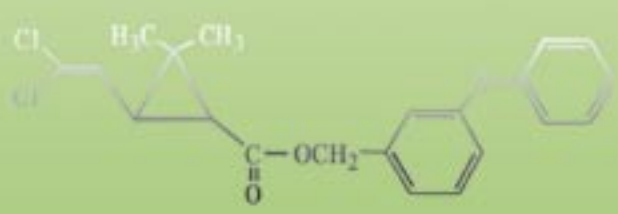
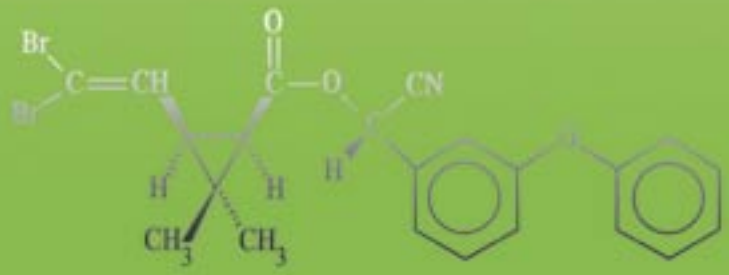
WHO/CDS/WHOPES/GCDPP/2005.10
WHO/PCS/RA/2005.1



SAFETY OF PYRETHROIDS FOR PUBLIC HEALTH USE



World Health Organization
Communicable Disease Control, Prevention
and Eradication
WHO Pesticide Evaluation Scheme (WHOPES)
&
Protection of the Human Environment
Programme on Chemical Safety (PCS)

WHO/CDS/WHOPES/GCDPP/2005.10
WHO/PCS/RA/2005.1

SAFETY OF PYRETHROIDS FOR PUBLIC HEALTH USE

World Health Organization

Communicable Disease Control, Prevention
and Eradication
WHO Pesticide Evaluation Scheme (WHOPES)
&
Protection of the Human Environment
Programme on Chemical Safety (PCS)

CONTENTS

PREFACE

The purpose of this document is to critically review current knowledge on the safety of pyrethroids and whether existing WHO recommendations for pyrethroid applications should be revised or modified. This review does not consider the use of pyrethroids in space spraying and vapour applications (e.g. in mosquito coils and aerosols).

The first draft of this document was prepared by Dr Claudio Colosio, Teresa Mammone, Manuela Tiramani and Marco Maroni from the International Centre for Pesticide Safety, Busto Garolfo, Italy. The document was sent for peer review by a number of individuals and institutions known for their expertise in pesticide toxicity and risk assessment. Comments were received from Dr Klaus E. Appel, Federal Institute for Risk Assessment, Berlin, Germany; Dr A. Bartholomaeus, Department of Health and Ageing, Canberra, Australia; Professor A. Boobis, Imperial College London, UK; Dr E. Bosshard, Federal Office for Agriculture, 3003 Bern, Switzerland; Dr D. McGregor, Lyon, France; Professor J.G. McLean, Victoria, Australia; Ms J. Murawski, Association of Flight Attendants, American Federation of Labor – Congress of Industrial Organizations, AFL–CIO; Dr J. Palermo Neto, MS, PhD, Universidade de São Paulo, Brazil; Dr J. Pauluhn, Institute of Toxicology, Bayer AG, Wuppertal, Germany; Dr W. Phang, Office of Pesticide Programs, US EPA; Dr D. Renshaw, Food Standards Agency, UK; and Dr L. Ritter, University of Guelph, Ontario, Canada. The authors revised the document on the basis of comments received, and the staff of the WHO Programme on Chemical Safety (PCS) and the WHO Pesticide Evaluation Scheme (WHOPES) verified that the comments had been dealt with appropriately. WHOPES and PCS are most grateful to the authors and peer reviewers for their important contribution, and also acknowledge the financial support provided by the Global Collaboration for Development of Pesticides for Public Health (GCDPP).

1 INTRODUCTION

Pyrethroids are widely used in public health because of their relative safety for humans, high insecticidal potency at low dosages and rapid knock-down effects. The safety and efficacy of pyrethroids for different applications in vector control, as well as in disinsection of aircrafts, have been assessed by the World Health Organization (WHO). WHO recommendations on the use of pyrethroids include the following compounds:

- *Indoor residual spraying*: alpha-cypermethrin, bifenthrin, cyfluthrin, deltamethrin, etofenprox and lambda-cyhalothrin.
- *Treatment of mosquito nets*: alpha-cypermethrin, cyfluthrin, deltamethrin, etofenprox, lambda-cyhalothrin and permethrin.
- *Aircraft disinsection*: permethrin and D-phenothrin.

The purpose of this document is to critically review current knowledge on the safety of pyrethroids to establish whether existing WHO recommendations for pyrethroid applications should be revised or modified in light of new information on health risks. This review does not consider the use of pyrethroids in space spraying and household insecticide products (e.g. in mosquito coils).

The most recent WHO assessments of the safety of these chemicals (*Table 1*; bifenthrin: IPCS, 1993; cyfluthrin: IPCS, 1997b; λ-cyhalothrin: IPCS, 2000a, 2004a; α-cypermethrin: IPCS, 1996, 2004b; deltamethrin: IPCS, 2001; etofenprox: IPCS, 1994; permethrin: IPCS, 2000b; D-phenothrin: IPCS, 1989, 1990e) were used as the basis for this review, with additional information that became available afterwards. For this purpose the following databases were searched: EXTOXNET, EPA, IARC, the International Programme on Chemical Safety (IPCS), Joint FAO/WHO Meeting on Pesticide Residues (JMPR), WHO Pesticide Data Sheets and other relevant WHO

publications. A systematic search in the literature database PubMed, with particular attention to papers published after 1990, was also carried out. Furthermore, reports on cases were considered where exposure to pesticides, notably from aircraft disinsection, was alleged to have induced adverse health effects. The available literature is listed at the end of this document.

Table 1. **Development of JECFA/JMPR acceptable daily intakes for WHO-recommended pesticides for public health use, 1981–2004**

Pesticide	1981	1982	1984	1987	1988	1992	1993	1996	1997	1999	2000	2002	2004
Bifenthrin						0.02							
Cyfluthrin				0.02					0.02				
Cyhalothrin[a]			0.02								0.002t	0.002[b]	0.002
Alpha-cypermethrin								0.02					0.02
Cypermethrin	0.05							0.05					
Deltamethrin		0.01									0.01		
Etofenprox							0.03						
Permethrin		0.05		0.05						0.05		0.05	
D-phenothrin		0.2	0.04		0.07								

JECFA/JMPR = Joint FAO/WHO Expert Committee on Food Additives/Joint FAO/WHO Meeting on Pesticide Residues.
[a] No JECFA or JMPR assessment has been done on λ-cyhalothrin.
[b] Temporary acceptable daily intake.

2 PYRETHROIDS – STRUCTURE AND INSECTICIDAL ACTIVITY

Pyrethroids (also known as synthetic pyrethroids) are insecticides chemically similar to pyrethrins found in natural pyrethrum extracted from the flowers of chrysanthemum, known for centuries for their insecticidal activity (CPCN, 2001). First developed in 1973, pyrethroids are more stable to light than natural pyrethrum and possess very good insecticidal activity. The first pyrethroid (fenvalerate) was commercialized in 1978. At present, the class of pyrethroids includes 42 active ingredients, differing in chemical structure or in relative stereoisomer composition (NPTN, 1998).

Natural pyrethrins are esters of a cyclopropanecarboxylic acid and a cyclopentenolone alcohol. Structural modifications to one or other of these moieties have produced the diverse pyrethroids that are commercially available as insecticides. The presence of two chiral centres, at carbon-1 and carbon-3 of the chrysanthemic acid moiety of pyrethrin I, produces two pairs of diastereomers that are designated as *trans* and *cis*. That designation is based on the orientation of substituents of carbon-1 and carbon-3 in relation to the cyclopropane ring or the similarly restricting structure that may have been introduced to replace this ring in the synthetic members of the series. The acid moieties of the natural pyrethrins are exclusively in the 1R, *trans* configuration. When esters were prepared from the four resolved chrysanthemic acid isomers, those with the R configuration at cyclopropane C-1 were insecticidal, whereas the enantiomeric 1S compounds, though physically identical, were without insecticidal activity (Soderlund et al., 2002).

This stereospecificity extends to compounds such as fenvalerate, in which the 2S configuration of the non-cyclopropane acid moiety is structurally congruent with 1R cyclopropane-carboxylates and gives insecticidal esters, whereas the corresponding 2R esters are inactive (Soderlund et al., 2002).

Stereospecific determinants of insecticidal activity are implicit even in achiral acid moieties, such as 2,2,3,3-tetramethylcy-clopropanecarboxylic acid, the acid moiety of the insecticide fenpropathrin. Removal of one methyl group from this symmetrical acid creates a chiral cyclopropanecarboxylate that obeys the same structure–activity rules as those elaborated for chrysanthemic acid isomers. Stereoisomerism is a less common feature of pyrethroid alcohol moieties. Nevertheless, when a chiral centre is present in the alcohol moiety at the carbon bearing the hydroxyl group (e.g. allethrin and deltamethrin), only one epimer has high insecticidal activity even when esterified to an acid moiety that contains the appropriate stereochemical configuration for high insecticidal activity (Soderlund et al., 2002). As well as for insecticidal activity, stereoisomerism is relevant also in light of pyrethroids' toxicity to mammals. In general, stereoisomers showing the highest levels of insecticidal activity are also those most toxic to humans.

In commercial formulations, pyrethroids are usually dissolved in solvents and may be mixed with piperonyl butoxide, a synergistic compound that enhances the effectiveness of the active ingredient (Binka et al.,1996).

Apart from their use in agriculture, pyrethroids play an important role in public health programmes. Globally, more than 520 tonnes of active ingredient of pyrethroids is annually used in vector control programmes alone (Zaim & Jambulingam, 2004).

3 MECHANISMS OF TOXICITY

Pyrethroids are historically divided into two types, according to their chemical structure: *type I pyrethroids*, which do not contain an alpha-cyano group in their molecule (for example, allethrin, resmethrin, D-phenothrin, and permethrin) and which cause mainly tremors (T-syndrome); and *type II pyrethroids*, which do contain an alpha-cyano group (for example, deltamethrin, cypermethrin, cyfluthrin and fenvalerate) and which cause choreoathetosis and salivation (CS-syndrome) (Tordoir et al., 1994). However, it should be noted that the syndromes are dependent on the animal model used. Many pyrethroids, such as permethrin, exhibit both T and CS characteristics, and sometimes these two syndromes combine (Soderlund et al., 2002, Aldridge, 1990).

The toxicity of pyrethroids in mammals is caused by similar mechanisms as the insecticidal activity, so these two properties are usually correlated. The marked difference in the toxicity of pyrethroids to insects (target organisms) and mammals is apparently caused by differences mainly in the voltage-sensitive sodium channels (Narahashi, 2000; Soderlund et al., 2002).

Pyrethroids impair ion transport through the membrane of nerve axons, causing muscular paralysis in the insect; death seems to follow a nervous system impairment that occurs a few minutes after pesticide absorption (Reigart & Roberts, 1999; Mueller-Beilschmidt, 1990). Pyrethroid insecticides act on the nerves of both insects and higher animals, inducing a transient increase in sodium permeability of the nerve membrane during excitation. This action results in relatively short trains of repetitive nerve impulses in sensory (afferent) nerve fibres (Pollack et al., 1999). Pyrethroids without an alpha-cyano group (type I pyrethroids) cause a moderate protraction of the sodium channel permeability in the nerve membrane, while alpha-cyano pyrethroids (type II pyrethroids) cause a long-lasting protraction of sodium permeability of the nerve membrane during excitation

(*EXTOXNET*, 1994a–e; EPA, 2000). Invertebrates and some cold-blooded species are more susceptible to the toxic effects of pyrethroids than vertebrates (Narahashi et al., 1998).

Repeated oral doses to rats for 7 days induce axonal degeneration to the sciatic nerve. Degeneration, however, occurs only with doses high enough to cause death in some other treated rats (Aldridge, 1990).

The interaction of pyrethroids with macromolecular components of the sodium channel is reversible. Removal of pyrethroids from the nervous system is rapid: a 50% recovery of effects has been shown to occur from 30 minutes to 3–4 hours after poisoning (Aldridge, 1990).

Interaction with sodium channels is not the only mechanism of action proposed for pyrethroids in insects and vertebrates (Ray & Forshaw, 2000). Some authors have suggested that the effects on the central nervous system depend on an antagonism of gamma-aminobutyric acid (GABA)-mediated inhibition, modulation of nicotinic cholinergic transmission, enhancement of noradrenalin release, or action on calcium channels. GABA is an important mediator of inhibitory neurotransmission in the mammalian nervous system and a target site for the action of several therapeutic drugs and toxicants. Release of GABA by presynaptic nerve terminals activates a chloride channel on the postsynaptic membrane, leading to hyperpolarization of the postsynaptic nerve terminal and thus enhancing the excitatory threshold of the postsynaptic neuron. This would result in an indirect neuroexcitatory effect. However, since some studies in vitro show that the GABA receptor blockade is not observed at concentrations of pyrethroid that disrupt sodium channel function, it is unlikely that GABA inhibition represents the primary mechanism of action, thus explaining the neuroexcitatory effects of pyrethroids (Soderlund et al., 2002). Neurotransmitter release is probably secondary to the increased sodium entry in the neural cell (Ray & Forshaw, 2000).

4 TOXICOKINETICS

Absorption of pyrethroids through the gastrointestinal tract and the skin is variable and depends on the vehicle of administration (Soderlund et al., 2002; Bateman, 2000; Clark, 1995). From comparative toxicity studies it has been concluded that absorption from the respiratory tract is effective. While for the general population the main route of exposure to agricultural pesticides is through residues in food, studies carried out on workers suggest that, similarly to any other pesticide, dermal exposure is the most significant route of absorption for agricultural applicators and sprayers (Zhonghua et al., 1991; Zhang et al., 1991). The exposure scenario for pesticides used for public health purposes is quite variable, from exposure to larvicides in drinking-water, to dermal and inhalation exposure from bednets, or from space spraying and vapour of household insecticides (e.g. mosquito coil).

