at doses up to 1000 mg/kg bw/day for 21 days caused no toxicity in rabbits. In short-term oral toxicity studies in rats, liver enlargement (NOAEL: 200 mg/kg bw/day) and hepatic enzyme induction (LOAEL: 85 mg/kg bw/day) were found in a 3-week study and effects on the liver, the kidneys, and anaemia in a 13-week study (NOAEL: 57 mg/kg bw/day). In mice, effects on the liver were observed in a 13-week oral study (NOAEL: 47 mg/kg bw/day) and in dogs, effects on the liver and anaemia in a 52-week oral study (NOAEL: 14 mg/kg bw/day).

In a 2-year oral toxicity and carcinogenicity study in rats, with dose levels of 4-5, 43-56, and 170-250 mg/kg bw/day, a dose-related increased incidence of follicular adenomas of the thyroid was found in both sexes. The incidence was statistically significantly increased compared with the control group in the high-dose females only. High-dose females also showed a statistically significantly increased incidence of hepatocellular adenomas and high-dose males a statistically significantly increased incidence of benign skin tumours. The only

observed non-neoplastic effect was an increase in the activity of serum transaminases in high-dose males, indicating liver injury. In an 18-month oral study in mice, with dose levels of 14-17, 350-410, and 690-830 mg/kg bw/day, a statistically significantly increased incidence of alveolar bronchial adenomas was found in high-dose females and of alveolar bronchial carcinomas in males at the 2 highest dose levels. Non-neoplastic liver changes were seen in both sexes at the 2 highest dose levels. Pyrethrum extracts did not induce gene mutations, cytogenetic effects, or unscheduled DNA synthesis in *in vitro* assays, in the presence or absence of a metabolic activation system. The committee concluded that pyrethrins have no genotoxic or mutagenic potential, but no *in vivo* tests have been reported. In view of the absence of genotoxicity or mutagenicity of the pyrethrum extract and the stimulatory effect of pyrethrins on liver metabolism, as shown by the induction of cytochrome P450 enzymes in rats, the committee is of the opinion that the carcinogenicity in rats and mice is induced through a non-genotoxic mechanism, for which a threshold exposure level exists.

In 2-generation reproduction toxicity studies in rats, the only reported effects were treatment-related reduced body weights of F0 parental animals and of pups at birth and during lactation of the F1 and F2 offspring. The NOAEL for parental and reproduction toxicity was 10 mg/kg bw/day. In two developmental toxicity studies in rats, no maternal or developmental toxicity was observed up to the highest doses tested (30 and 75 mg/kg bw/day, respectively). In rabbits, the NOAEL for maternal toxicity was 25 mg/kg bw/day and for developmental toxicity 250 mg/kg/day, the highest dose tested.

The committee takes the 13-week inhalation study in rats, with a NOAEL for systemic effects of 38 mg/m^3 as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, the committee establishes an overall assessment factor of 27. This factor covers the following aspects: intra- and interspecies variation and differences between experimental conditions and the exposure pattern of the worker. Thus, applying this factor of 27 and the preferred-value approach, a health-based occupational exposure limit of 1 mg/m^3 is recommended for pyrethrum. This HBROEL will protect workers from respiratory tract irritation as well and has a sufficient margin of safety concerning the effects observed in the 2-year oral rat study.

The committee recommends a health-based occupational exposure limit for pyrethrum of 1 mg/m^3, as the inhalable fraction, as an 8-hour time-weighed average (TWA). The committee notes that this value holds for pyrethrum purified from sensitising lactones.

Although quantitative data on skin absorption are lacking, acute lethal toxicity data do not suggest significant skin absorption*. Therefore, the committee does not recommend a skin notation.

References

ACG99   American Conference of Governmental Industrial Hygienists (ACGIH). Pyrethrum. In: TLVs and other occupational exposure values - 1999. [CD ROM]. Cincinnati OH, USA: ACGIH®, 1999.

ACG04a   American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2004. Cincinnati OH, USA: ACGIH®, 2004: 124.

