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Announcement by the German Federal Environment Agency

Internal pyrethroid exposure among the general population in Germany and reference values for pyrethroid metabolites in urine

Opinion of the Human Biomonitoring Commission of the German Federal Environment Agency

Content

Introduction

Pyrethroids are used as insecticides. Following the ban of numerous organochloropesticides, they are nowadays mainly used - along with organophosphates and carbamates - in plant protection and pest control [1]. The use of these chemicals, in particular their inappropriate use, may lead to increased exposure among consumers, whether this be through contaminated foodstuffs or by spending time in rooms treated with the relevant substances. In addition, there is a regular incidence of accidental poisoning with pyrethroids or pesticide mixtures containing pyrethroids.

Test procedures that are sufficiently sensitive to enable determination of the pyrethroid exposure of the general public are available to the environmental medicine community, and there is a sizeable amount of actual exposure data for the German population. The Human Biomonitoring Commission has therefore derived reference values for the pyrethroid metabolites *cis*-Cl2CA, *trans*-Cl2CA (*cis*- and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid) and 3-PBA (3-phenoxybenzoic acid) in urine of the

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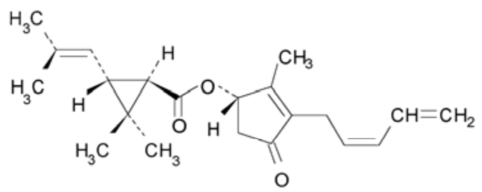
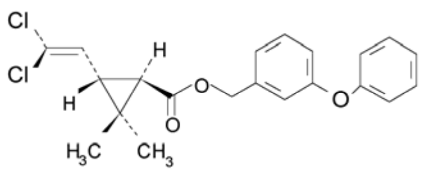
general population. Comparison with these reference values can be used to evaluate individual results recorded in tests related to specific incidents, and may also be used in additional larger-scale investigations to monitor and evaluate trends in the pyrethroid exposure of the general public in Germany.

Use and distribution

The use of extracts from the flowers of various chrysanthemum varieties used for insect control has been known for centuries [2]. The substances responsible for the insecticidal effects of these extracts are the pyrethrines. Pyrethrines were used as a model to produce synthetic pyrethroids, whose structure resembles that of pyrethrin but which are more photostable and less sensitive to hydrolysis [3, 4] (see figure 1).



Pyrethrin 1



Permethrin

Figure 1: **Comparison of the structure of pyrethrins (pyrethrin 1) and pyrethroids (permethrin)**

In 2001, a total of 52 tons of pyrethroids were used in Germany in plant protection, equivalent to 0.8 % of the total amount of plant protection insecticides used. The amount of pyrethroids being used is decreasing; in 1998 the total was still as much as 61 tons [5]. For pest control in buildings, ca. 6 tons of pyrethroids were sold in Germany in 2000 [6]. The pyrethroid used most frequently in Germany is permethrin, a mixture of the isomers *cis*- and *trans*-permethrin [1]. Its uses include the protection of wool carpets from insects and beetles (“eulanization”) [7], but it is also used as a therapeutic agent in the treatment of scabies

(Sarcoptes scabiei) and head lice (Pediculus humanus capitis) [8,9] and the treatment of parasites in domestic pets.

Release into the environment and residues in foodstuffs

The maximum amounts of permitted pyrethroids in vegetable foodstuffs legally allowed in Germany lie in the range of 0.02 – 1 mg/kg [10]. In official testing of foodstuffs, pyrethroids are rarely detected above the limit of detection. In practice, no cases are found where the limits imposed by the regulation on maximum residue levels are exceeded [11]. However, these monitoring programs only cover the source substances (as the sum of the isomers) and do not include their metabolites which are formed when they decompose in the environment.

Toxicology

Pyrethroids are toxic to mammals to a relatively low degree, the LD50 values lie between ca. 20 mg per kg body weight and > 5000 mg per kg body weight, depending on the mammal (mouse, rat) and pyrethroid involved [1, 12]. A comparison of acute toxicity values of pyrethroids for mammals and for insect is shown in table 1.