The penetration of pyrethroids into the skin is slow and may cause a typical local paraesthesia (tingling and burning sensations; see Section 6.2), which may persist for several hours (Bateman, 2000).

After absorption, pyrethroids are rapidly distributed throughout the body, mainly in the adipose tissue, stomach, intestine, liver and kidneys and the nervous system. Pyrethroids are rapidly and extensively metabolized, mainly in the liver, by hydrolases and cytochrome P450-dependent monooxygenases, with the breakdown of the molecule at the oxygen bridge and the formation of acids and alcohols which typically exhibit lower acute toxicity than the parent compounds and which are not indicated as causative agents for long-term effects (Soderlund et al., 2002; Crawford, 1981; NPTN, 1998; *EXTOXNET*, 1994a–e).

Since a number of carboxylesterases responsible for this reaction are inhibited or competed by organophosphates (OPs), simultaneous exposure to OPs may increase pyrethroid toxicity (Ray & Forshaw, 2000).

Pyrethroids do not accumulate in the body and their excretion is rather rapid, even after repeated administrations: typically, 90% of the administered dose is excreted in urine and faeces within a week after treatment (IPCS, 1999; Aldridge, 1990; Vijverberg & van den Bercken., 1990). Studies carried out on human volunteers have shown that, after oral administration of cypermethrin doses of 0.25, 0.5, 1 and 1.5 mg/subject, about 75% of the dose is excreted in 24 hours; the rate of excretion is similar for all dosages. After a 2-day period, no detectable amounts of metabolites were found in urine (van Sittert et al., 1985).

The ratio of excretion between urine and faeces varies with the compound and the route of administration (Soderlund et al., 2002, Vijverberg & van den Bercken, 1990). Non-metabolized pyrethroids (allethrin, bifenthrin, cyfluthrin, cyhalothrin, cypermethrin, fenpropathrin, flucythrinate, fluvalinate, permethrin, pyrethrins, tetramethrin, but not deltamethrin, esfenvalerate, fenvalerate) were detected in breast milk from women not exposed to pyrethroids at work, at concentrations of 0.015–0.34 mg/kg fat (Zehringer & Herrmann, 2001).

The determination of pyrethroids and their metabolites in urine might be used for biological monitoring of exposure, although the interpretation of the results is complicated given the lack of reference values. The main metabolites in urine are: *cis*- and *trans*-3-(2,2'-dichloro-vinyl)-2,2'-dimethylcyclopropane-carboxylic acid (*cis*- and *trans*-Cl_2CA) for permethrin; dichlorovinyl-dimethyl-cyclopropane carboxylic acid (Cl_2CA), 3-phenoxybenzoic acid (3-PBA) and the 3-(4'-hydroxyphenoxy) benzoic acid (4-HPBA) for cypermethrin; and dibromovinyl-dimethyl-cyclopropane carboxylic acid (Br_2CA) and 3-PBA for

deltamethrin (Maroni et al., 2000; Leng, 1997, 2003). In occupationally exposed subjects, the unchanged parent compounds may also be detected in urine (Zhang et al., 1991; Chen et al., 1991).

A recent survey conducted in Germany suggests that pyrethroid metabolites may be detected in urine samples of the general population unexposed to known sources of pyrethroids, probably as a consequence of dietary intake. The 95th percentile for the urinary metabolites *cis*- and *trans*-Cl_2CA was 0.5 and 1.4 µg/l, respectively, while the 95th percentile for Br_2CA and F-PBA was 0.3 and 0.27 µg/l, respectively (Schettgen et al., 2002).

5 TOXICITY IN EXPERIMENTAL ANIMALS

5.1 Acute toxicity

The mechanism of action of pyrethroids in vertebrates is similar to that in insects, mainly involving the nervous system. Two distinct acute poisoning syndromes are described in mammals, especially rats. The so-called "*T-syndrome*", which is mainly induced by natural pyrethrins and type I pyrethroids, is characterized by tremors, extreme sensitivity to sensory stimuli, ataxia, convulsions and, in some cases, paralysis. The so-called "*CS-syndrome*", mainly induced by type II pyrethroids, is characterized by hypersensitivity to external stimuli, choreoathetosis (sinuous writhing), salivation and, in some cases, paralysis (Narahashi, 2000). Laboratory data suggest different susceptibility to acute effects in various animal species, the mouse being the most susceptible. In dogs, symptoms and signs of acute poisoning are similar to those observed in rats, but salivation and upper airway hypersecretion and gastrointestinal symptoms are more prominent.

Systemic toxicity after dermal exposure to pyrethroids is low (Table 2; Clark, 1995), but pyrethroids have localized effects on the skin: after local application to guinea-pigs of six pyrethroids (cypermethrin, deltamethrin, esfenvalerate, fenvalerate, flucythrinate and permethrin), the animals showed an increase in scratching, licking or biting at the site of dermal application. The symptoms usually occurred within 1 hour after application (Cagen et al., 1984).

Inhalation exposure to cyfluthrin (a type II pyrethroid) in rats produced concentration-dependent changes in the respiratory pattern, accompanied by hypothermia, without clinical signs (a syndrome called sensory irritation). Concentration rather than dose as the determinant of the response was supported by the finding of a similar no-observed-adverse-effect concentration (NOAEC) in a 13-week study, where the daily exposure was 6 hours. The NOAEC was 0.1 mg/m^3 for 1-hour exposure (Pauluhn, 1996; Pauluhn & Machemer, 1998). For other pyrethroids, either type I or II, no comparative data on the production of sensory irritation are available.

At present, WHO classifies bifenthrin, deltamethrin, cyfluthrin, alpha-cypermethrin, lambda-cyhalothrin, and permethrin as *moderately hazardous* (class II), and phenothrin and etofenprox as *unlikely to present acute hazard in normal use* (IPCS, 2002).

Table 2. **Acute oral and dermal toxicity of pyrethroid insecticides commonly used for public health purposes (IPCS, 2002)**

Compound	Oral toxicity LD_{50} rat (mg/kg/bw)	Dermal toxicity (LD_{50} rat) (mg/kg/bw)
alpha-cypermethrin	79[a]	>100[d]
bifenthrin	55[a]	>2000[e]
cyfluthrin	254[a,b]	>5000[f]
deltamethrin	135[a]	>2900[g]
D-phenothrin	>10 000[c]	>10 000[h]
etofenprox	>10 000	>2140[i]
lambda-cyhalothrin	56[a]	632[j]
permethrin	500[a]	>2000[k]

[a] The toxicity of pyrethroids is highly variable according to isomer ratios, the vehicle used for oral administration and the husbandry of the test animals. The LD_{50} values shown here, which form the basis of the WHO classification of pesticides by hazard (IPCS, 2002), are based on administration in corn oil (unless otherwise stated) and are much lower than those in aqueous solutions.
[b] Rat; in acetone:oil (1:10); in Cremophor EL/dw, a value of 16.2 mg/kg has been reported (IPCS, 1997b).
[c] Rat; vehicle not reported (IPCS, 1990).
[d] Mouse; in corn oil (IPCS, 1996).
[e] Rabbit; vehicle not reported (IPCS, 1993).
[f] Rat; vehicle not reported (IPCS, 1997b).
[g] Rat; aqueous suspension (IPCS, 2001).
[h] Rat; vehicle not reported (IPCS, 1990e).
[i] Rat, vehicle not reported (IPCS, 1994).
[j] Rat; in polyethylene glycol paste (IPCS, 1990a).
[k] Rabbit; vehicle not reported (IPCS, 2000b).

5.2 Short-term toxicity

The main target organ for short-term toxicity of pyrethroids is the nervous system. The effects of pyrethroids on the nervous system in short-term toxicity studies are described in Section 5.7.

Daily oral cyhalothrin administration in mice at levels of up to 2000 mg/kg diet for 28 days showed toxic effects at dosages of 100 mg/kg and above. The observed effects were dose-related and included (besides ataxia and hypersensitivity to external stimuli) liver changes and atrophy of the red pulp of the spleen. Some deaths occurred at the highest dosage level. At 25 mg/kg diet, the only effect seen was piloerection (IPCS, 2000a).

In rats orally treated with deltamethrin at a dose of 100 mg/kg diet, no histopathological changes either in the nervous system or in other tissues and organs were observed. However, in studies carried out on cyfluthrin at the highest dosage of 2000 mg/kg diet, thymic atrophy, adrenal enlargement with vacuolization and incomplete spermatogenesis occurred (IPCS, 1990a–e, 1997).

Pyrethroid-related sensory irritation in the respiratory tract was studied by nose-only exposure studies in mice and rats. Aerosolized cyfluthrin (0, 0.44, 6 or 47 mg/m^3) was selected because of the greater potency of the alpha-cyano pyrethroids to evoke sensory effects. Rats appeared to be more susceptible than mice. Measurements performed repeatedly during exposure (6 hours/day, 5 days/week for 4 consecutive weeks) showed that at 47 mg/m^3, but not at lower exposures, clinical signs were observed, and a concentration-dependent decrease of the resortion rate was observed at concentrations $\geq$6 mg/m^3. No effects were observed at 0.44 mg/m^3, and no alteration was observed in responsiveness over the period of exposure. The magnitude of changes in breathing patterns was similar to that observed following acute 1-hour exposure. These findings

indicate that the observed effects are non-cumulative and reversible in nature (Pauluhn, 1996).

An oral administration study carried out on rats treated with deltamethrin at doses of 0, 0.1, 1, 2.5 and 10 mg/kg bw/day for 13 weeks showed reduced body-weight gain in males at doses of 2.5 and 10 mg/kg bw/day. The no-observed-effect level (NOEL) for this effect was 1 mg/kg bw/day (IPCS, 1990b, 2001).

In a short-term inhalation study, for which limited details are available, rats exposed to deltamethrin powder at concentrations of 3, 9.6 and 56.3 mg/m^3 (87% of the particles respirable, d<5.5 μm) for 6 hours/day, 5 days/week for 3 weeks and then for 4 days during a fourth week, did not show any death or any pathological finding, but irritation and weight loss were observed. These effects were "slight" at 3 mg/m^3 (IPCS 1990b).

5.3 Carcinogenicity

Increases in the incidence of certain tumours in rodents treated with pyrethroids over their lifetime have been observed occasionally. However, there is no clear indication of carcinogenicity relevant for human risk assessment.

In three long-term studies of deltamethrin by oral administration in mice, no carcinogenic effect was observed. In two studies in rats, similarly no tumorigenic activity was observed, but in one study, thyroid adenomas were increased in females (IPCS, 2001). In an initiation-promotion study in mice by skin painting, deltamethrin showed initiating, but not promoting or complete, carcinogenic acitivity (Shukla et al., 2001).

D-phenothrin was administered to rats at levels of 0, 300, 1000 or 3000 ppm in the diet for 105 (males) or 118 (females) weeks. No increase in mortality was registered; the only appreciable finding was a slight increase in the incidence of hepatocytic hypertrophy in males at 3000 ppm (Cabral et al., 1986, 1990).

The study showed an increase also in the incidence of preputial gland adenomas and carcinomas, with incidences at 0, 300, 1000 and 3000 ppm of 1, 1, 1 and 4 adenomas and 0, 0, 1 and 3 carcinomas, respectively. The 1988 JMPR considered this finding unlikely to be of toxicological significance (IPCS, 1989).

Permethrin was tested for carcinogenicity in mice and rats by oral administration in the diet. There was a high incidence of lung adenomas both in treated and control mice, with a statistically non-significant increase at the concentration of 2500 mg/kg of diet. No increased tumour incidence was observed in treated rats (Ishmael & Litchfield, 1988).

For alpha-cypermethrin, no studies on carcinogenicity are available. Cypermethrin was tested for carcinogenicity in rats and mice, and showed no evidence of carcinogenicity in rats. In mice, an increase in benign alveologenic tumours was observed at the highest dose in females, but this was within the historical control range (IPCS, 1996). Noting that alpha-cypermethrin is a mixture of selected isomers present in cypermethrin, and that cypermethrin contains 25% of alpha-cypermethrin, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that there is no reason to consider alpha-cypermethrin a carcinogen, and no need to perform carcinogenicity studies with alpha-cypermethrin (IPCS, 1996). However, in a recent two-stage carcinogenicity study on mouse skin, using DMBA as initiator and TBPA as promoter, cypermethrin was reported to function as an initiator, promoter and also as a complete carcinogen (Shukla et al., 2002).

Cyhalothrin has been tested for carcinogenicity in rats and mice. In rats, no increase in tumours at any site was observed. In female mice, an increase in mammary adenocarcinomas was observed, but the incidence was not different from the historical controls of the laboratory; JECFA considered it not to be related to cyhalothrin treatment (IPCS, 2000a).

Cyfluthrin was tested for carcinogenicity in rats and mice and did not show carcinogenic potential (IPCS, 1997b).

Bifenthrin was tested for carcinogenicity in rats and mice and did not show carcinogenic potential in rats, but an increased incidence of submucosal urinary bladder haemangiomas was observed in males at the highest dose; the NOAEL for carcinogenicity was 10 times higher than that for neurotoxicity. JMPR considered that a carcinogenic activity of bifenthrin cannot be excluded but, considering the negative genotoxicity, bifenthrin is unlikely to cause a carcinogenic hazard to humans (IPCS, 1993).

Etofenprox was studied for carcinogenicity in mice and rats. No evidence of carcinogenicity was observed in mice, but in female rats an increased incidence of follicular cell adenomas in the thyroid was observed at the highest dose. As etofenprox also caused activation of the thyroid, and was devoid of any genotoxicity, JMPR derived the acceptable daily intake (ADI) from other toxicity, for which the LOAEL was 1/7 of that for carcinogenicity (IPCS, 1994).