ACG04b   American Conference of Governmental Industrial Hygienists (ACGIH). 2004 TLVs® and BEIs® based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, 2004: 48.

Amb51   Ambrose AM, Robbins DJ. Comparative toxicity of pyrethrins and allethrin. Fed Proc 1951; 10: 276.

Arb02   Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002: 36 (At-vejledning C.0.1).

Ash72   Ashwood-Smith MJ, Trevino J, Ring R. Mutagenicity of dichlorvos. Nature 1972; 240: 418.

Bae73   Baer RL, Ramsey DL, Biondi E. The most common contact allergens. Arch Dermatol 1973; 108: 74-8.

Bie91   Bielucke J. Primary eye irritation in rabbits (New Zealand white). Philadelphia PA, USA: Biosearch Inc, 1991; unpublished report, cited in FAO00

Bon73   Bond HW, Mauger K, Deffo J. Toxicity of pyrethrins in combination with certain chemicals and drugs. Pyrethroid Post 1973; 12: 59

Bra95   Bravo BG, Pichardo AR, Fernandez S, et al. Airborne erythema-multiforme-like eruption due to pyrethrum. Contact Dermatitis 1995; 33: 433.

Bud96   Budavari S, ed. The Merck Index. An encyclopedia of chemicals, drugs, and biologicals. 12th ed. Rahway NJ, USA: Merck & Co, Inc, 1997: 1261.

Car50   Carpenter C, Weil C, Pozzani U, et al. Comparative acute and subacute toxcity of allethrin and pyrethrins. Arch Ind Hyg Occup Med 1950; 2: 420-32.

Car77   Carlson JE, Villaveces JW. Hypersensitivity pneumonoits due to pyrethrum. JAMA 1977; 237: 1718-9.

Cas71   Casida J, Kimmel E, Elliot M, et al. Oxidative metabolism of pyrethrins in mammals. Nature 1971; 230: 326-7.

Cas80   Casida J. Pyrethrum flowers and pyrethroid insecticides. Environ Health Perspect 1980; 34: 189-202.

Cas95a   Casida JE, Quistad GB, eds. Pyrethrum flowers: production, chemistry, toxicology and uses. Oxford, England: Oxford University Press, 1995.

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*   See ECE98 for criteria to assess the need to assign a skin notation.

Cas95b   Casida JE, Quistad GB. Metabolism and synergism of pyrethrins. In: Casida JE, Quistad GB, eds. Pyrethrum flowers: production, chemistry, toxicology and uses. Oxford, England: Oxford University Press, 1995: 258-76 (Chapter 13).

Cla90   Class TJ, Ando T, Casida JE. Pyrethroid metabolism: microsomal oxidase metabolites of (S)-bioallethrin and the six natural pyrethrins. J Agric Food Chem 1990; 38: 529-37.

Cul88   Culver CA, Malina JJ, Talbert RL. Probable anaphylactoid reaction to a pyrethrin pediculicide shampoo. Clin Pharm 1988; 7: 846-9.

Cur89   Curren RD. Unscheduled DNA synthesis assay in rat primary hepatocytes with a confirmatory assay. Rockville MD, USA: Microbiological Associates, Inc, 1989; unpublished report, cited in FAO00

DFG04   Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2004. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH Verlag & Co. KGaA, 2004: 101 (rep no 40).

Ead88   Eadsforth CV, Bragt PC, van Sittert NJ. Human dose-excretion study with the pyrethroid insecticides RIPCORD and FASTAC. Xenobiotica 1988; 18: 603-14.

EC04   European Commission: Directorate General of Employment and Social Affairs. OELs already included in Commission Directives. http://europe.eu.int/comm/employment_social/health_safety/areas/oels4_en.htm.

ECE98   European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). Examination of a proposed skin notation strategy. Brussels, Belgium: ECETOC, 1998; special report no 15.

Eil90   Eil C, Nisula BC. The binding properties of pyrethroids to human skin fibroblast androgen receptors and to sex hormone binding globulin. J Steroid Biochem 1990; 35: 409-14.