The locus of action of the pyrethroids is the sodium channel of the sodium-potassium pump in nerve cells, where reversible stereospecific interactions with receptor macromolecules can occur. Among mammals, pyrethroids lacking a cyano group, such as permethrin, are associated with the T syndrome, i.e. with tremors in the whole organism as the main symptom. Deltamethrin and other pyrethrins containing a cyano group, on the other hand, give rise to the CS syndrome, which is characterised by choreoathetosis and salivation. Other pyrethrins such as fenpropathrin lead to both tremors and salivation in what is classified as the TS syndrome [14, 15]. In animal experiments, pyrethroids turn out to be non-carcinogenic, non-mutagenic and non-teratogenic [16]. Additional work on their toxicology can be found in Appel and Gericke [17], Perger and Szadkowski [18], Scherb and Weigel [19] and Weigelt and Scherb [20].

Table 1

Toxicity of insecticides for insects and mammals (LD 50) according to M. Elliott [13]

	Rats [mg/kg]	Insects [mg/kg]	Proportion
Carbamates	45	2.8	16
Organophosphates	67	2.0	33
Chlorinated hydrocarbons	230	2.6	91
Pyrethroids	2000	0.45	4500

Toxicological data were used by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) as well as the German Federal Institute for Risk Assessment (*Bundesinstitut für Risikobewertung*, BfR) to establish exposure limit values: the ADI value (acceptable daily intake) for long term intake of substances with a low acute toxicity, and the ARfD value (acute reference dose) for plant protection agent substances with a high acute toxicity which can trigger effects harmful to health even through a single intake or intake over a short time period. The ADI values for different synthetic pyrethroids lie in the range between 0.002 and 0.07 mg per kg body weight and day, and the ARfD values lie in the range between 0.01 and 1.5 mg per kg body weight (table 2) [21].

Table 2

ADI and ARfD values of the BfR and the WHO for plant protection agent residues in foodstuffs. Values in mg per kg bodyweight [21]

Substance	ADI value (BfR)		ADI value (WHO)		ARfD (BfR)		ARfD (WHO)	
	Value	Year	Value	Year	Value	Year	Value	Year
Cypermethrin	0.05	1989	0.05	1981	0.2	2001		
Deltamethrin	0.01	2004	0.01	2000	0.01	2004	0.05	2000
Fenvalerate	0.02	1991	0.02	1986				
Permethrin	0.05	1991	0.05	1999			1.5	2002
d-Phenothrin			0.07	1988				
Cyfluthrin	0.003	2003	0.02	1987	0.02	2003		
Cyhalothrin			0.002	2000				
λ-Cyhalothrin	0.005	2001			0.0075	2000		

The effects that were observed on human beings after using pyrethroids were: tremors, pain or burning and irritation of the skin and eyes, increased salivation, temporary paresthesia, irritations of the respiratory tract [17, 22]. According to evaluations made by the department for documentation and evaluation of poisoning incidents (*Dokumentations- und Bewertungsstelle für Vergiftungen*) at the Federal Institute for Risk Assessment (previously the Federal Institute for consumer health protection and veterinary medicine (*Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin*)), the following symptoms were found with cases of acute pyrethroid poisoning (e.g. cases of intoxication resulting from suicide attempts): irritations of the respiratory tract, eyes, skin and mucous membranes, allergy-like symptoms, headaches, tiredness, sensitivity disorders, general weakness [23].

The effects of chronic exposure to low-level doses are the subject of controversial discussion. At the beginning of the 1990’s, Müller-Mohnssen [24] listed the following effects as caused by pyrethroid exposure in the case of pyrethroid poisoning, defined as "involving a direct temporal correlation between exposure and appearance of the symptoms": continual headaches, nausea, anosmia, losses to the field of vision, motility disorders in stomach and intestinal tract, as well as unspecific complaints. According to the author’s information, several thousand people in Germany are suffering from these effects. However, detailed investigations by the department for documentation and evaluation of poisoning incidents failed to confirm these claims [25].

Since then, two large-scale prospective studies have been published that investigate the possible effects of chronic pyrethroid exposure due to indoors pest control or to treatment of carpeting with permethrin [26-29]. Following indoors pest control measures, testing of house dust and indoor air was undertaken at varying intervals (up to one year after the pyrethroid use) and human biomonitoring data were collected from the inhabitants. Neurophysiological tests (EEG, acoustically and visually evoked potentials, nerve conduction velocities) and immunological tests (immunoglobulin, complement factors, cytokinins und cellular immunity markers) were carried out and subjects questioned about anamnestic symptoms and complaints. None of the tests revealed any durable evidence for links with indoors use of pyrethroids [26-28]. In the case of residents of apartments with permethrin-treated carpeting, too – even though higher concentrations of permethrin were found in the house dust – investigations failed to reveal any evidence for significant correlations between the pyrethroid concentrations in house dust, the metabolite concentration in the inhabitants’ urine and the symptoms asked about such as irritations of the skin or eyes, or gastrointestinal or central nervous system complaints (headaches) [26, 29]. On the other hand, Böge et al. [30] describe significant improvements in the state of health of individuals who had had carpets or carpeting containing pyrethroids removed, when compared to individuals who did without such measures.