Deltamethrin, fenvalerate and permethrin have been evaluated by the International Agency for Research on Cancer (IARC, 1991): they were all classified in Group 3 (not classifiable as to carcinogenicity to humans).

5.4 Genotoxicity

Cyfluthrin, cypermethrin, deltamethrin, etofenprox, permethrin and D-phenothrin were consistently negative in studies on genotoxicity in bacteria, yeasts, mammalian cells in vitro and rodents in vivo (IPCS, 1990e, 1994, 1996, 1997a–b, 2001). While a wide range of genotoxicity tests were negative for bifenthrin, positive results have been reported for the mouse lymphoma assay in one of two studies, and for unscheduled

DNA synthesis (UDS) in rats (slightly positive at a high dose level; IPCS, 1993).

In recent studies, λ-cyhalothrin was reported to induce micronuclei in fish, and also chromosomal aberrations in bone marrow and micronuclei in polychromatic erythrocytes in rats (Campana et al., 1999; Cavas et al., 2003; Celik et al., 2003). Given the wide range of negative genotoxicity studies (reverse mutation in bacteria, cell transformation in vitro, cytogenetic effects in the bone marrow, dominant lethal mutations in mice) on cyhalothrin and an even more extensive range of negative tests (reverse mutations in bacteria, gene mutations in mammalian cells in vitro, UDS in vitro, micronucleus formation in mice in vivo) on λ-cyhalothrin, JECFA concluded that the data as a whole suggested that cyhalothrin presents no genotoxic hazard to humans (IPCS, 2004a).

5.5 Reproductive toxicity

Pyrethroids do not impair the mating capacity and fertility in the experimental model. No significant pre-implantation losses have been observed, and post-implantation losses have been observed only at high doses. The fertility of female rats is affected only for oral doses equal to 250 mg/kg/day or above. No evidence of teratogenic activity is observed in mice, rats or rabbits, even at doses able to produce clinical signs of maternal toxicity (Vettorazzi, 1979; IPCS, 1990a–e, 1996, 1997b, 2000a; Sumida et al., 2001). Fertility, sexual behaviour and a large number of reproductive end-points, such as organ weights, sperm quality, plasma testosterone concentrations and testicular histology, were examined in adult male offsprings after exposure of the dams from day 1 of pregnancy to day 21 of lactation to deltamethrin at dose levels of 1, 2 or 4 mg/kg/kg bw/day (Andrade et al., 2002). No signs of maternal toxicity were detected at the dose levels tested. Significant effects were seen only on testicular and epididymal absolute weights and on the diameter of

seminiferous tubules in the group treated with the highest dose (4 mg/kg).

5.6 Variation of sensitivity with age

Neonates and weanling rats are more sensitive than adults to the acute lethal effects of type II pyrethroids deltamethrin and cypermethrin; clinical signs were also produced at lower levels of these pyrethroids in weanling rats than in adults (Sheets, 2000). However, when weanling rats were treated with relatively low doses of cismethrin (3, 6, 12 mg/kg), permethrin (30, 60, 120 mg/kg), deltamethrin (1, 2, 4 mg/kg) or cypermethrin (9, 29, 38 mg/kg), the dose–response of the startle response of the young animals was not different from adults. Studies on brain concentrations of deltamethrin seem to support the notion that the increased susceptibility of the neonate to high doses is probably related to a limited metabolic detoxification capacity (Sheets, 2000).

5.7 Neurotoxicity and neurobehavioural effects

5.7.1 Adult animals

Since the nervous system is the target of pyrethroid toxicity, several acute and subchronic neurotoxicity studies have been conducted on pyrethroids such as bifenthrin, permethrin, cyfluthrin, lambda-cyhalothrin, cypermethrin and deltamethrin.

In acute oral neurotoxicity studies the effects of pyrethroids were transient and were observed at doses from 10 mg/kg to 300 mg/kg within 1–14 days after treatment. In subchronic neurotoxicity studies that involved dietary exposure for 13 weeks, the signs of pyrethroid intoxication were observed at doses ranging from 29 mg/kg to 170 mg/kg; they generally persisted, but did not worsen, with continued treatment beyond 4 weeks of exposure (Soderlund et al., 2002).

Physiological and neurochemical studies of pyrethroid-intoxicated animals confirm that acute pyrethroid intoxication is associated with altered nerve function, principally involving neuroexcitatory effects in the brain, spinal cord and peripheral nervous system. There is no single region of the nervous system that is the locus of pyrethroid intoxication and that identifies a mechanism of toxic action (Soderlund et al., 2002).

Several studies have been performed to study the neurobehavioural effects of pyrethroids. Most of them have been carried out at relatively high exposure levels (McDaniel & Moser 1993; Moniz et al., 1994; Husain et al., 1996) and, while demonstrating adverse effects, do not significantly contribute to the risk assessment. However, in two studies relatively low exposure levels were used (De Souza Spinoza et al., 1999; Righi & Palermo-Neto, 2003).

Crofton and Reiter (1984, 1988) compared the effects of type I and type II pyrethroids (cismethrin, cyfluthrin, cypermethrin, deltamethrin, fenvalerate, flucythrinate, fluvalinate, permethrin, RI 11679, RU 26607) on motor activity in rats. All compounds were administered orally in corn oil and caused a dose-dependent decrease in motor activity after 1.5–2 hours. No differences in this response were noted between compounds type I and type II pyrethroids, the smallest doses producing a significant effect varying between 2.5 mg/kg for flucythrinate and 200 mg/kg for permethrin.

Crofton and Reiter (1988) also assessed the effects of pyrethroids on the acoustic startle response of rats. An increased amplitude of the startle response was seen after exposure to the two type II pyrethroids tested, while a mixed response (increase, decrease or no effect) was seen after exposure to type I pyrethroids.

Abnormal motor functions, decreased grip strength and reflex changes were also observed in rats after a single gavage dose of

≥60 mg/kg cypermethrin or ≥75 mg/kg permethrin (McDaniel & Moser, 1993). Some neurobehavioural parameters, but not all, were affected in rats by a single oral (not specified) dose of 10 mg fenvalerate/kg, approximately 1/10 of a dose required for convulsions to occur (Moniz et al., 1994). At a dose level of 7 mg/kg bw/day (enough to significantly decrease body-weight development), changes were observed in the activities of monoamine oxidase, acetylcholinesterase and Na-K-ATPase, concomitant with behavioural changes in rats (Husain et al., 1996).

Intraperitoneal administration of deltamethrin (2 mg/kg), permethrin (60 mg/kg), cis-permethrin (30 mg/kg) to rats caused a dose-dependent reduction in the frequency of a previously learnt behaviour (bar-pressing reinforced by food). Oral administration of either cypermethrin or permethrin to rats caused similar reduction in food-reinforced learnt behaviour (Bloom et al., 1983; Stein et al., 1987).

In an extensive study with many behavioural end-points, De Souza Spinosa and co-workers (1999) observed behavioural changes in rats after a single gavage dose of ≥10 mg/kg bw/day of fenvalerate, but not at the dose level of 1 mg/kg bw/day. Righi & Palermo-Neto (2003) noted gross behavioural changes in rats at a dose level of 3 mg cyhalothrin/kg bw/day, given for 7 days by gavage. The NOAEL in this study was 1 mg/kg bw. In a very extensive clinical and neurobehavioural study of deltamethrin in rats, the single-dose NOAEL for neurotoxicity was 5 mg/kg. When dosing was continued for 90 days, the NOAEL reported was 14 mg/kg (Nemec, 1998a,b, cited in IPCS, 2001).

A detailed morphological evaluation of the effects of permethrin on the nervous system of rats was performed in two long-term feeding studies at concentrations of 0, 20 or 100 mg/kg diet. Examination of the central and peripheral nervous systems, including extensive morphometric data, teased myelinated fibres

of distal sural and tibial nerves, and of the maxillary division of the fifth cranial nerve, did not reveal any change that could be attributed to the treatment (Dyck et al., 1984).

5.7.2 Neurodevelopmental effects

Effects of low-level exposure to deltamethrin (1 mg/kg bw/day by gavage in corn oil) in utero during gestation days 14–20 were studied on selected neurobehavioural, neurochemical and immunohistochemical parameters in rats at 6 and 12 weeks' postnatal period. No gross abnormalities and, with the exception of a delay in the development of the surface-righting reflex, no effects on the developmental landmarks were observed. However, the study showed an increase in hippocampal acetylcholinesterase activity and a decrease in (3)H-quinuclidinyl benzilate binding in the hippocampal region (suggesting impairment in cholinergic-muscarinic receptors) and a decrease in learning behaviour (shock-motivated visual discrimination in a Y-maze) at 6 and 12 weeks (Aziz et al., 2001).

The effects of prenatal administration to rat pups of 0.08 mg/kg deltamethrin on physical, reflex and behavioural–developmental parameters, on forced swimming and open-field behaviours and on striatal monoamine levels were studied. Maternal and offspring body weight, physical and reflex development were unaffected by exposure to the pesticide. No changes were observed in swimming and open-field behaviour, nor were there any changes in striatal monoamines or their metabolites in the male and female offspring (Lazarini et al., 2001).

In a study on rats, oral administration of 10 mg/kg fenvalerate (the only dose level studied) to the dams on GD18 and PND1–5 caused no changes in stereotypic behaviour or brain hypothalamic monoamine levels, but there was an increased immobility in the open-field behaviour of the male offspring (Moniz et al., 1999). After dermal administration to rats of cyhalothrin (1 ml of 0.02% aqueous solution once daily)

throughout pregnancy, no differences were observed in the locomotion of inhibitory avoidance test of offspring at 90 days of age, but exploratory behaviour was decreased (Gomes et al., 1991b).

Oral administration of deltamethrin (0.7 mg/kg bw/day by gavage in a sonicated mixture of egg lecithin, peanut oil and water on 7 consecutive days) to neonatal mice during rapid brain growth (postnatal days 10–16) induced changes in the density of muscarinic cholinergic receptors in the brain shortly after exposure. The effect was observed also in adult animals treated in the neonatal period. The most important finding in these studies is increased motor activity 4 months after neonatal exposure (Eriksson & Nordberg, 1990; Eriksson & Fredriksson, 1991). The quantitative interpretation of these findings to human health is still unclear because of the administration procedure – at only a slightly higher dose (1.2 mg/kg bw), the animals showed choreoatetotic symptoms; furthermore, the effects may not be relevant to humans because of differences in temperature regulation between newborn mice and humans (Pauluhn & Schmuck, 2003).

Changes in muscarinic receptor distribution and behavioural changes were also observed in adults after similar perinatal administration of bioallethrin (Eriksson & Nordberg, 1990; Eriksson & Fredriksson, 1991; Ahlbom et al., 1994; Talts et al., 1998).

When cyhalothrin was administered to Wistar rat dams in drinking-water from whelping to weaning at a level of 0.02% (giving an approximate daily dose of 25 mg/kg bw), no effects on the dams, or overt signs of neurotoxicity or effects on the motor activity in the offspring, were observed. However, a transient decrease in avoidance latency was observed in the offspring on days 97 and 104, which was no more statistically significant on day 111 (Moniz et al., 1990). The maternal dose was relatively high, but the dose to the pups probably quite low.

5.8 Immunotoxicity

The effects on the immune system after exposure to several pyrethroids were investigated in some studies. In particular, the effect of daily oral administration of cypermethrin was studied in rabbits for its influence on the humoral immune response after vaccination with *Salmonella typhimurium*, as well as on cell-mediated immunity. Doses at 1/10 LD_{50} induced a significant dose-dependent decrease of serum antibody titres. The skin redness measured in the tuberculin skin test showed the same dose-dependent tendency. In sub-acute experiments with rats, a significant dose-dependent decrease was observed both in the anti-ovalbumin titre of blood sera measured in passive haemagglutination test and in the autologous rosette-formation of T-lymphocytes (Desi et al., 1985).

Several immunological parameters were altered in mice after oral administration for 28 days of alpha-cypermethrin at a level of 1/2 or 1/5 of the acute oral LD_{50} (Luty et al., 2000). Immunological changes were also observed in mice after 28 days of dermal application of 1/10 or 1/2 of the dermal LD_{50} (Luty et al., 1998).

Deltamethrin and alpha-cypermethrin were administrated by gavage for 28 days in rats. The effects found at the doses of 5 or 10 mg/kg bw were: increased weight of mesenterial lymph nodes, decreased thymus weight in immunized animals and an increase in antibody production and splenic natural killer-cell activity. An effect on relative adrenal weight was seen in the 10 mg/kg bw group. Altogether, the above-mentioned data do not suggest a major immunotoxic effect (Madsen et al., 1996).

The immunotoxic effect of a 28-day oral exposure of 11.1, 22.2 and 55.4 mg/kg bw cypermethrin was investigated in 4-week-old male Wistar rats. The highest dose resulted in a significant increase in the relative liver weight, and all the three doses resulted in (although inconsistent) changes in the haematocrit

and mean cell volume of red blood cells. The maximum of delayed-type hypersensitivity reaction decreased at all the three doses (Institoris et al., 1999).

Topical application of permethrin (25 µl, equivalent to 1100 mg/kg bw) in mice caused 32% inhibition of splenic T-cell proliferation. Apoptosis was significantly increased in CD4(-)8(-) and CD4(-)8(+) thymocytes, and the CD4(+)CD8(+) thymocyte subpopulation was most severely diminished, suggesting a possible chemical-induced apoptotic mechanism of thymic atrophy. Permethrin also caused splenic hypocellularity by 31% at 15 µl (660 mg/kg bw), and by 50% at 25 µl (1100 mg/kg bw), an effect that may relate to inhibited proliferation or reduced seeding from the hypocellular thymus (Prater, 2002).