Ell72a   Elliott M, Janes N, Casida J, et al. Mammalian metabolites of pyrethroids. Pyrethrum Post 1972; 11: 94-103.

Ell72b   Elliott M, Janes N, Kimmel E, et al. Metabolic fate of pyrethrin I, pyrethrin II and allethrin administered orally to rats. J Agric Food Chem 1972; 20: 300-13.

FAO65   Food and Agriculture Organization (FAO)/World Health Organization (WHO): Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Group on Pesticide Residues (JMPR). Pyrethrins. In: Evaluation of the toxicity of pesticide residues in food. Rome, Italy: World Health Organization, 1965; FAO meeting report no PL/1965/10; WHO/Food Add/26.65. (www.inchem.org/documents/jmpr/jmpmono/v065pr40.htm).

FAO71   Food and Agriculture Organization (FAO)/World Health Organization (WHO): Joint Meeting of the FAO Working Party of Experts and the WHO Expert Group on Pesticide Residues (JMPR). Pyrethrins. In: 1970 evaluations of some pesticide residues in food. Rome, Italy: World Health Organization, 1970; AGP:1970/M/12/1; WHO/Food Add/71.41 (www.inchem.org/documents/jmpr/jmpmono/v070pr21.htm.

FAO00   Food and Agriculture Organization (FAO)/World Health Organization (WHO): Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. Pyrethrum extract (pyrethrins) (addendum). In: Pesticides residues in food –

1999. Part II. Toxicological. Geneva, Switzerland: WHO, 2000; WHO/PCS/00.4 (www.inchem.org/documents/jmpr/jmpmono/v99pr11.htm).

Gab91 Gabriel D. Acute dermal toxicity in rabbits (New Zealand white). Philadelphia PA, USA: Bioresearch Inc, 1991; unpublished report, cited in FAO00.

Gab92 Gabriel D. Summary of results of acute oral toxicity study. Philadelphia PA, USA: Bioresearch Inc, 1992; unpublished report, cited in FAO00.

Gol88a Goldenthal EI. Evaluation of pyrethrum extract in a 13-week dose range-finding study in rats. Mattawan MI, USA: International Research & Developmental Corp, 1988; unpublished study, cited in FAO00.

Gol88b Goldenthal EI. Evaluation of pyrethrum extract in a 13-week dose range-finding study in mice. Mattawan MI, USA: International Research & Developmental Corp, 1988; unpublished study, cited in FAO00.

Gol88c Goldenthal EI. Toxicity study in dogs. Mattawan MI, USA: International Research & Developmental Corp, 1988; unpublished study, cited in FAO00 .

Gol90a Goldenthal EI. Evaluation of pyrethrum extract in a 1-year chronic toxicity study in dogs. Mattawan MI, USA: International Research & Developmental Corp, 1990; unpublished study, cited in FAO00.

Gol90b Goldenthal EI. Evaluation of pyrethrum extract in a two-year dietary toxicity and oncogenicity study in rats. Mattawan MI, USA: International Research & Developmental Corp, 1990; unpublished study, cited in FAO00.

Gol90c Goldenthal EI. Evaluation of pyrethrum extract in an 18-month dietary oncogenic study in rats. Mattawan MI, USA: International Research & Developmental Corp, 1990; unpublished study, cited in FAO00.

Gol92 Goldenthal EI. 21-day repeated dose dermal toxicity with pyrethrum extract in rabbits. Mattawan MI, USA: International Research & Developmental Corp, 1992; unpublished study, cited in FAO00.

Gri73 Griffin CS. Mammalian toxicology of pyrethrum. Pyrethrum Post 1973; 12: 50-8.

Gos84 Gosselin RE, Smith RP, Hodge HC, eds. In: Clinical toxicology of commercial products. 5th ed. Baltimore MD, USA: Williams & Wilkins, 1984: 352-55 (Therapeutics index; section III).

Hea69 Head SW. The composition of pyrethrum extract. Pyrethrum Post 1969; 10: 17.

Her93 Hermansky SJ, Hurley JM. Acute oral neurotoxicity study with pyrethrins in rats (Sprague-Dawley). Export PA, USA: Bushy Run Research Center, 1993; unpublished report, cited in FAO00.