Intake of pyrethroids

The main route for pyrethroid intake among the general public is apparently via residues in food. In official foodstuff testing, pyrethroids are only rarely registered at levels above the limit of detection; in practice, cases exceeding the limits imposed by the regulation on maximal residue levels are not found [11]. In contrast to, for example, organophosphate exposure, no data on estimated pyrethroid exposure via food have been published. Estimates from comprehensive human biomonitoring data yield a mean pyrethroid intake of less than 1 µg/d (95th percentile: 2-6 µg/d) [31]. The intake thus lies significantly below the ADI values.

A further possible intake route is the indoors use of pyrethroids. Since pyrethroids are only slightly volatile, they are usually not detectable in indoor air or only in very low concentrations in the lower nanogramm-per-m^2 range [32]. For this reason, these substances tend to be analysed using house dust samples. In Germany, several large-scale investigations into pyrethroid concentrations in house dust now exist [33, 34] including representative data from German Environmental Surveys (GerES) undertaken in 1985, 1990/91 [35] and 1998 [36]. In these investigations, 8 pyrethroids were analysed (cyfluthrin, cyhalothrin, cypermethrin, α-cypermethrin, deltametrin, empenthrin, d-phenothrin and permethrin), of which only permethrin was regularly detected, while the other pyrethroids were only detected in very few instances (< 2% of the samples above the detection limit). In 1998, permethrin was found in 91% of the house dust samples tested. The median amount detected was 0.17 mg/kg, the 95th percentile was 14.5 mg/kg and the maximal value 171 mg/kg [36].

This external exposure does not however usually lead to a noticeable or significant increase in the internal exposure of indoor users. Thus in their investigation of 254 adults, Butte et al. were unable to find any correlation between the permethrin concentration in dust samples from the apartment (95th percentile: 73 mg/kg) and the excretion of the relevant pyrethroid metabolites [37].

In the BMBT's prospective study mentioned above [26], rooms with permethrin-treated carpeting showed detectable permethrin concentrations in house dust samples that were significantly higher (median: 9.65 mg/kg; 90th percentile: 129.1 mg/kg) than in rooms without such carpeting. The concentration in the indoor air however remained low (median: 1.9 ng/m^3; 90th percentile: 5.8 ng/m^3) and did not reveal any significant correlations to the dust sample concentration. Nor did this study show any significant correlation between the permethrin contained in carpet or dust samples and the internal exposure of the inhabitants (pyrethroid metabolites in urine samples) [27, 30].

Another large-scale environmental medicine study investigated children below 6 years of age, including small children, who could take up dust in hand-to-mouth activity while playing on the floor and for this reason are considered to be a group at risk of pyrethroid exposure via dust. This investigation failed to find any evidence for additional exposure of the children to pyrethroids via dust in the range below background exposure (95th percentile: 4.5 mg/kg, maximum value: 19 mg/kg) [38].

On the other hand, the pilot study (for the period March 2001 – March 2002) to the German Environmental Survey for Children (GerES IV) 2003/2006, which included measurements of pyrethroid metabolite concentrations in children's urine, identified the pyrethroid content in house dust samples as a clear influencing factor alongside the age of the children following a multivariant statistical evaluation [39].

Individual cases have also been described in which members of the general population with no occupational exposure to pyrethroids show high exposure levels. In one case, a woman repeatedly showed pyrethroid metabolite concentrations in urine which exceeded the background levels by between 10 and 50 times. The cause was evidently the regular prophylactic anti-flea treatment of her dog using a preparation containing a high pyrethroid dosage [40].