When cypermethrin was given during gestation (50 mg/kg, 1/20 of the LD_{50}, on days 7–16) to pregnant rats by gavage in corn oil, the pups showed an increase in the blood NK cells and antibody-dependent cytotoxic activity (Santoni et al., 1997). A marked and long-lasting increase was observed in adrenaline and noradrenalin plasma concentrations, concomitant with an increased output of CD5+, CD4+ and CD8+ T-cells from the spleen to the peripheral blood and a consequent lymphocytosis (Santoni et al., 1998, 1999).

After an intraperitoneal dose of deltamethrin, thymus atrophy was observed in mice in a dose-dependent manner (Enan et al., 1996). The lowest effective dose was 6 mg/kg.

5.9 Endocrine effects

Only few data are available on pyrethroid endocrine effects.

Intraperitoneal administration of fenvalerate in male rats for 45 days at doses of 100 and 200 mg/kg bw/day (a dose level that also induced hyperexcitability, tremors and paralysis) induced

significant increase in thyroid hormones' (T3 and T4) serum concentration (Kaul, 1996). However, a study conducted in rats treated for 21 days at a daily dose of 0.2 mg/rat [1] of a commercial formulation containing lambda-cyhalothrin at the concentration of 20% showed a reduction of T3 and T4 serum concentrations, with a concomitant increase of TSH serum levels (Akhtar et al., 1996).

DNA fragmentation indicative of apoptosis and vacuolization of Sertoli cells was observed in testes of rats treated intraperitoneally with deltamethrin (1 mg/kg bw/day for 21 days). Simultaneously, elevated levels of plasma malondialdehyde, indicative of lipid peroxidation, were observed (El Gohary et al., 1999). Because of intraperitoneal administration route, this finding is difficult to interpret quantitatively.

In vitro studies using human endometrial and breast cancer cell lines, carried out on fenvalerate, sumithrin, d-*trans* allethrin and permethrin, did not show any progestinic or antioestrogenic activity, but fenvalerate and sumithrin showed estrogenic activity at 10 µmol/l, and fenvalerate and *d-trans* allethrin significantly antagonized the action of progesterone in breast cancer cells (Garey & Wolf, 1998).

In a study on rats, oral administration of 10 mg/kg fenvalerate (only dose level studied) to the dams on GD18 and PND1-5 caused a decrease in the sexual behaviour of the male offspring (Moniz et al., 1999). After dermal administration to rats of cyhalothrin (1 ml of 0.02% aqueous solution once daily) throughout the pregnancy, testis descent (together with other developmental landmarks such as development of fur, ear opening, eye opening) was delayed. There were no effects on the sexual behaviour at 90 days of age, however (Gomes et al., 1991a–b).

[1] The weight of rats is not given.

6 EFFECTS ON HUMANS

Occupational exposure to pyrethroids may occur through dermal contact and inhalation of dust and sprays. While inhalation is the main route of exposure in industrial workers, the skin is the main route of exposure in workers applying the compounds in agriculture or public health (IPCS, 1990).

When pyrethroids were introduced in China at the beginning of the 1980s, Chinese cotton growers were not adequately informed about the health risk related to the use of these compounds, and handled them without taking any precautions. As a consequence, in the 1980s, the well-known outbreaks of acute deltamethrin and fenvalerate poisoning described in the literature occurred. After 1988, no clinical case of occupational pyrethroid poisoning has been reported.

Exposure of the general population may occur by inhalation, skin contact with products, by eating foods containing residues of pyrethroids applied as pesticides or veterinary drugs, or through accidental swallowing or drinking of pyrethroid products. Recent studies carried out in the European Union and the United States have shown detectable amounts of pyrethroid metabolites in urine samples from the general population (Schettgen et al., 2002; Baker et al., 2000). No evidence of adverse effects has been reported for such levels of exposure.

6.1 Acute poisoning

The symptoms of acute pyrethroid poisoning in humans, as well as in other mammals, are supposed to be subdivided into two classes. However, since most of the reports on human poisoning are related to the more potent type II pyrethroids, it is not yet certain whether the T-Syndrome applies also to humans (Ray & Forshaw, 2000).

Symptomatic acute cases generally follow accidental overexposure or lack of care in handling the compounds at the workplace, whereas accidental ingestion of high doses is the main cause of poisonings for the general population. Acute poisoning very rarely poses a life-threatening risk to the exposed subjects, but severe poisonings and even potential for causing mortality may arise if concentrated formulations are swallowed (Hayes, 1982; Bateman, 2000).

In occupational poisonings, the initial symptoms are skin burning, itching or dizziness. These sensations reported in exposed subjects might not be the result of skin reactions, but signs of peripheral nerve involvement (He et al., 1988; O'Malley, 1997).

About half of the occupational patients develop abnormal facial sensitization (paraesthesia); in the case of swallowing, the main symptoms are epigastric pain, nausea and vomiting (He et al., 1989).

The systemic symptoms include dizziness, headache, nausea, anorexia and fatigue and, in the most severe cases, fasciculation in large muscles of the extremities.

Only paraesthesia could clearly be attributed to exposure to pyrethroids, whereas nausea, headache and dizziness might be induced by organic solvents (He et al., 1989).

The nervous system is the target organ of the toxic action of pyrethroids, but the effects on the respiratory tract can also be observed, such as massive haemorrhages and oedema of the lungs following inhalation at concentrations above or near lethal concentrations (Soderlund et al., 2002).

The use of pyrethroid/organophosphorous mixtures may accentuate human poisonings. The volatile solvents usually present in the commercial formulations may also enhance pyrethroid toxicity (Ray & Forshaw, 2000). Other synergists (piperonyl butoxide and sulfoxide) block the mixed function oxidases, enzymes which detoxify a wide variety of compounds. However, this kind of interaction is observed only in the experimental model after high-dose administration, and has not been demonstrated after exposure at the workplace or in public health uses.

In follow-up studies, the affected workers showed a complete recovery (He et al., 1988, 1989; Tong Ying, 1988; IPCS, 1990a–e, 1997; Wesseling, 2001; Bateman, 2000; Ray & Forshaw, 2000). The prognosis of acute occupational poisonings from pyrethroids is usually good, without any chronic or long-term consequence.

Müller-Mohnssen recently reported a case series of subjective symptoms in people with preceding exposure to pyrethroids. The most frequently observed changes were: cerebro–organic disorders, such as reduced intellectual performance, and personality disorders, sensory and motor polyneuropathy, most frequently in the lower legs, and vegetative disorders (Müller-Mohnssen, 1999). However, although the authors suggested the possibility of residual effects of acute poisoning lasting more than two years in acutely poisoned subjects, any statistical–epidemiological evaluation of these cases is lacking. Therefore, the attribution of the observed changes to the previous acute poisoning is uncertain.

Similarly to what was observed in animals, a transient irritation was also observed in human volunteers exposed for a 1-hour period to cyfluthrin at concentrations of approximately 0.1 mg/m^3; exposures to 0.2 mg/m^3 induced marked irritation (Pauluhn & Machemer, 1998).

6.2 Paraesthesia

A health survey was carried out among spraymen exposed to 2.5% deltamethrin emulsifiable concentrate in cotton fields in China. The subjects were exposed to deltamethrin at 5–12 μg/m^3 concentrations in the air of the respiratory zone and 0.013–0.347 μg/cm^2 on skin parts in contact. One half of the 44 sprayers complained of itching and burning sensations on their faces. No signs of acute deltamethrin poisoning were observed during physical examination (He et al., 1988, 1989). No exposure-related differences were detected in haematological parameters or in heart, lung, liver, kidney or nervous system functions, and the electrophysiological assessment of peripheral nerve function did not reveal any abnormality (He et al., 1988; Chen et al., 1991; Zhang et al., 1991). No correlation was observed between urine pyrethroid metabolite excretion and severity of symptoms (Zhang et al., 1991).

An evaluation of the role of deltamethrin in these poisoning cases carried out recently concluded that, "paraesthesia could clearly be attributed to exposure to deltamethrin, whereas nausea, headache and dizziness are known to be induced by organic solvents. The signs reported by He et al. (1988, 1989) were therefore not typical of deltamethrin poisoning but may have been due to the emulsifiable concentrate as a whole" (IPCS, 2001).

Itching, pricking sensations, numbness, burning of the skin and the eyes or tingling of the skin are the symptoms most commonly reported after contact with pyrethroids (Le Quesne et al., 1980; Tucker & Flannigan, 1983; Kolmodin-Hedman, 1982; He et al., 1988; Chen et al., 1991; Zhang et al., 1991). Symptoms usually start 1–6 hours after exposure (Kolmodin-Hedman, 1982; He et al., 1989; Zhang et al., 1991) and last not more than 24 hours, but in some cases they may last up to 3 days

(for example after local application of large doses of active ingredients – 13.8 mg/cm^2 skin) (Aldridge, 1990).

The exact mechanism of action is unknown but is thought to be an expression of the action of these compounds on the nervous system (Wilks, 2000), mainly because of a transient reduction in the threshold of sensory nerve fibres or sensory nerve endings following direct contact with pyrethroids (IPCS, 1990b). In most cases symptoms affect the facial area, because this is the area most commonly exposed in pesticide applicators (Wilks, 2000).

Different studies report widely different concentrations of deltamethrin that cause itching, burning or numbness on the face: 5–12 µg/m^3 (He et al., 1988) and 0.01–0.89 µg/m^3 in the breathing zone (Zhang et al., 1991).

The application of fenvalerate on the ear lobes of volunteers caused a statistically significant increase in paraesthesia, with a latent period of 0.5–6 hours and a peak about 8 hours after application. The symptoms (numbness, itching, burning, tingling and warmth) lasted about 24 hours (IPCS, 1990c).

It is therefore concluded that paraesthesia is a rather common symptom of dermal exposure to pyrethroids, which has been reported even at low, airborne pyrethroid concentrations. It is not indicative of systemic health risks and is transient in nature, but may be considered a discomfort by sensitive individuals. Since it is usually observed before the onset of clear signs of toxicity, paraesthesia should be searched during the anamnestic assessment of exposed subjects as an exposure indicator suggesting the need for adequate preventive interventions.

6.3 Allergic reactions

Immediately after the introduction into the market of natural unrefined pyrethrins, the allergenic capacity of these compounds was discovered. Some individuals showed manifestations of sensitivity to pyrethrum, including hay fever, contact dermatitis, asthmatic attacks, and even anaphylactic reactions with collapse (Ramirez, 1930).

Sensitivity to unrefined pyrethrum, as judged by skin tests, occurs in over 40% of those who are sensitive to ragweed or have shown positive reactions to unrefined pyrethrum extracts (Zucker, 1965; Ellenhorn, 1988). Causative factors in the contact allergy from pyrethrum were natural sesquiterpene lactones, which are sensitizing and occur in crude extracts derived from chrysanthemum species. Today, the extraction and purification process is such that the active insecticidal principle present in modern mixtures should not contain any sensitizing sesquiterpene lactone (Zenz et al., 1994). However, the possibility of severe asthma attacks after contact with pyrethrins cannot be totally ruled out, as indicated by a fatality that happened to a child suffering from chronic pulmonary disease, who gave her dog a bath using a shampoo containing pyrethrins at the concentration of 0.2% (Wagner, 2000).

Since no clear evidence of sensitizing effects has been shown for either purified natural pyrethrins or pyrethroids, it may be concluded that sensitization does not represent a significant health risk related to modern pyrethroid exposure.

6.4 Carcinogenicity

It has not been possible to study adequately the carcinogenicity of pyrethroids epidemiologically. However, such studies are not a priority since laboratory studies in animals have not revealed a carcinogenic hazard relevant to humans.

6.5 Effects observed in public health uses

6.5.1 Bednet impregnation and use

Pyrethroids are the only group of insecticides currently recommended for treatment of mosquito nets (Zaim et al., 2000). This is because of the rapid knock-down effects and high insecticidal potency of pyrethroids at low dosages, combined with their relative safety for human contact and domestic handling. In some cases the efficacy of pyrethroids is augmented by their apparent repellence towards mosquitoes.

In some cases, bednet users have reported headache, skin irritation, burning sensation in the eyes, lacrimation and nausea, but these symptoms were considered to be transient (Yadav, 1995). Moreover, since most of the effects observed by Yadav are not typical for pyrethroids, and since paraesthesia, the most common effect attributable to these compounds, was not shown in the group of bednet users, it may be concluded that these effects are unlikely to be attributable to pyrethroids or to pyrethroids only.

A study carried out on a group of five bednet impregnators showed that the impregnation of 15 nylon bednets with cyfluthrin at the dose of 50 mg/m^2 did not cause any symptom or laboratory change. A group of 23 bednet users (12 males and 11 females, aged 12–52 years) participated in the survey, but only 8 of these subjects consented to the examination at the end of the one-month study period. The survey did not show any health or laboratory impairment in these subjects after one month of usage of nets impregnated at the dose of 50 mg/m^2 of cyfluthrin (Satpathy et al., 1997). The levels of exposure of these subjects were not measured. The findings of Satpathy were confirmed by Misra, who concluded that no major effects are expected to occur in these conditions of exposure (Misra, 1999).

Even though data on the levels of exposure of bednet users are scarce, some studies available in the literature are adequate for risk assessment purposes. In 1995, Boman carried out an experimental study on a net measuring 9.5 m^2 impregnated with a dose of 50 mg cyfluthrin/m^2. The net was hung in a closed room, at tropical temperature and humidity. Samples were taken daily for the first 9 days and after a 30-day period. Each sample was collected over a 6-hour period. Mean cyfluthrin levels 10 cm inside the net ranged from 0.02 to 0.055 µg/m^3, while concentrations outside the net were slightly lower. The difference was attributed by the author to a better air exchange (Boman, 1995).

Based on Boman's data, Barlow et al. (2001) evaluated the levels of exposure of bednet users, through extrapolation from the highest concentration observed by Boman (0.055 µg/m^3), taken as the worst case scenario for the breathing zone. Based on these data, the authors calculated inhalation intakes of 0.0056 µg/kg bw/day for adults, 0.011 µg/kg bw/day for children and 0.0086 µg/kg bw/day for a period of 8 hours for adults and 12 hours for children and newborn infants.