Hof91 Hoffmann GM. Acute inhalation toxicity study in rats (Sprague-Dawley). Philadelphia PA, USA: Bioresearch Inc, 1991; unpublished report, cited in FAO00.

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational exposure limits 2002. Sudbury (Suffolk), England: HSE Books, 2002: 24.

Hun72 Hunter B, Newman AJ. Toxicity of pyrethrins and piperonyl butoxide in dietary administration to rats. (Preliminary survey). Alconbury Cambridgeshire, England: Huntingdon Research Centre, 1972; confidential report, cited in Gri73.

Khe82 Khera KS, Whalen C, Angers G. Teratogenic study on pyrethrum and rotenone (natural origin) and ronnel in pregnant rats. J Toxicol Environ Health 1982; 10: 111-9.

138-29   Pyrethrum (pyrethrins)

Kim68   Kimbrough RD, Gaines TB, Hayes WJ Jr. Combined effect of DDT, pyrethrum, and piperonyl butoxide on rat liver. Arch Environ Health 1968; 16: 333-41.

Leh39   Lehman AJ. Pharmacological considerations of insecticides. Q Bull Assoc Food Drug Off US 1949; 13: 65-70.

Leh65   Lehman AJ. Summaries of pesticide toxicity. Topeka KS, USA: Association of Food and Drug Officials of the US, 1965.

Lor47   Lord KA, ARIC MA, Johnson CG. The production of dermatitis by pyrethrum and attempts to produce a non-irritant extract. Br J Dermatol 1947; 59: 367-75.

Lor72   Lorber M. Hematoxicity of synergized pyrethrin insecticides and related chemicals in intact, totally and subtotally splenectomized dogs. Acta Hepatogastroenterol 1972; 19: 66-78.

Mal68   Malone JC, Brown NC. Toxicity of various grades of pyrethrum to laboratory animals. Pyrethrum Post 1968; 9: 3-8.

Mar41   Martin JT, Hester KH. Dermatitis caused by insecticidal pyrethrum flowers (chrysanthemum cinerarilfolium). Br J Dermatol 1941; 53: 127-42.

McC21   McCord CP, Kilker CH, Minster DK. Pyrethrum dermatitis. A record of the occurrence of occupational dermatoses among workers in the pyrethrum industry. JAMA 1921; 77: 448-9.

Mit72   Mitchell J, Dupuis G, Towers G. Dermatitis from pyrethrum (chrysanthemum Spp). The roles of pyrethrum, a sesquiterpine lactone, and of pyrethrin. Br J Dermatol 1972; 86: 568-73.

Mor82   Morgan DP. Recognition and management of pesticide poisonings. 3rd ed. Washington DC, USA: US Environmental Protection Agency, 1982; rep no. EPA 540, 9-80.

Mor83   Moriya M, Ohta T, Watanabe K, et al. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res 1983; 166: 185-216.

New92   Newton PE. 90-day inhalatin toxicity study of pyrethrum extract in the rat via whole body exposure. East Millstone NJ, USA: Bio/dynamics, Inc, 1992; unpublished report, cited in FAO00.

Pat88   Paton DL, Walker JS. Pyrethrin poisoning from commercial-strength flea and thick spray. Am J Emerg Med 1988; 6: 232-5.

Put89   Putman DL, Morris MJ. Chromosome aberrations in Chinese hamster ovary (CHO) cells. Rockville MD, USA: Microbiological Associates, Inc, 1989; unpublished report, cited in FAO 99

Ram30   Ramirez MA. Pyrethum: an etiological factor in vasomotor rhinitis and asthma. J. Allergy 1930; 1: 149-55.

Ray91   Ray DE. Pesticides derived from plants and other organisms. In: Hayes WJ Jr, Laws ER Jr, eds. Classes of pesticides. New York, USA: Academic press, Inc, 1991: 585-93 (Handbook of pesticide toxicology; Vol 2).