Resorption and metabolism

When orally ingested, permethrin is resorbed in the human organism at a rate of ca. 60%. In blood it is split very quickly by esterases or hydrolases; the maximal concentrations in plasma are reached after ca. 4 hours [2, 41]. The hydrolytic splitting produces an isomer mixture of *cis*- and *trans*-Cl2CA (3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid) and 3-phenoxybenzyl alcohol, which is then oxidised to 3-PBA (3-phenoxybenzoic acid) in the organism. Voluntary test persons orally ingested 30 µg cyfluthrin per kg body weight; their urinary excretions of the metabolites *cis*- and *trans*- 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid and 4-fluor-3-phenoxybenzoic acid showed a half-life of 6.4 ± 0.64 hours. 94% of the metabolites were excreted renally during the first 48 hours following ingestion [42, 43]. Analogous observations were made for cypermethrin [40].

The structural formulae of the metabolites Cl2CA and 3-PBA can be seen in figure 2, which also provides an overview of the metabolism of permethrin. *Cis*- and *trans*-Cl2CA are the specific metabolites of permethrin, cypermethrin and cyfluthrin. Br2CA is the specific metabolite of deltamethrin. Most pyrethroids also form 3-PBA, with exceptions such as cyfluthrin, whose metabolite is F-PBA (see table 3). The metabolites are excreted in urine partially in the form of corresponding conjugates (glucuronides, sulfates etc.) [42, 43].

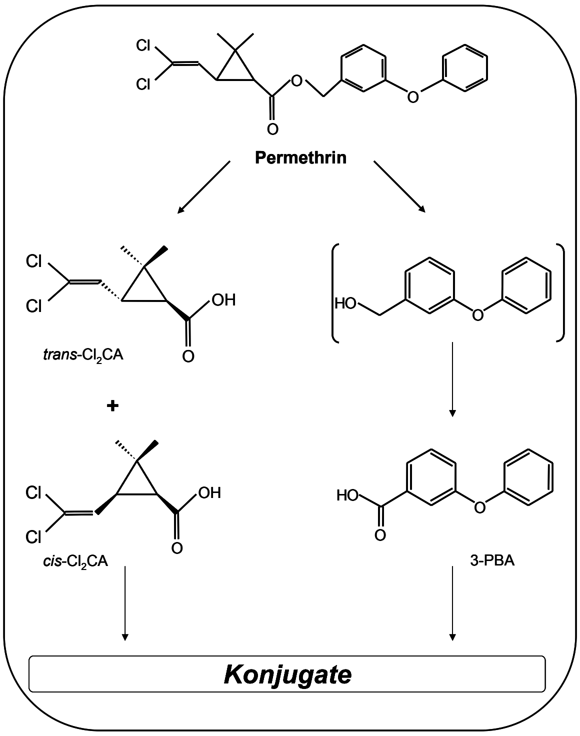


Figure 2: Metabolism of permethrin

In case of oral intake or intake by inhalation, the ration of *trans*-isomers to *cis*-isomers of the cyclopropane carboxylic acid metabolites is 2:1; in the case of dermal intake, the ratio observed is 1:1 [44].

Table 3

Metabolites of various pyrethroids

	***cis/trans*-Cl2CA**	**Br2CA**	**3-PBA**	**F-PBA**
Pyrethrum				
Permethrin	**X**		**X**	
Cypermethrin	**X**		**X**	
Deltamethrin		**X**	**X**	
Cyfluthrin	**X**			**X**
Fenvalerate			**X**	
Phenothrin			**X**	
Cyphenothrin			**X**	

Analytical determination pyrethroid metabolites in urine

For biomonitoring purposes, basically two approaches are to be considered: determination of the unaltered pyrethroids in plasma, or recording the metabolites that are excreted in urine, above all the cyclopropane carboxylic acids and the phenoxybenzoic acids. The first approach offers the advantage that it directly establishes the effective concentration in the body. On the other hand, the method of determining pyrethroid metabolites in urine is superior with regard to its diagnostic sensitivity and analytical provability [45].

In 1997, Angerer and Ritter [46] described an analytical method for testing for pyrethroid metabolites in urine which was evaluated with respect to its analytical reliability and comprehensibility by the analytical chemistry working group of the German Research Foundation's Senate Commission for the Testing of Harmful Work Substances (*Arbeitsgruppe analytische Chemie der Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe*) and approved [45]. The method covers *cis*–(2,2-dibromovinyl)-2,2-dimethyl cyclopropane-1-carboxylic acid (Br2CA), cis- and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane-1-carboxylic acid (*cis*-Cl2CA and *trans*-Cl2CA) and 4-fluor-3-phenoxybenzoic acid (F-PBA) and 3-phenoxybenzoic acid (3-PBA) by gas chromatography / mass spectrometry (GC/MS). The detection limit of 0.5 µg/l for 3-phenoxybenzoic acid using this method is not sufficiently sensitive for use in environmental medicine.