The comparison of the exposure data estimated by Barlow with an ADI (oral exposure) of 0.01 mg/kg/bw (NOEL = 1 mg/kg bw/day, safety factor 100) shows that the estimated inhalation exposure is significantly lower. Since this exposure seems to be the most relevant worst-case scenario for bednet users, it can be stated that the risk for bednet users is acceptable. Since the above described risk assessment is carried out in the worst-case scenario, the conclusions could be extrapolated for the whole group of pyrethroids recommended by WHO for bednet treatment.

It should be noted that the maximum estimated concentrations at the breathing zone were 0.05 µg/m^3, that is 100 times lower than those expected to cause paraesthesia according the study of He (He et al., 1988), but in the range of dose that the study of Zhang

and co-workers suggested as able to cause the onset of the symptom (Zhang et al., 1991), that is 0.01–0.89 μg/m^3. Moreover, the estimated maximum quantities that could be deposited on the skin (Barlow, 2001) were within the range of magnitude (20–160 μg/day) potentially able to trigger paraesthesia.

It may be concluded that, if pyrethroids are used with the recommended precautions, no major symptoms of poisoning, other than paraesthesia, can be expected in bednet users. Since paraesthesia is a transient and rather common symptom of low dose exposure to pyrethroids, limited to the site of exposure, and can be considered a nuisance effect rather than a symptom of severe toxicity, no major health risk is anticipated for bednet users (Wilks, 2000).

Concern in bednet treatment may arise about the quantity of insecticide supplied over the counter for the treatment of nets by householders. Taking into account the acute toxicity of the active ingredients proposed by WHO, a safety factor may be calculated, defined as the reciprocal of the number of single application packs (*Table 3*). This factor is highest for etofenprox 10% EW (133) and deltamethrin 25% (12.5), but low with permethrin 10% EC (0.7). It is evident that ingestion of the contents of even a single application pack of permethrin 10% EC could be lethal to a child. Insecticides for home treatment of mosquito nets should therefore be presented in single-unit doses. Moreover, if presented as liquid formulation in bottles, use of child-proof caps should be mandatory. A bittering agent should be incorporated in the tablet formulations to prevent deliberate or accidental ingestion.

Table 3. **Estimates of the relative safety of insecticides for over-the-counter supply (updated and modified from WHO, 1999)**

Product	Oral LD_{50} for a 10-kg child (A)[a]	Amount required for the treatment of a single bednet (B)	Proportion of LD_{50} for a 10-kg child contained in a single application pack (C) = B/A	Safety factor (A/B)
alpha-cypermethrin 10% SC	50 ml	6 ml	0.12	8.3
cyfluthrin 5% EW	42 ml	15 ml	0.36	2.8
deltamethrin 1% SC	100 ml	40 ml	0.40	2.5
deltamethrin 25% WT	20 g	1.6 g	0.08	12.5
etofenprox 10% EW	4000 ml	30 ml	0,007	133.3
permethrin 10% EC	50 ml	75 ml	1.5	0.67

[a] Estimated from acute toxicity information on the product provided by the manufacturer in rats, assuming that the chemical is equitoxic to children and rats.

6.5.2 Aircraft disinsection

Pesticides are applied in aircraft to prevent the spreading of vectors and parasites and the diseases they cause in humans. Periodic residual applications of pesticides to passenger cabins, coupled with the use of an aerosol spray, represent an effective treatment method for aircraft leaving areas where vector-borne diseases are endemic.

WHO in 1987 and, most recently, in 1995, published recommendations for aircraft disinsection (WHO, 1987, 1995).

- Pre-flight spraying involves the aircraft cabin being sprayed on the ground with an aerosol containing a residual insecticide before passengers board the aircraft. Pre-flight spraying may be combined with the blocks-away or top-of-descent spraying methods.
- The blocks-away method involves aerosol spraying of the passenger cabin after the doors have been locked following embarkation but before take-off.
- Top-of-descent spraying is an in-flight spraying carried out as the aircraft starts its descent to the arrival airport.
- Residual spraying involves the regular application of a residual insecticide to internal surfaces of the aircraft, except in food preparation areas, at intervals based on the duration of effectiveness. In addition, spot applications are made to surfaces that are frequently cleaned.

Many reports completed by flight attendants or airline personnel suggest the possibility of the onset of symptoms in passengers and crew members consequent to pyrethroid application. The reported symptoms varied from metallic taste, slight and unspecific irritation of eyes, throat and upper respiratory tract and, in some cases, skin, to severe respiratory symptoms such as dyspnoea, cough and even asthma. In some cases, flu, headache and allergic reactions were reported. Available data suggest that the most severe symptoms were observed in sensitized subjects (i.e. asthma patients). These symptoms were attributed by the

affected subjects to aircraft disinsection (Bonvie & Bonvie, 1993, 1994, 1995a–b, 1998; Sutton et al., 2003).

Unfortunately, in many of these reports details on the type of active ingredient used and methods of application are lacking. In most of the reported cases the observed symptoms are not typical of pyrethroids, and might be attributable to other etiological factors, such as solvents present in the formulation, other pesticides and even, in some cases, the microclimatic conditions in the aircraft. The possibility of a "psychological" reaction, related to the well known awareness of the general public to pesticides, should also be considered.

The WHO recommendation for pre-flight spraying is to spray 35 g of the formulation containing 2% permethrin per 100 m^3; for top-of-descent spraying, the same amount of 2% D-phenothrin should be used (WHO, 1995). Thus the momentaneous nominal concentration of the pyrethroid in aircraft air would be 7000 $\mu g/m^3$, with a considerably higher concentration close to the nozzle of the spray can and a rapid drop in the concentration after the spraying.

An experimental study on exposure levels consequent to aircraft disinsection with the blocks-away method has recently been reported (Berger-Preiss et al., 2004). Data were collected in aircrafts during spraying operations with two aerosol products, the first containing pyrethrum [2] (1.25%) and piperonyl butoxide (2.6%), and the second D-phenothrin (2%). Concentrations of the active ingredients were determined in air, surfaces and dust collected from the passenger cabin. Data on the inhalation and dermal exposure of crew members and passengers were also collected.

[2] Pyrethrum is not a WHO-recommended insecticide for aircraft disinsection.

The pyrethrin [3] concentrations measured during the spraying operation and over a time period of 40 minutes afterwards varied between 3 and 80 µg/m^3 (piperonyl butoxide: 54–581 µg/m^3) in the passenger cabin air; D-phenothrin concentrations ranged from 127 to 280 µg/m^3. The concentrations found on individual surfaces showed a wide range: very low concentrations were determined on vertical surfaces (folding tables and overhead bins) (median values: pyrethrin <1 ng/cm^2; piperonyl butoxide <17 ng/cm^2; D-phenothrin <3 ng/cm^2), while the concentrations on the seats, in the area of the head-rests and below the seats were higher, with median values between 24–39 ng/cm^2 (pyrethrin), 144–233 ng/cm^2 (piperonyl butoxide) and 219–1005 ng/cm^2 (D-phenothrin). The concentrations in dust samples collected from the seats and the floor were mostly <75 mg/kg.

Personal exposure measurements for the crew member doing the spraying, carried out during the spraying operation and over a time period of 20 minutes afterwards, showed concentrations of 23–82 µg/m^3 for pyrethrins, 164–484 µg/m^3 for piperonyl butoxide and 116–348 µg/m^3 for D-phenothrin. Inhalable maximum doses were 20 µg for pyrethrins (116 µg of piperonyl butoxide) and 80 µg for D-phenothrin. The percentage of active ingredients found in the respirable fraction ranged from 7 to 27. Finally, by using 100 g of the spray, a maximum of about 800 µg pyrethrins (9000 µg piperonyl butoxide) were found on the entire body surface.

More than 90% of the total amount inhaled was inhaled within the first 5–10 minutes; the airborne concentrations 1–2 hours after the spraying were less than 0.05 µg/m^3 for pyrethrin and less than 0.2 µg/m^3 for phenothrin. The duration of the flight is therefore of minor importance in the determination of exposure levels.

[3] Sum of cinerin I & II, jasmolin I & II and pyrethrin I & II.

It may be assumed that the surface areas exposed to pyrethroid residues on aircraft seats are the back, thighs and back of the head and neck. Based on the surface area data estimates reported in the United States Environmental Protection Agency (EPA) guidelines (EPA, 1998), the total exposed area is 2560 cm^2 for an adult male body, leading to a maximum estimated amount of 2.56 mg potentially absorbable through the skin (1.005 ng/cm^2 x 2.56 cm^2). Considering 10% dermal absorption, the dermal intake for exposure consequent to a single flight in a disinsected aircraft would be 0.0036 mg/kg, based on a body weight of 70 kg (adults). For children, based on a body weight of 10 kg and a height of 80–100 cm, the total exposed area would be 500 cm^2. Therefore, the estimated absorbed dose would be 0.005 mg/kg.

Based on the maximum inhalable dose of 80 µg, and assuming the absorption of 100% of the inhaled D-phenothrin, the inhalation exposure consequent to a single flight in a disinsected aircraft would be 0.001 mg/kg, for an adult with a body weight of 70 kg. For children, based on the maximum calculated inhalable dose of 18 µg and considering a body weight of 10 kg, the estimated absorbed dose is 0.0018 mg/kg. It can therefore be concluded that the total absorbed dose (skin plus respiratory absorption) is 0.0046 mg/kg bw for adults and 0.0068 mg/kg bw for children.

The comparison of these estimated intakes with the ADI established by JMPR for D-phenothrin (ADI = 0–0.07 mg/kg/day; *Table 4*) leads to the conclusion that no systemic health risk is anticipated for aircraft passengers, including children, or crew members as a consequence of aircraft disinsection. However, the airborne D-phenotrin concentration during spraying (348 $\mu g/m^3$) is significantly higher than concentrations able to cause paraesthesia measured by He and Zhang for other pyrethroids or for the concentration of cyfluthrin reported to cause upper respiratory tract irritation in volunteers (He et al., 1988; Zhang et al., 1991; Pauluhn &

Machemer, 1998): Pauluhn suggested that in human exposure to cyfluthrin, a type II pyrethroid, the "upper respiratory tract sensory irritation", may arise for 1-hour exposure at concentrations slightly above 0.1 mg/m^3 (Pauluhn, 1998). Since Pauluhn did not address his study to type I compounds, his findings do not necessarily apply to permethrin and D-phenotrin, but in a risk assessment evaluation the possible onset of upper respiratory tract sensory irritation needs to be taken into account.

Sutton et al. (2003) constructed a model to assess permethrin concentrations in the air of aircraft after residual spraying, and concluded that 45 minutes after the spraying, when mechanical ventilation at 11 air changes per hour was used, the airborne concentrations of permethrin would be below 1.6 µg/m^3. Limited measurement data from 10 aircraft tended to support this model: 0–3.5 hours after spraying, the concentrations varied between 2.2 and 230 µg/m^3, and 0.25–3.8 hours after the spraying, between >LOD [approximately 0.15 µg/m^3] – 1040 µg/m^3.

Thus it is clear that the blocks-away and top-of-descent spraying methods will lead to a markedly higher exposure than residual spraying; the latter being performed before the passengers board the aircraft, and usually by personnel wearing personal protecting gear.

It has been roughly estimated that the threshold for the induction of paraesthesia by pyrethroids is approximately 0.2 mg/cm^2 (Ray, 1991). In the Fraunhofer experimental study, measurements were made of the surface concentrations of phenothrin after simulated in-flight spraying. The highest concentration measured on the body surface of the sprayer was 4 µg/cm^2, most values being less than 1 µg/cm^2. On the passenger seats, the concentrations did not exceed 2 µg/cm^2 (Berger-Preiss, 2003).

After residual spraying with permethrin, Sutton et al. (2003) reported a mean concentration for all wipe samples of arm rests, walls and floor runners, of 18 μg/cm^2, with a variation between 0.002–418 μg/cm^2 and a mean concentration for fabric (pieces cut out of seat covers of 4 μg/cm^2 (0.3–11 μg/cm^2)).

Paraesthesias and, in inhalation exposure, upper respiratory tract irritation, are the most frequently reported adverse effects following exposure to pyrethroids. They may occur among aircraft passengers and crew after in-flight pyrethroid spraying, and among the crew after pre-flight spraying. Current evidence suggests that, while they may cause transient discomfort, pyrethroids do not indicate or predict serious health effects.

Allergic reactions are highly unlikely to occur from either pyrethroids or natural pyrethrins purified from allergens.

These conclusions are consistent with the Report of the Informal Consultation on Aircraft Disinsection (WHO, 1995, 1998c).

6.5.3 Indoor residual application

Indoor residual application is aimed at ensuring the safe and correct application of a residual insecticide to indoor surfaces on which vectors may rest (WHO, 1995, 1999, 2000). Indoor residual spraying is extensively used for malaria and Chagas disease vector control. Trained personnel usually apply the insecticide after occupants have left their rooms. In rooms occupied by sick people who cannot be moved, application is not performed. Household items, including water, food, cooking utensils and toys, are removed from the house before application, and furniture is taken out or covered. Items that cannot be removed are usually covered.

Indoor residual spraying is normally done using hand-operated compression sprayers. The insecticide may be mixed separately in a bucket and poured into the sprayer. Water-soluble sachets, tablets and insecticide granules are added directly to the water-

filled tank. Occupants are advised to stay outside until the spray is dry and to sweep or mop the floor before children or pets are allowed to re-enter. Sprayed surfaces must not be cleaned.

Based on the application modalities described above, it can be concluded that levels of pyrethroid exposure are affected mainly by pesticide volatilization from the roof and walls of the room; the respiratory tract is therefore the most relevant route of absorption. Prolonged skin contact to walls is not anticipated, and furniture is not expected to be contaminated because it is not exposed to the spray.