Ric72   Rickett RE, Tyszkiewicz K, Brown NC. Pyrethrum dermatitis. I. The allergenic properties of various extracts of pyrethrum flowers. Pestic Sci 1972; 3: 57-66.

Ric73   Rickett RE, Tyszkiewicz K. Pyrethrum dermatitis. II. The allergenicity of pyrethrum oleoresin and its cross-reactions with the saline extract of pyrethrum flowers. Pestic Sci 1973; 4: 801-10.

Rob99   Roberts TR, Hutson DH, eds. Pyrethrum. In: Insecticides and fungicides. Cambridge, UK: The Royal Society of Chemistry, 1999: 694-701 (Metabolic pathways of agrochemicals; Pt 2).

Rom91a   Romanelli P. Primary skin irritation in rabbits (New Zealand white). Philadelphia PA, USA: Bioresearch Inc, 1991; unpublished report, cited in FAO00.

Rom91b   Romanelli P. Sensitisation study in guinea pig (Hartley strain). Philadelphia PA, USA: Bioresearch Inc, 1991; unpublished report, cited in FAO00.

San89   San RHC, Springfield KA. Salmonella/mammalian-microsome plate incorporation mutagenicity assay (Ames test) with a confirmatory assay. Rockville MD, USA: Microbiological Associates, Inc, 1989; unpublished report, cited in FAO00.

Sch87a   Schardein JL. Evaluation of pyrethrum extract in a definitive rat teratology study. Mattawan MI, USA: International Research & Developmental Corp, 1987; unpublished report, cited in FAO00.

Sch87b   Schardein JL. Evaluation of pyrethrum extract in a definitive rabbit teratology study. Mattawan MI, USA: International Research & Developmental Corp, 1987; unpublished report, cited in FAO00

Sch89   Schardein JL. Two generation reproduction study in rats with pyrethrum extract. Mattawan MI, USA: International Research & Developmental Corp, 1989; unpublished report, cited in FAO00.

Sch95   Schoenig GP. Mammalian Toxicology of Pyrethrum Extract. In: Casida JE, Quistad GB, eds. Pyrethrum flowers: production, chemistry, toxicology and uses. Oxford, UK: Oxford University Press, 1995: 249-57 (Chapter 12).

Sel95   Pharmacokinetics and metabolism of ^{14}C pyrethrin I in the rat. Irvine CA, USA: Biological Test Center, 1995; unpublished study, cited in FAO 99.

Seq36   Sequeira JH, Lond FR, Eng FR. Pyrethrum dermatitis. Br J Dermatol 1936; 48: 473-6.

Sod77   Soderlund DM, Casida JE. Effects of pyrethroid structure on rates of hydrolysis and oxidation by mouse liver microsomal enzymes. Pestic Biochem Physiol 1977; 7: 391-401.

Spr73   Springfield AC, Carlson GP, DeFeo JJ. Liver enlargement and modification of hepatic microsomal drug metabolites in rats by pyrethrum. Toxicol Appl Pharmacol 1973; 24: 298-308.

Swe00   Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000; Ordinance AFS 2000:3.

SZW04   Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2004. The Hague, the Netherlands: Sdu Uitgevers, 2004: 39.

Tom97   Tomlin CDS, ed. In: The Pesticide Manual – world compendium. 11th ed. Farnham Surrey, UK: British Crop Protection Council, 1997: 1057-8.

TRG04   TRGS 900. Technische Regeln für Gefahrstoffe. Grenzwerte in der Luft am Arbeitsplatz. BArbBl 2004; (7/8).

Ver72   Verschoyle RD, Barnes JM. Toxicity of natural and synthetic pyrethroids to rats. Pestic Biochem Physiol 1972; 2: 308-11.

Wag00   Wagner SL. Fatal asthma in a child after use of an animal shampoo containing pyrethrin. West J Med 2000; 173: 86-7.

Wax94   Wax PM, Hoffman RS. Fatality associated with inhalation of a pyrethrin shampoo. Clin Toxicol 1994; 32: 457-60.