This method can be described as follows (see also figure 3). 10 ml urine are subjected to acidic hydrolysis and a solid phase extraction on RP 18 material. After elution using methanol, the analytes are derivated using a mixture of concentrated sulphuric acid / methanol, extracted using n-hexane and quantified by means of GC/MS. The detectability limits are 0.2 µg/l for *cis*- and *trans*-Cl2CA and F-PBA, 0.1 µg/l for Br2CA and 0.5 µg/l for 3-PBA.

conjugated metabolites in urine (10 ml)

↓ **addition of the internal standard (2-PBA), hydrolysis using 2 ml $H_2SO_{4\ concentrated}$**

free pyrethroid metabolites

↓ **solid phase extraction on RP-18-material**

elution using methanol

↓ **derivation using MeOH/H_2SO_4**

methyl esters of metobolites in MeOH

↓ **extraction using 2 ml n-hexane narrowing under N_2 to ~ 100 µl**

GC/MS

Figure 3: Analysis of pyrethroid metabolites – flow chart

Internal exposure of the general population

Several investigations from the past few years deal with the concentration of pyrethroid metabolites in the urine of population groups, including children, with no occupational exposure to pyrethroids. Most of these studies were carried out in Germany.

The first was a large-scale investigation published in Butte et al. [37]. Urine samples from 254 healthy adults (60 % female) from the region (*Landkreis*) of Pinneberg in the Federal State of Schleswig-Holstein were tested for pyrethroid metabolites. The average age of the test persons was 55 (41-65 years). The investigation included the determination of 3-PBA and of the cyclopropane carboxylic acids, without distinguishing between the *cis*- and *trans*-

isomers of the cyclopropane carboxylic acids. The median values of the group tested lay below the detection limit of 0.2 µg/l, the 95th percentiles were 0.51 µg/l for the cyclopropane carboxylic acids and 0.57 µg/l for 3-PBA (table 4).

Further published studies were able to cover the *cis*- and *trans*-cyclopropane carboxylic acids separately. Hardt et al. [47] conducted tests in 1998 involving 45 adult volunteers from the area of the cities Erlangen and Nuremberg with an average age of 34 years (17-61 years). F-PBA was not detected for any of the test persons, *cis*-Cl2CA and Br2CA were detected for 9 % the participants, and *trans*-Cl2CA for 89 %, with a median value of 0.4 µg/l. The 95th percentiles for *cis*-Cl2CA, *trans*-Cl2CA and Br2CA were 0.6 µg/l, 0.9 µg/l and 0.1 µg/l respectively (table 4).

The largest study so far investigating the determination of pyrethroid metabolite in human urine in Germany was carried out in 1998 in Frankfurt / Main [38]. This study formed part of an environmental medicine investigation of the residents of what used to be “US housing”. When this housing was erected in the 1950’s, flooring adhesives containing PAHs were used, which gave rise to considerable anxiety among the residents in 1997-98 and consequently, human biomonitoring investigations were carried out. As part of this investigation, pyrethroid metabolites were analysed, although pyrethroids were not thought to have been used in the apartments and no carpeting (which might have been treated with permethrin) was present. When the house dust was tested, the only member of the pyrethroid group that was detectable was permethrin, at significantly lower levels than in the representative investigation of the German Environmental Survey [36]. The median, 95th percentile and maximal values in the Frankfurt investigation were < 1 mg/kg, 4.8 mg/kg and 19 mg/kg respectively [38]. The urine samples that were tested were taken from a total of 1177 residents, including 331 children below the age of 6 years and 247 children between 6 and 12 years old. *Cis*-Cl2CA was detectable in 30% of the samples and *trans*-Cl2CA in 60%. The detection rates for Br2CA and F-PBA were 16% and 19% respectively. The 95th percentiles were 0.51 µg *cis*-Cl2CA/l, 1.43 µg *trans*-Cl2CA/l, 0.3 µg Br2CA/l and 0.27 µg F-PBA/l (table 4). The investigation revealed no dependency on age of the test persons nor on the time of year in which the samples were collected [38].