Sprayers effectuating indoor pyrethroid spraying were shown to be exposed because the urinary concentrations of pyrethroid metabolites were elevated on the first day after the spraying (Leng et al., 1997, 2003); no parent pyrethroids were detected in blood. These workers also showed decreases in some blood components linked to immune function; the changes were all within the reference range and were transient (Hadnagy et al., 2003).

No exposure to pyrethroid spray to occupants is anticipated, because inhabitants leave their rooms before application and re-enter only after the applied solution is dried.

Since no data are available on airborne pyrethroid concentration after indoor residual application, an estimate of exposure levels can be made by comparison with the airborne concentrations measured in bednet treatment, where the space under the net may represent a sort of indoor environment delimitated by treated surfaces.

The concentration of pyrethroids under the net immediately after the application is 0.02–0.055 $\mu g/m^3$. It may therefore conservatively be assumed that the same concentration is present in the room treated with the indoor residual application method. This is a worst-case hypothesis scenario, because the

reduction of the volatilization over time and the natural degradation of the applied compound are not taken into account.

Assuming a daily respiratory volume of 12 m^3, the absorption of 100% of the active ingredient and an indoor permanence of 24 hours a day, a daily absorption of 0.66 µg/day may be estimated, that is about 0.009 µg/kg for an adult and about 0.07 µg/kg for a 10-kg child (even assuming the same ventilation rate of an adult).

These estimates are about 1000 times lower than the lowest ADI established for the pyrethroids recommended by WHO for indoor residual application.

Based on this very conservative estimate, it may be concluded that no health risk is anticipated for subjects living in treated rooms.

The estimated environmental concentrations of 0.055 µg/m^3 are lower than those expected to cause paraesthesia or respiratory tract irritation suggested by the studies of He et al (1988) and Pauluhn & Machemer (1998), but in the range of dose that the study of Zhang and co-workers suggested as able to cause the onset of paraesthesia (0.01–0.89 µg/m^3) (He et al., 1988; Zhang et al., 1991).

A study was carried out to investigate indoor exposure to permethrin in 80 private homes in Germany containing wool textile floor coverings. Insecticide was applied during manufacture of the wool yarn. The concentration of pesticide was monitored in wool fibres, house dust and airborne particles. Pyrethroid metabolites were measured in urine samples collected from subjects living in houses where fitted carpets were placed. While concentrations in house dust ranged from <1 to 659 mg/kg, permethrin concentration in airborne particles was lower (arithmetic mean 2.8 ng/m^3).

Pyrethroid metabolite concentrations in urine were in the same range as those reported for the general population without specific pyrethroid exposure. These data suggest the absence of a significant indoor exposure to pyrethroids (Berger-Preiss et al., 2002; Schettgen et al., 2002).

Based on the above data, it may be concluded that no systemic health risk is anticipated for people living in apartments equipped with impregnated woollen textile floor coverings. This may also be true for people living in rooms treated with the indoor residual application method. However, as the concentrations of pyrethroids in treated houses after residual spraying are not far from the concentrations eliciting paraesthesia (see above), the possibility of paraesthesia onset in susceptible subjects cannot definitely be ruled out.

7 CONCLUSIONS

The data made available after 1990 refine and improve the knowledge on pyrethroid toxicity, but the whole body of new data does not reveal hazards not known at the time of WHO recommendations.

Sensory irritation of the upper respiratory tract was observed in animals exposed for a 1-hour period to concentrations above 0.1 mg/m^3 cyfluthrin; the NOAEC for this effect was similar in a 13-week study. Information on this effect is not available for other pyrethroids.

Immune effects have been observed only at doses higher than NOAEL for other effects and at several orders of magnitude higher than those implied in WHO-recommended uses. The evidence provided by these experimental studies cannot therefore be taken as indicative of a risk of immune disruption for humans exposed to low doses of pyrethroids. Studies on endocrine effects, especially on use of WHO-recommended pyrethroids, are scarce and do not provide consistent results.

Some neurobehavioural effects have been observed in experimental animals, with NOAELs no different from those used previously in WHO hazard characterization. Neuro-developmental effects have been observed at dose levels at which other effects have not been reported. The following arguments should be considered in the interpretation of the neurotoxic effects observed in neonatal mice, consisting of changes in the density of muscarinic receptors at low doses:

- the unclear biological significance of the observed findings;
- the differences of mouse brain development process to that of humans;
- the lack of standardization and comparability of the methods applied in neurotoxicological studies.

Based on the above considerations, further investigation of neurotoxicity is needed before conclusions can be drawn on this subject.

In general, no remarkable toxicity was detected or peculiar treatment-related effects observed in chronic toxicity studies. In the oral two-year studies in mice and rats, the NOELs vary for individual compounds, with values in the order of 1–7 mg/kg bw/day (*Table 4*). For exposure via the dermal route, the NOELs are higher, with values ranging from 100 to 5000 mg/kg bw/day (not shown) (IPCS, 1990a–e, 1997).

Pyrethroids are not carcinogenic, genotoxic or toxic to reproduction in experimental animals. While data from humans are very limited, it is unlikely that these insecticides pose a carcinogenic or reproductive toxicity hazard to humans.

At present, the lowest ADI recommended by WHO for pyrethroids used in public health applications under review in this document is that established for deltamethrin (0.01 mg/kg bw/day), based on a NOAEL of 1 mg/kg bw/day.

Table 4 summarizes the NOAELs and respective ADIs, calculated on the basis of a safety factor (SF) of 100, for the pyrethroids currently recommended by WHO for use in public health applications under review in this document.[4]

Table 4. **No-observed-adverse-effect level (NOAEL) and acceptable daily intake (ADI) of pyrethroid insecticides commonly used in public health (IPCS, 1989, 1993, 1994, 1996, 1997b, 2000a–b, 2001)**

Active ingredient	Relevant NOAEL (mg/ai/kg bw/day)	ADI (mg/ai/kg bw/day) SF=100
alpha-cypermethrin	1.5	0–0.02
bifenthrin	1.5	0–0.02
cyfluthrin	2	0–0.02
deltamethrin	1	0–0.01
D-phenothrin	7	0–0.07
etofenprox	3.1	0–0.03
lambda-cyhalothrin[a]		
permethrin	5	0–0.05

NOTE: The ADI, expressed as mg/kg bw, is the level of daily exposure to pesticides that, after an entire lifetime of humans, appears to be unable to cause any appreciable risk, on the basis of all the facts known at a given time. It has been calculated from the relevant NOAEL, with the application of a safety factor.

[a] The Joint FAO/WHO Expert Committee on Food Additives has given an ADI of 0–0.002mg/kg for_cyhalothrin, from a lowest-observed-adverse-effect level of 1 mg/kg bw/day, and a "safety factor of 500" (IPCS, 2004a).

The most relevant new information on pyrethroids after 1990 is the availability of biological indicators of dose adequate for detecting low doses or traces of pyrethroids absorbed in the living environment or through the diet. This creates the

[4] As the NOAELs and ADIs are from studies using oral exposure, they apparently give very limited information vis-à-vis local effects such as dermal effects and respiratory tract sensory irritation.

possibility of collecting exposure data on subjects exposed to pyrethroids as a consequence of public health uses. However, such data do not reflect the pattern of exposure: short-term (minutes) high-level exposure and long-term low-level exposure give similar results.

Episodes of discomfort have sometimes been reported after exposure to pyrethroids following public health uses, particularly aircraft disinsection, but recovery has usually been complete shortly after the end of the exposure; long-lasting symptoms in some reported cases are rarely attributable to pyrethroid exposure.

This finding is consistent with the data collected in this document, which suggest that the onset of paraesthesia cannot definitely be ruled out in all the three different uses recommended by WHO for public health purposes (indoor residual application, bednet treatment and aircraft disinsection). Moreover, in indoor residual application and particularly in aircraft disinsection, when carried out with the blocks-away or top-of-descent method, environmental pyrethroid concentration can reach levels high enough to cause upper respiratory tract sensory irritation. No long-term or serious health risks are anticipated from pyrethroids used for public health purposes as recommended by WHO.

In some cases, symptoms reported after aircraft disinsection resemble “multiple chemical sensitivity” (MCS) or “chemical intolerance”, which has been given as an explanation to subjective respiratory problems and even asthma attacks after exposure to chemicals at concentrations lower than the minimum concentrations able to cause any symptom in most of the general population (Miller, 1996; Baldwin et al., 1997; Ross, 1997). However, there is currently no clear nosological definition of the “multiple chemical sensitivity syndrome” and, while some authors suggest it as a disease, some others hypothesize that MCS is not a physical entity but rather a

particular type of psychosomatic reaction. Since among the application modalities proposed for aircraft disinsection by WHO, the highest concentrations are anticipated with the blocks away and top-of-descent methods, particular attention should be paid to ensure that this kind of application is made strictly according to the directions for use of the involved compound.

In conclusion, pyrethroids are insecticides characterized by a moderate acute toxicity and do not show any evidence of long-term toxicity in humans. They do not pose any significant health risk when they are used in compliance with their directions for use, which are intended to limit human exposure within the levels recommended for their specific applications.

Toxicological information from laboratory animals or humans made available following WHO recommendations on public health use of these compounds has not revealed any previously unknown hazards. There is no need, therefore, for WHO to modify its existing recommendations on pyrethroid use in public health. The use of products complying with WHO specifications[5] should be observed in order to avoid any risk caused by potential toxic or sensitizing impurities.

Despite the absence of demonstrated or predicted health effects, unnecessary exposure to pyrethroids – as for all chemicals – should be avoided: they should be only used when there is a need, and levels of exposure and amounts used should be kept to a minimum that still guarantees the desired public health effect.

8 REFERENCES

Ahlbom J, Fredriksson A, Eriksson P (1994). Neonatal exposure to a type-I pyrethroid (bioallethrin) induces dose-response changes in brain muscarinic receptors and behaviour in neonatal and adult mice. *Brain Res.*, 645:318–324.

Akhtar N, Kaiani SA, Ahmad MM, Shahab M (1996). Insecticide-induced changes in secretory activity of the thyroid gland in rats. *Journal of Applied Toxicology*, 16(5):397–400/Sep–Oct.

Aldridge WN (1990). An assessment of the Toxicological Properties of Pyrethroids and their Neurotoxicity. *Toxicology*, 21(2):89–104.

Andrade AJ, Araujo S, Santana GM, Ohi M, Dalsenter PR (2002). Reproductive effects of deltamethrin on male offspring of rats exposed during pregnancy and lactation. *Regul. Toxicol. Pharmacol.*, 36:310–317.

Aziz MH, Agrawal AK, Adhami VM, Shukla Y, Seth PK, (2001). Neurodevelopmental consequences of gestational exposure (GD14-GD20) to low dose deltamethrin in rats. *Neuroscience Letters*, 300(3):161–165.

Baker SB, Barr DB, Driskel WJ, Beeson MD, Needham LL (2000). Quantification of selected pesticide metabolites in human urine using isotope dilution high performance liquid chromatography/tandem mass spectrometry. *J. Expo. Anal. Env. Epid.*, 10:789–798.

Baldwin CM, Bell IR, O'Rourke MK, Lebowitz MD (1997). The association of respiratory problems in a community sample with self-reported chemical intolerance. *European J. Epidemiol.*, 13(5):547–552.

Barlow SM, Sullivan FM, Lines J (2001). Risk assessment of the use of deltamethrin on bednets for the prevention of malaria. *Food & Chemical Toxicology*, 39(5):407–422.

Bateman DN (2000). Management of pyrethroid exposure. *Journal of Toxicology – Clinical Toxicology*, 38(2):107–109.

Berger-Preiss E, Levsen K, Leng G, Idel H, Sugiri D, Ranft U (2002). Indoor pyrethroid exposure in homes with woollen textile floor coverings. *Int. J. Hyg. Environ. Health. Oct.*, 205(6):459–472.

Berger-Preiss E (2003). *Exposizionsszenarium zur Problematik der Inflight-Spray-Massnahme in Flugzeugen [Exposure scenario for the problems of in-flight spray procedures in aircraft]*. Hanover, Fraunhofer-Institut für Toxikologie und Experimentelle Medizin.

Berger-Preiss E, Koch W, Behnke V, Gerling S, Kock H, Elflein L, Appel K (2004). In-flight spraying in aircrafts: determination of the exposure scenario. *Int. J. Hyg. Environ. Health* (in press).

Binka FN, Kubaje A, Adjuik M, Williams LA, Lengeler C, Maude CH et al. (1996). *Trop. Med. Int. Health*, 1:147–154.

Bloom AS, Staatz CG, Dieringer T (1983). Pyrethroid effects on operant responding and feeding. *Neurobehav. Toxicol. Teratol.*, May-June; 5(3):321–324.

Boman W (1995). *How safe are pyrethroids-treated mosquito nets? An evaluation based on the example of Solfac EW 050*. Leverkusen, Germany, Bayer AG Animal Health Division (Public Health no. 12).

Bonvie L, Bonvie B (1993). Flying in the mist. *Buzzworm's Earth Journal*, Nov/6(1):38.

Bonvie L, Bonvie B (1994). A new bomb in the bug war. *The Chicago Tribune*, 10/2/94ARE.

Bonvie L, Bonvie B (1995a). Pesticide sprays finally bug U.S. airlines. *St Louis Post-Dispatch*, 1/22/95.

Bonvie L, Bonvie B (1998). Bugs remain. *The Chicago Tribune*, 3/8/98.

Bonvie L, Bonvie B(1995b). Travel Dangers May Have Been Hidden. *St Louis Post-Dispatch*, 1/22/95.

Cabral JRP, Galendo D, Laval M, Lyandrut N (1986). Carcinogenicity study of the pesticide deltamethrin in mice and rats. Summary Report in Poster Session at IUPAC Meeting, Ottawa, August 1986.

Cabral, JRP, Galendo D, Laval M, Lyandrat N (1990). Carcinogenicity studies with deltamethrin in mice and rats. *Cancer Lett.*, 49:147–152.