138-31   Pyrethrum (pyrethrins)

Wei66   Weir RJ. Reproduction study. Rats neopynamin and pyrethrin. Falls Church VA, USA: Hazleton
         Laboratories, Inc, 1966; unpublished report, cited in FAO71 and Gri73.

Wes94   Wester RC, Bucks DAW, Maibach HI. Human in vivo percutaneous absorption of pyrethrin and
         piperonyl butoxide. Food Chem Toxicol 1994; 32: 51-3.

Zuc65   Zucker A. Investigation on purified pyrethrum extracts. Ann Allergy 1965; 23: 335-9.
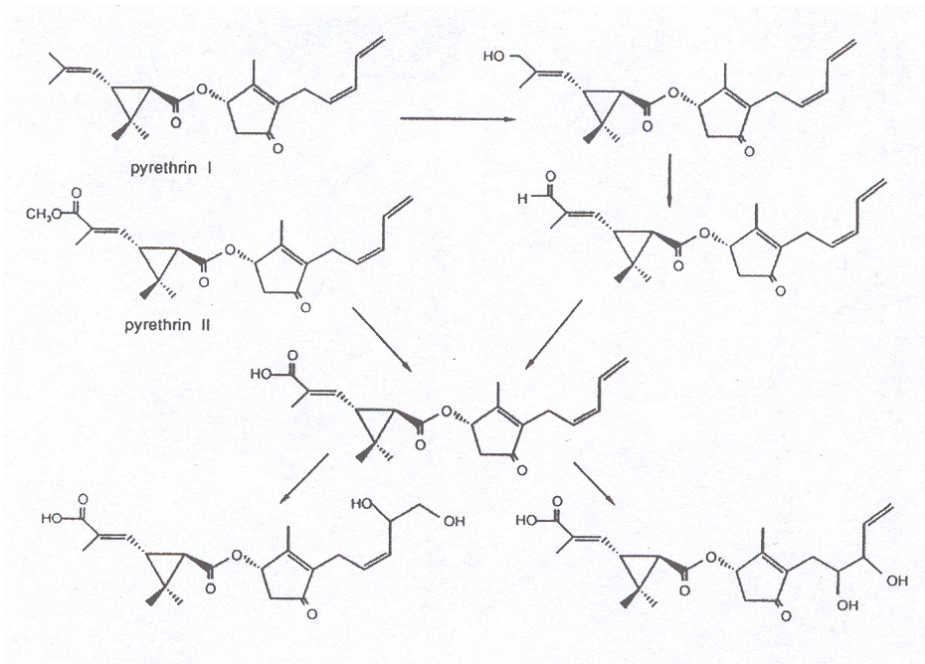
Figure 1 Metabolism of pyrethrin I and II in orally treated rats (from Cas95b).

Annex II

Occupational exposure limits for pyrethrum in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	5	8 h	administrative		SZW04
Germany						
- AGS	-	5[c]	8 h			TRG04
	-	20[c]	15 min			
- DFG MAK-Kommission	-	5[c]	8 h		sens	DFG04
	-	10[c]	15 min[d]			
Great-Britain						
- HSE	-	5	8 h	OES		HSE02
	-	10	15 min			
Sweden	-	-				Swe00
Denmark	-	5	8 h			Arb02
USA						
- ACGIH	-	5	8 h	TLV	A4[e]	ACG04b
- OSHA	-	5	8 h	PEL		ACG04a
- NIOSH	-	5	10 h	REL		ACG04a
European Union						
- SCOEL	-	5[f]	8 h	ILV[g]		EC04

[a]   S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b]   Reference to the most recent official publication of occupational exposure limits.

[c]   Measured as the inhalable fraction of the aerosol.

[d]   Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.

[e]   Classified in carcinogenicity category A4, i.e., not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of lack of data. *In vitro* or animal data do not provide indications of carcinogenicity which are sufficient to classify the agent in one of the other categories.

[f]   In January 2003, SCOEL (SCOEL/SUM/95 final) recommended an occupational exposure limit for pyrethrum (purified from sensitising lactones) of 1 mg/m^3.

[g]   Listed among compounds for which OELs are already included in Commission Directives.