Table 4

Concentrations of pyrethroid metabolites in the urine of persons not occupationally exposed to pyrethroids in Germany – investigations of the general population

Authors [reference] year of study	N	Parameters	LOQ µg/l	% > LOQ	P 50 µg/l	P 95 µg/l	Max µg/l
Butte et al. [37] 1995/96	254	*cis/ trans* Cl2CA	0.2		< 0.2	0.51	11.6
	adults	3-PBA	0.2		< 0.2	0.57	15.6
	(41-65 yrs)	spontaneous urine					
Hardt et al. [47] 1997/98	45	*cis*-Cl2CA	0.2	9	< LOD	0.6	1.6
	adults	*trans*-Cl2CA	0.2	89	0.4	0.9	3.8
	(17-61 yrs)	Br2CA	0.1	9	< LOD	0.1	0.5
		F-PBA	0.2	0	< LOD	< LOD	< LOD
		24-h urine					
Heudorf and Angerer [38] 1998	1177	*cis*-Cl2CA	0.2	30	< LOD	0.51	9.76
	children	*trans*-Cl2CA	0.2	60	0.24	1.43	17.82
	and adults	Br2CA	0.1	16	< LOD	0.30	9.19
	(0-65 yrs)	F-PBA	0.2	19	< LOD	0.27	5.11
		spontaneous urine					
Schettgen et al. [51] 2002	46	*cis*-Cl2CA	0.05	52	0.06	0.29	1.5
	adults	*trans*-Cl2CA	0.05	72	0.11	0.64	3.5
		Br2CA	0.05	13	< LOD	0.17	0.4
		F-PBA	0.05	4	< LOD	< LOD	0.2
		3-PBA	0.05	70	0.16	0.67	1.7
		spontaneous urine					
Becker et al. [39] 2001/2002	396 children (2-17 yrs)	*cis*-Cl2CA	0.1	56	0.11	0.74	13.0
		trans-Cl2CA	0.1	74	0.19	1.73	75.9
		Br2CA	0.1	22	< LOD	0.52	20.9
		F-PBA	0.1	<1	< LOD	< LOD	0.12
		3-PBA	0.1	90	0.29	2.35	19.2
		morning urine					
Egerer et al. [48], 2003/2004	211 adults (19-75 yrs),	*cis*-Cl2CA	0.03	40	< LOD	0.16	2.35
		trans-Cl2CA	0.03	47	< LOD	0.37	3.85
		Br2CA	0.02	28	< LOD	0.14	1.20
		3-PBA	0.02	67	0.04	0.51	3.52
		spontaneous urine					

LOQ = limit of quantification; %<LOQ = proportion of the values below the LOQ; P 50, P 95 = sample percentile; LOD = limit of detection

The results from the pilot study (in the period March 2001-March 2002) to the GerES IV 2003/2006 involving 396 children aged between 2 and 17 years reveal somewhat higher metabolite concentrations in urine compared with the data from Frankfurt (children and adults). The 95th percentiles were 0.74 µg *cis*-Cl2CA/l, 1.73 µg *trans*-Cl2CA/l, 0.52 µg Br2CA/l, <0.1 µg F-PBA/l and 2.35 µg 3-PBA/l (table 4) [39]. The maximal values were significantly higher than those found in the previous studies (table 4). However, the study established that the amounts of

3-PBA and *trans*-Cl2CA contained in the urine decreased significantly (p≤0,001) in correlation with decreasing age of the children, and that the amounts of 3-PBA, *cis*-Cl2CA and *trans*-Cl2CA contained in the urine increased significantly in correlation with increasing permethrin concentrations in house dust [39].

A short while ago, a further study was published [48] involving 211 adult volunteers not occupationally exposed to pyrethroids. The 95th percentiles of the metabolite concentrations in urine were 0.16 µg *cis*-Cl2CA/l, 0.37 µg *trans*-Cl2CA/l, 0.14 µg Br2CA/l and 0.51 µg 3-PBA/l (table 4). With another group of 30 volunteers (21-55 years of age) not occupationally exposed to pyrethroids, only small deviations (between 0.04 and 0.05 µg/l per metabolite) were found between the concentrations in 24 h and 8 h urine samples, morning urine samples or spontaneous urine samples. In other words, according to this study, spontaneous urine sampling seems to provide a good alternative to 24 h urine sampling [48].