Cagen SZ, Malley LA, Parker CM, Gardiner TH, Van Gelder GA, Jud VA (1984). Pyrethroid-mediated skin sensory stimulation characterized by a new behavioural paradigm. *Toxicol. Appl. Pharmacol.*, 76(2):270.

Campana MA, Panzeri AM, Moreno VJ, Dulout FN (1999). Genotoxic evaluation of the pyrethroid lambda-cyhalothrin using the micronucleus test in erythrocytes of the fish Cheirodon interruptus interruptus. *Mutat. Res.*, 438:155–161.

Cavas T, Ergene-Gozukara S (2003). Evaluation of the genotoxic potential of lambda-cyhalothrin using nuclear and nucleolar biomarkers on fish cells. *Mutat. Res.*, 534:93–99.

Celik A, Mazmanci B, Camlica Y, Askin A, Comelekoglu U (2003). Cytogenetic effects of lambda-cyhalothrin on Wistar rat bone marrow. *Mutat Res.*, 539:91–97.

Chen S, Zhang Z, He F, Yao P, Wu Y, Sun J, Liu L, Li Q (1991). An epidemiological study on occupational acute pyrethroid poisoning in cotton farmers. *Br. J. Ind. Med.*, 48:77–81.

Clark JM (1995). Effects and mechanism of action of pyrethrin and pyrethroid insecticides. In: Chang LW, Dyer RS, eds. *Handbook of neurotoxicology*. New York, Marcel Dekker, Inc: 511–546.

Compendium of pesticide common names (CPCN) (2001). Pyrethroid insecticides – http://www.hclrss.demon.co.uk – last update.

Crawford MJ (1981). The metabolism of pyrethroid insecticides in rats: excreted metabolites. *Pestic. Sci.*, 12:399–411.

Crofton KM, Reiter LW (1984). Effects of two pyrethroid insecticides on motor activity and acoustic startle response in the rat. *Toxicol. Appl. Pharmacol.*, 75:318–328.

Crofton KM, Reiter LW (1988). The effects of Type I and II pyrethroids on motor activity and acoustic startle response in the rat. *Fund. Appl. Toxicol.*, 10:624–634.

De Souza Spinoza H, Silva YM, Nicolau AA, Bernardi MM, Lucisano A (1999). Possible anxiogenic effects of fenvalerate, a type II pyrethroid pesticide, in rats. *Physiol Behav.*, 67:611–615.

Desi I, Varga L, Dobronyi I, Szklerarik G (1985). Immunotoxicological investigation of the effects of a pesticide;cypermethrin. *Arch. Toxicol.*, Supplement. 8:305–309.

Dyck PJ, Shimono M, Schoening GP, Lais AC, Oviatt KF, Sparks MF (1984). The evaluation of a new synthetic pyrethroid pesticide (permethrin) for neurotoxicity. *J. Environ. Pathology, Toxicology & Oncology*, 5(4-5):109–117.

Ecobichon DJ (1996). Toxic Effects of Pesticides. In: Klaassen CD, Amdur OM, Doull J, eds. *Casarett and Doull's Toxicology: the basic science of poisons*, 5th ed. New York, NY, Klaassen CD, Amdur OM, and Doull J editors. MacMillan Publishing Company.

Ellenhorn M, Barceloux D (1988). *Medical Toxicology – diagnosis and treatment of human poisoning*. New York, NY, Elsevier Sciences Publishing, Inc.

El Gohary M, Awara WM, Nassar S, Hawas S (1999). Deltamethrin-induced testicular apoptosis in rats: the protective effect of nitric oxide synthase inhibitor. *Toxicology*, 132:1–8.

Enan E, Pinkerton KE, Peake J, Matsumura F (1996). Deltamethrin-induced thymus atrophy in male Balb/c mice. *Biochem. Pharmacol.*, 51:447–454.

EPA–US. Environmental Protection Agency (2000). Prevention, Pesticides and Toxic substances – Synthetic Pyrethroids for Mosquito Control.

EPA–US. Environmental Protection Agency, Office of Pesticides and Toxic Substances (1998). Health Effects Test Guideline 870.6200, Neurotoxicity Screening Battery.

Eriksson P, Fredriksson A (1991). Neurotoxic effects of two different pyrethroids, bioallethrin and deltamethrin, on immature and adult mice: changes in behavioural and muscarinic receptor variables. *Toxicol. Appl. Pharmacol.*, 108:78–85.

Eriksson P, Nordberg A (1990). Effects of two pyrethroids, bioallethrin and deltamethrin, on subpopulations of muscarinic and nicotinic receptors in the neonatal mouse brain. *Toxicol. Appl. Pharmacol.*, 102:456–463.

EXTOXNET, Extension Toxicology Network-Pesticide Information Profiles (Revised March 1994a). Pyrethrins And Pyrethroids http://ace.orst.edu/info/extoxnet/ghindex.html

EXTOXNET, Extension Toxicology Network-Pesticide Information Profiles (1994b). Pyrethrins and Pyrethroids http://ace.orst.edu/info/extoxnet/ghindex.html

EXTOXNET, Extension Toxicology Network-Pesticide Information Profiles (1994c). α-Cypermethrin http://ace.orst.edu/info/extoxnet/ghindex.html

EXTOXNET, Extension toxicology network-pesticide information profiles (1994d). Cyfluthrin http://ace.orst.edu/info/extoxnet/ghindex.html

EXTOXNET, Extension Toxicology Network-Pesticide Information Profiles (1994e). Deltamethrin http://ace.orst.edu/info/extoxnet/ghindex.html

FAO, 1982. FAO plant production and protection paper 42. Pesticide residues in food. 1981 evaluations. Monograph on Deltamethrin. Food and Agriculture Organization of the United Nations, Rome, Feb–Apr.

Garey J, Wolff MS (1998 Oct 29). Estrogenic and antiprogestagenic activities of pyrethroid insecticides. *Biochem. Biophys. Res. Commun.*, 251(3):855–859.

Gomes MS, Bernardi MM, Spinosa HS (1991a). Effects of prenatal pyrethroid insecticide exposure on the sexual development of rats. *Vet. Hum. Toxicol.*, 33:427–428.

Gomes MS, Bernardi MM, Spinosa HS (1991b). Pyrethroid insecticides and pregnancy: effect on physical and behavioural development of rats. *Vet. Hum. Toxicol.*, 33:315–317.

Hadnagy W, Leng G, Sugiri D, Ranft U, Idel H (2003). Pyrethroids used indoors – immune status of humans exposed to pyrethroids following a pest control operation – a one year follow-up study. *Int. J. Hyg. Environ. Health*, 206:93–102.

Hayes WJ Jr (1982). Pesticides Studied in Man. Williams and Wilkins. Baltimore, London., Occupational Health Services, Inc. "Pyrethrum." Material Safety Data Sheet. 1 April 1987. New York: OHS, Inc.

He F, Wang S, Liu L, Chen S, Zhang Z, Sun J. (1989). Clinical manifestations and diagnosis of acute pyrethroid poisoning. *Arch, Toxicol.,* 63(1):54–58.

He F, Sun J, Han K, Wu Y, Yao P, Wang S, Liu L (1988). Effects of pyrethroid insecticides on subjects engaged in packaging pyrethroids. *Br. J. Ind.*, 45(8):548–551.

Huggins CE (2000). *Common insecticide ingredient may cause allergic reactions*. Reuters - Chronic Neuroimmune Diseases.

Husain R, Husain R, Adhami VM, Seth PK (1996). Behavioural, neurochemical and neuromorphological effects of deltamethrin in adult rats. *J. Toxicol. Environ. Health*, 48:515–526.

IARC (International Agency on Research on Cancer) (1991). *IARC Monographs on the evaluation of carcinogenic risks to humans. Occupational exposures in insecticide application, and some pesticides*. Lyons, IARC (volume 53).

Institoris L, Siroki O, Undeger U, Desi I, Nagyamajtenyi L (1999). Immunotoxicological effects of repeated combined exposure by cypermethrin and the heavy metals lead and cadmium in rats. *Int. J. Immunopharmacology*, 21(11):735–743.

IPCS – International Programme on Chemical Safety (1989). d-Phenothrin. In: *Pesticide Residues in Food. Evaluations 1988. Part II – Toxicology*. Joint FAO/WHO Meeting on Pesticide Residues (JMPR). FAO Plant production and Protection Paper 93/2. Rome, Food and Agriculture Organization of the United Nations, 53–60.

IPCS – International Programme on Chemical Safety (1990a). Cyhalothrin. Environmental Health Criteria 99. Geneva, World Health Organization.

IPCS – International Programme on Chemical Safety (1990b). Deltamethrin. Environmental Health Criteria 97. Geneva, World Health Organization.

IPCS – International Programme on Chemical Safety (1990c). Fenvalerate. Environmental Health Criteria 95. Geneva, World Health Organization.

IPCS – International Programme on Chemical Safety (1990d). Permethrin. Environmental Health Criteria 94. Geneva, World Health Organization.

IPCS – International Programme on Chemical Safety (1990e). d-Phenothrin. Environmental Health Criteria 96. Geneva, World Health Organization.

IPCS – International Programme on Chemical Safety (1993). Bifenthrin. In: *Pesticide Residues in Food. Evaluations 1992. Part II – Toxicology*. Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Geneva, World Health Organization (WHO/PCS 93.34):79–102.

IPCS – International Programme on Chemical Safety (1994). Etofenprox. In: *Pesticide Residues in Food. Evaluations 1993. Part II – Toxicology*. Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Geneva, World Health Organization (WHO/PCS 94.4):215–232.

IPCS – International Programme on Chemical Safety (1995). *Report of the Informal Consultation on Aircraft Disinsection*. Geneva, World Health Organization (WHO/PCS/95.51):57.

IPCS – International Programme on Chemical Safety (1996). Cypermethrin and ά-Cypermethrin. In: *Toxicological Evaluation of Certain Veterinary Drug Residues in Food*. Prepared by the forty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva, World Health Organization (WHO Food Additives Series No. 38):133–170.

IPCS – International Programme on Chemical Safety (1997a). *α-Cypermethrin*. Geneva, World Health Organization (Environmental Health Criteria No. 142).

IPCS – International Programme on Chemical Safety (1997b). Cyfluthrin. In: *Toxicological Evaluation of Certain Veterinary Drug Residues in Food*. Prepared by the forty-eighth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva, World Health Organization (WHO Food Additives Series No. 39):79–106.

IPCS – International Programme on Chemical Safety (2000a). Cyhalothrin. In: *Toxicological Evaluation of Certain Veterinary Drug Residues in Food*. Prepared by the fifty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva, World Health Organization (WHO Food Additives Series No. 45):41–74.

IPCS – International Programme on Chemical Safety (2000b). Permethrin. In: *Pesticide Residues in Food. Evaluations 1999. Part II – Toxicological*. Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Geneva, World Health Organization (WHO/PCS 00.4):161–200.

IPCS – International Programme on Chemical Safety (2001). Deltamethrin. In: *Pesticide Residues in Food. Evaluations 2000. Part II – Toxicological*. Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Geneva, World Health Organization (WHO/PCS 01.3):79–110.

IPCS – International Programme on Chemical Safety (2004a). Cyhalothrin (Addendum). In: *Toxicological Evaluation of Certain Veterinary Drug Residues in Food*. Prepared by the sixty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva, World Health Organization (WHO Food Additives Series; in preparation).

IPCS – International Programme on Chemical Safety (2004b). Cypermethrin and alpha-cypermethrin (Addendum). In: *Toxicological Evaluation of Certain Veterinary Drug Residues in Food*. Prepared by the sixty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva, World Health Organization (WHO Food Additives Series; in preparation).

Ishmael J, Litchfield MH (1988). Chronic toxicity and carcinogenic evaluation of permethrin in rats and mice. *Fundam. Appl. Toxicol.*, 11:308–322.

Kaul PP, Rastogi A, Hans RK, Dryhj TF, Dryh PK, Dtimsl RC (1996). Industrial Toxicology Research Centre, Lucknow, India. Fenvalerate-induced alterations in circulatory thyroid hormones and calcium stores in rat brain. *Toxicol. Lett.*, 89(1):29–33.

Kolmodin-Hedman B, Swensson A, Akerblom M (1982). Occupational exposure to some synthetic pyrethroids (permethrin and fenvalerate). *Arch. Toxicol.*, 50(1):27–33.

Lazarini CA, Florio JC, Lemonica IP, Bernardi MM (2001). Effects of prenatal exposure to deltamethrin on forced swimming behavior, motor activity, and striatal dopamine levels in male and female rats. *Neurotoxicol. Teratol.,* Nov-Dec; 23(6):665–673.

Le Quesne PM, Maxwell IC, Butterworth STG (1980). Transient facial sensory symptoms following exposure to synthetic pyrethroids. A clinical and electrophysiological assessment. *Neurotoxicology*; 2:1–11.

Leng G, Kuhn KH, Idel H (1997). Biological monitoring of pyrethroids in blood and pyrethroid metabolites in urine: Applications and limitations. *Sci. Total Environ.*, 199:173–181.

Leng G, Ranft U, Sugiri D, Hadnagy W, Berger-Preiss E, Idel H (2003). Pyrethroids used indoors--biological monitoring of exposure to pyrethroids following an indoor pest control operation. *Int. J. Hyg. Environ. Health*, 206:85–92.

Luty S et al, Latuszynska J, Halliop J, Tochman A, Obuchowska D, Przylepa E, Korczak E (1998). Toxicity of dermally applied alpha-cypermethrin in rats. *Ann. Agric. Environ. Med.*, 5:109–116.

Luty S, Latuszynska J, Obuchowska-Przebirowska D, Tokarska M, Haratym-Maj A (2000). Subacute toxicity of orally applied alpha-cypermethrin in Swiss mice. *Ann. Agric. Environ. Med.*, 7:33–41.

Mackinson FW, Stricoff RS, Partridge LJ Jr, eds. (1981). NIOSH-OSHA. *Occupational health guidelines for chemical hazards*. Washington, DC, United States Government Printing Office (DHHS (NIOSH) Publication nos. 81–123 (3 Vols)).

Madsen C, Claesson MH, Ropke C (1996). Institute of Toxicology, National Food Agency, Soeberg, Denmark. Immunotoxicity of the pyrethroid insecticides deltametrin and alpha-cypermetrin. *Toxicology*, 107(3):219–227.

Maroni M, Colosio C, Ferioli A, Fait A (2000). Biological monitoring of pesticide exposure: a review. *Toxicology*, vol. 143, Issue no. 1.

McDaniel KL, Moser VC (1993). Utility of a neuro behavioural screening battery for differentiating the effects of two pyrethroids, permethrin and cypermethrin. *Neurotoxicol. Teratol.*, 15:71–83.

Miller CS (1996). Chemical sensitivity: symptom, syndrome or mechanism for disease. *Toxicology*, 111(1-3):69–86.

Misra SP, Webber R, Lines J, Jaffar S, Bradley DJ (1999). Malaria control: bednets or spraying? Spray versus treated nets using deltamethrin - A community randomized trial in India. *Transactions of the Royal Society of Tropical Medicine & Hygiene*, 93(5):456–457.

Moniz AC, Bernardi MM, Spinosa HS (1994). Effects of a pyrethroid type II pesticide on conditioned behaviors of rats. *Vet. Hum. Toxicol.*, 36:120–124.

Moniz AC, Bernardi MM, Souza-Spinosa HS, Palermo-Neto J (1990). Effects of exposure to a pyrethroid insecticide during lactation on the behavior of infant and adult rats. *Braz. J. Med. Biol. Res*., 23:45–48.

Moniz AC, Cruz-Casallas PE, Oliveira CA, Lucisano A, Florio JC, Nicolau AA, Spinosa HS, Bernardi MM (1999). Perinatal fenvalerate exposure: behavioural and endocrinology changes in male rats. *Neurotoxicol. Teratol.*, 21:611–618.

Mueller-Beilschmidt (1990). Toxicology and Environmental Fate of Synthetic Pyrethroids. *J. Pesticide Reform*, 10(3)Fall 1990. Northwest Coalition for Alternatives to Pesticides, Eugene, OR – PANNA (Pesticide Action Network North America).

Müller-Mohnssen H (1999). Chronic sequelae and irreversible injuries following acute pyrethroid intoxication. *Toxicol. Lett.*, 107:161–176.

Narahashi T, Ginsburg KS, Nagata K, Song JH, Tatebayashi H (1998). Ion channels as targets for insecticides. *Neurotoxicology*, 19(4–5):581–590.

Narahashi T (2000). Neuroreceptors and ion channels as the basis for drug action: past, present, and future. *Journal of Pharmacology & Experimental Therapeutics*, 294(1):1–26.

National Pesticide Telecommunications Network (NPTN) Fact Sheets (1998). *Pyrethrins and pyrethroids*. http://npic.orst.edu/factsheets/pyrethrins.pdf

O'Malley M (1997). Clinical evaluation of pesticide exposure and poisonings. *Lancet*, 349(9059):1161–1166.

Pauluhn J (1996). Risk assessment of Pyrethroids following indoor use. *Toxicol. Lett.*, Nov. 88 (1–3):339–348.

Pauluhn J, Machemer LH, (1998). Assessment of pyrethroid-induced paraesthesias: comparison of animal model and human data. Institute of Toxicology, Bayer AG, Wuppertal, Germany. *Toxicol. Lett.*, Aug; 96–97:361–368.

Pauluhn J, Steffens W, Haas J, Machemer L, Miksche LK, Neuhauser H, Schule S (1996). Toxicologic evaluation of pyrethroids in indoor air: demonstrated with the example of cyfluthrin and permethrin. *Gesundheitswesen*, 58(10):551–556.

Pauluhn J, Schmuck G (2003). Critical analysis of potential body temperature confounders on neurochemical endpoints caused by direct dosing and maternal separation in neonatal mice: a study of bioallethrin and deltamethrin interactions with temperature on brain muscarinic receptors. *J. Appl. Toxicol.*, 23:9–18.

Pollack RJ, Kiszewski A, Armstrong P, Hahn C, Wolfe N, Rahman HA, Laserson K, Telford SR III, Spielman A (1999). Differential permethrin susceptibility of head lice sampled in the United States and Borneo. *Archives of Pediatrics & Adolescent Medicine*, 153(9):969–973.

Prater MR, Gogal RM Jr, Blaylock BL, Longstreth J, Holladay SD (2002). Single-dose topical exposure to the pyrethroid insecticide, permethrin in C57BL/6N mice: effects on thymus and spleen. *Food Chem. Toxicol.*, 40(12):1863–1873.

Ramirez MA (1930). An etiologic factor in vasomotor rhinitis and asthma. *J. Allergy*, 1:149–151.

Ray DE (1991). Pesticides derived from plants and other organisms. In: Hayes WJ Jr & Laws ERJ, eds. *Handbook of Pesticide Toxicology*. San Diego, Academic Press, 585–636.

Ray DE, Forshaw PJ (2000). Pyrethroid insecticides: poisoning syndromes, synergies, and therapy. *Journal of Toxicology – Clinical Toxicology*, 38(2)95–101.

Reigart J, Roberts R (1999). *Recognition and management of pesticide poisonings*, 5th ed. Washington, DC, United States Environmental Protection Agency
(Publication No. 735-R-98-003).

Righi DA, Palermo-Neto J (2003). Behavioural effects of type II pyrethroid cyhalothrin in rats. *Toxicol. Appl. Pharmacol.*, 191:167–176.

Ross GH (1997). Clinical characteristics of chemical sensitivity: an illustrative case history of asthma and MCS. *Environmental Health Perspectives*, 105 Suppl. 2:437–441.

Santoni G, Cantalamessa F, Mazzucca L, Romagnoli S, Piccoli M (1997). Prenatal exposure to cypermethrin modulates rat NK cell cytotoxic functions. *Toxicology*, 120:231–242.

Santoni G, Cantalamessa F, Spreghini E, Sagretti O, Staffolani M, Piccoli M (1999). Alterations of T cell distribution and functions in prenatally cypermethrin-exposed rats: possible involvement of catecholamines. *Toxicology*, 138:175–187.

Santoni G, Cantalamessa F, Cavagna R, Romagnoli S, Spreghini E, Piccoli M (1998). Cypermethrin-induced alteration of thymocyte distribution and functions in prenatally-exposed rats. *Toxicology*, 16;125(1):67–78.

Satpathy SK, Tyagi PK, Das SB, Srivastava P, Yadav RS (1997). Evaluation of possible toxic effects of Cyflutrin during short-term, relevant community exposure. *Bull. Environm. Contam. Toxicol.*, 59:681–687.

Schettgen T, Heudorf U, Drexler H, Angerer J. (2002). Pyrethroid exposure of the general Population is this due to diet. *Toxicol. Lett.*, 134(1–3):141–145.

Sheets LP (2000). A consideration of age-dependent differences in susceptibility to organophosphorus and pyrethroid insecticides. *Neurotoxicology*, 21(1–2):57–63.

Shukla Y, Arora A, Singh A (2001). Tumourigenic studies on deltamethrin in Swiss albino mice. *Toxicology*, 163:1–9.

Shukla Y, Yadav A, Arora A (2002). Carcinogenic and cocarcinogenic potential of cypermethrin on mouse skin. *Cancer Lett.*, 182:33–41.

Soderlund DM, Clark JM, Sheets LP, Mullin LS, Piccirillo VJ, Sargent D, Stevens JT, Weiner ML (2002). Mechanisms of pyrethroid neurotoxicity: implications for cumulative risk assessment. *Toxicology*, 171:3–59.

Stein EA, Washburn M, Walczak C, Bloom AS (1987). Effects of pyrethroid insecticides on operant responding maintained by food. *Neurotoxicol. Teratol.*, Jan–Feb; 9(1):27–31.

Sumida K, Ooe N, Nagahori H, Saito K, Isobe N, Kaneko H, Nakatsuka I (2001). An in vitro reporter gene assay method incorporating metabolic activation with human and rat S9 or liver microsomes. *Biochemical & Biophysical Research Communications*, 280(1):85–91.

Sumida K, Saito K, Ooe N, Isobe N, Kaneko H, Nakatsuka I (2001). Evaluation of in vitro methods for detecting the effects of various chemicals on the human progesterone receptor, with a focus on pyrethroid insecticides. *Toxicology Letters*, 118(3):147–55.

Sutton P, Vergara X, Beckman J, Das R (2003). *Occupational illness among flight attendants due to aircraft disinsection*. 1-44. State of California Health and Human Services Agency. Department of Health Services.

Talts U, Fredriksson A, Eriksson P (1998). Changes in behaviour and muscarinic receptor density after neonatal and adult exposure to bioallethrin. *Neurobiol. Aging*, 19:545–552.

Tong Ying (1988). *Clinical manifestations of 211 cases intoxicated by deltamethrin and fenvalerate* (unpublished report submitted to WHO by R. Uclaf).

Tordoir WF, Maroni M, He F (1994). *Health surveillance of pesticide workers. A manual for occupational health professionals* (ICOH–ICPS–WHO, vol. 91).

Tucker SB, Flannigan SA (1983). Cutaneous effects from occupational exposure to Fenvalerate. *Arch. Toxicol.*, 54:195–202.

US EPA. 1998-2. List of Active Products For Site: Aircraft (All or Unspecified), Aircraft (Feed/Food-Empty), Aircraft (Feed/Food-Full), Aircraft (Non Feed/Food). Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, *Public Information and Records Integrity Branch, produced 9/21/98.*

van Sittert NJ, Eadsforth CV, Bragt PC (1985). *Human oral dose-excretion study with RIPCORD*. The Hague, Shell Internationale Petroleum Maatschappy (HSE.85.008).

Vettorazzi G (1979). *International Regulatory Aspects for Pesticide Chemicals 89–90*. Boca Raton, FL, CRC Press.

Vijverberg HP, van den Bercken J (1990). Neurotoxicological effects and the mode of action of pyrethroid insecticides. *Crit. Rev. Toxicol.*; 21(2):105–126.

Wagner SL (2000). Fatal asthma in a child after use of an animal shampoo containing pyrethrin. *West. J. Med.*, 173:86–87.

Wesseling C, Hogstedt C, Fernandez P, Ahlbom A (2001). Time trends of occupational pesticide-related injuries in Costa Rica, 1982-1992. *Int. J. Occup. Environ. Health*, 7(1):1–6.

Wilks MF (2000). Pyrethroid-induced paraesthesia-a central or local toxic effect? *Journal of Toxicology – Clinical Toxicology*, 38(2):103–105.

WHO (1994). *Control of Tropical Diseases: 1. Progress Report. The Organization, Division of Control of Tropical Diseases*. Geneva, World Health Organization (Report No. CTD/MIP/94.4).

WHO (1994). *Control of Tropical Diseases: 1. Progress Report. The Organization, Division of Control of Tropical Diseases*. Geneva, World Health Organization (Report No. CTD/MIP/94.4).

WHO (1995). *Vector control for malaria and other mosquito-borne diseases. Report of a WHO study group*. Geneva, World Health Organization (WHO Technical Report Series No. 857).

WHO (1996). *Investing in health research for development. Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options*. Geneva, World Health Organization (Report No. TDR/Gen/96.1).

WHO (1998a). *Malaria*. Geneva, World Health Organization, (Fact Sheet No. 94/98).

WHO (1998b). *Report of the 2nd WHOPES Working Group Meeting – Review of alpha-cypermethrin 10%SC and 5%WP and cyfluthrin 5%EW and 10%WP, 22–23 June 1998*. Geneva, World Health Organization (WHO/CTD/WHOPES/98.10).

WHO (1998c). WHO recommendations on the disinsecting of aircraft. *Weekly-Epidemiological Record*, 73(15):109–111.

WHO (1999). *Safety of pyrethroid-treated mosquito nets*. Geneva, World Health Organization (WHO/CDS/CPE/WHOPES/99.5).

WHO (1999). *Safe and effective use of household insecticide products – Guide for the preparation of educational and training material*. Geneva, World Health Organization (WHO/CDS/CPC/WHOPES/99.1).

WHO (2000). *Manual for indoor residual spraying application of residual sprays for vector control*. Geneva, World Health Organization (CDS/WHOPES/GCDPP/.3).

WHO (2001). Health. In: Emergencies Rejecting 'business as usual' for Malaria Control in Emergencies by David Alnwick, Project Manager, Roll Back Malaria – Issue No 9/01.

Yadav RS (1995). *Studies of possible side effects of cyfluthrin bednets. Proceedings of the 7th BSP Malaria Meeting. London, 19–21 September 1995*. London, London School of Hygiene and Tropical Medicine.

Zaim M, Aitio A, Nakashima N (2000). Safety of pyrethroid-treated mosquito nets. *Medical & Veterinary Entomology*, 14(1):1–5.

Zaim M, Jambulingam P (2004). *Global insecticide use for vector-borne disease control*, 2nd ed. Geneva, World Health Organization (WHO/CDS/WHOPES/GCDPP/2004.9).

Zehringer and Herrmann (2001). Analysis of polychlorinated biphenyls, pyrethroid insecticides and fragrances in human milk using a laminar cup liner in the GC injector. *Eur. Food Res. Technol.*, 212:247–251.

Zenz C, Dickerson OB, Horvath EP (1994). *Occupational medicine*, 3rd ed. Philadelphia, Mosby.

Zhang Z, Sun J, Chen S, Wu Y, He F (1991). Levels of exposure and biological monitoring of pyrethroids in spraymen. *Br. J. Ind. Med.*, 48:82–86.

Zhonghua Yu Fang; Yi Xue, Za Zhi (1991). *Exposure levels and biological monitoring of pyrethroids in spraymen* [in Chinese]. Beijing, Institute of Occupational Medicine, Chinese Academy of Preventive Medicine.

Zucker A. (1965). Investigation on purified pyrethrum extracts. *Ann. Allergy*, 23:335–339.