Data from specific sampling is available to us from the BMBF studies on indoors pyrethroid exposure described above [26-29] and also from the environmental medicine consultation hours of an Augsburg clinic (*Klinikum Augsburg*) [49, 50]. While the BMBF studies found low exposure levels without exception, individual cases of high exposure levels (see table 5) were found among the environmental medicine patients of the Klinikum Augsburg; the cause of these were found in most cases to be the treatment of parasites in domestic pets [40].

Population reference values for pyrethroid metabolites in urine

In view of the fact that there is a need for reference values for pyrethroid exposure in the population, and since the results on pyrethroid excretion from different investigations in Germany agree very well with one another, the commission has established the following reference values for the general population on the basis of the available data (table 4):

***cis*-Cl2CA**	**1 µg/l**
***trans*-Cl2CA**	**2 µg/l**
3-PBA	**2 µg/l**

Some studies showed pyrethroid metabolite in urine concentrations by volume whose median values were somewhat higher among younger subjects and somewhat lower among older subjects, but this does not apply to the 95th percentiles. For this reason, it was not necessary to establish reference values differentiated by age-group.

Table 5

Concentrations of pyrethroid metabolites in the urine of persons in Germany with no occupational exposure to pyrethroids – individual investigations

Authors [reference] year of study cause	N	Parameters	LOQ µg/l	% > LOQ	P 50 µg/l	P 95 µg/l	Max µg/l
Hardt et al. [49] 1999/2000 environmental outpatients ward Augsburg	59 (23-79 yrs)	cis-Cl2-CA	0.2	34	< LOD	0.6	1.6
		trans-Cl2-CA	0.2	44	< LOD	0.8	1.8
		Br2CA	0.1	39	< LOD	0.3	0.5
		MPBA	0.2	7	0.3	1.4	2.3
BMFT [27], Berger-Preiß et al. [30], 2001 carpeting in apartment	145 residents* 284 samples**	*cis*-Cl2-CA	0.2	7	< LOD	0.5 / 0.2	1.5 / 2.8
		trans-Cl2-CA	0.2	14	< LOD	0.7 / 0.6	2.8 / 5.1
		3-PBA	0.2	19	< LOD	0.9 / 0.9	2.5 / 5.0
BMFT [27], Leng et al. [28], 2001 ; pest control in apartment	61 residents**	*cis*-Cl2-CA*	0.2	7 / 12.5	0.1/0.1	0.5/0.1	1.2/0.7
		trans-Cl2-CA	0.2	? / ?	0.1/0.1	0.1/1.3	1.2/2.1
		DBCA	0.2	? / ?	0.1/0.1	-/0.3	0.1/0.5
		3-PBA	0.2	5 /16	0.1/0.1	0.2/1.8	0.8/2.4
		FPBA	0.2	? / ?	0.1/0.1	-/0.1	0.1
Hardt et al. [50] 1999-2003 environmental outpatients ward Augsburg	348 patients attending the consultations (> 18 yrs)	*cis*-Cl2-CA*	0.2		< LOD	0.8	11.4
		trans-Cl2-CA	0.2		< LOD	1.2	44.8
		DBCA	0.1		< LOD	0.3	1.1
		3-PBA	0.2		0.26	2.0	39.9
Hardt et al. [50] 1999-2003 environmental outpatients ward Augsburg	23 children attending the consultations (< 17 yrs)	*cis*-Cl2-CA*	0.2				6.6
		trans-Cl2-CA	0.2				25.9
		DBCA	0.1				7.1
		3-PBA	0.2				29.2

LOQ = limit of quantification; %<LOQ = proportion of the values below the LOQ; P 50, P 95 = sample percentile; LOD = limit of detection; * sample at intervals up to 12 months;
** before pest control treatment / 6-12 months after pest control treatment

Measures in case of exceeded reference values

In cases where reference values are exceeded, control measurements should be made to check whether the exposure continues to obtain. Values above the reference values that have been reliably measured (and checked several times) should be taken as grounds for undertaking an environmental medicine investigation in search of the source, within reasonable bounds. Apart from cases of accidental poisoning, possible sources include indoors contamination following inappropriate pest control measures (treatment of rooms or of domestic pets) or food contaminated with pyrethroids.

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