

Chronic sequelae and irreversible injuries following acute pyrethroid intoxication

H. Müller-Mohnssen

Physiological Institute, Ludwig Maximilians University, Munich Pettenkoferstr. 6, 80336 Munich, Germany

Accepted 31 January 1999

Abstract

For patients the author has observed, the majority of complaints following an acute pyrethroid intoxication disappeared after the end of exposure. Residuals frequently observed after more than 2 years were: (1) cerebro-organic disorders (reduced intellectual performance with 20–30% reduction of endurance during mental work, personality disorder), visual disturbances, dysacusia, tinnitus; (2) sensomotor-polyneuropathy most frequently in the lower legs; (3) vegetative nervous disorders (paroxysmal tachycardia, pollakisuria, increased heat-sensitivity, orthostatic hypotonia and reduced exercise tolerance due to circulatory disorder). Non-neurological symptoms include deficiency of cellular and humoral immune system established by laboratory findings: opportunistic infections, especially *Candida*-infections of the gastro-intestinal tract, relapsing infections of the urinary and respiratory tract, the latter often aggravating to respiratory obstruction. Most of the patients exhibit positive epi- or intracutaneous test against pyrethroids or pyrethrines, and acquainted sensitivity also to other antigens. Many of these patients exhibit pathological autoimmune diagnostical findings and developed autoimmune diseases as for instance scleroderma-like syndrome, myasthenia-like syndrome with progredient muscle atrophy, autoimmun-hemolysis and autoimmun-thrombocytopenic purpura. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Pyrethroid intoxication; Irreversible residues; Casuistics

1. Introduction

In a collective of 144 adults who had fallen ill after indoor pyrethroid exposure 31 (22%) suffered from acute, 26 (18%) from subacute and 87 (60%) from chronic intoxication (average age 39.6 years; 32% males). In accordance with observations of He et al. (1989), acute and subacute pyrethroid intoxication caused 10–45 days clinical treatment and 2–8 months working incapability (Müller-Mohnssen and Hahn, 1995). After this

period the patients returned to work although recovery was incomplete. In phases of good condition after 14 months, the original physical capability seemed to be completely regained. However, during chemical, mental, or physical stress, the initial symptoms temporarily recurred. In the age group past 40 years the periods of deterioration were extended and the restitution distinctly reduced.

Recently, the question is discussed whether or not acute pyrethroid intoxication after indoor ex-

posure can lead to chronic sequelae or organically manifested irreversible injuries. The present paper contributes to this topic by analyzing of cases of acute poisoning in which the attending physicians had no doubt about the causal relationship between symptoms and pyrethroid exposure.

2. Method.

2.1. Recruitment and selection of patients

In the interest of monitoring of early health disturbances the author informed the German-speaking public about the possible health risk of pyrethroid application by television reports. Due to long geographic distances, the dialogue with the patients was conducted by letter and telephone. By means of a four part questionnaire, the following parameters were documented:

1. anamnesis of exposure, supplemented by laboratory findings,
 2. complaint spectrum recorded by a standardized 97 item questionnaire to neurological neuropsychological and immunological disturbances on a five point Lickert scale (a suitable questionnaire for children is not yet available),
 3. time course of disease was recorded by a telephone anamnesis as well as by the patients self-written or proof-read 'case-report'. For the same purpose the complaint-spectrum was recorded repeatedly in yearly intervals,
 4. medical reports and results of clinical findings.
- A causal relationship between pyrethroid exposure and the exposed subject's complaints was assumed if the following criteria were met by the patient (Müller-Mohnssen and Hahn, 1995):

1. In the case of acute intoxication: a high-concentration exposure due to self-application of insecticides (spraying or brushing) can be documented, or in case of chronic intoxication: pyrethroids are detected in the patient's environment and his or her bodyfluids or tissues: more than 10 mg pyrethroid/kg dust, more than 1.5 µg/l metabolites in urine and more than 1 µg/kg by hair analysis (Hoppe, 1994) (values for permethrin).

2. The clinical picture resembles that of a multitude of patients which have been exposed to the same chemical substance.
3. The influence of insecticides other than pyrethroids is negligible and concomitant diseases were excluded by the physicians in charge.
4. A latency period regularly observed in a multitude of exposed persons: in case of acute intoxication the latency period between a documented exposure and the onset of illness, in case of chronic intoxication the time interval between the end of a permanent exposure and the obvious mitigation of complaints. This time interval keeps within ≈ 2 weeks and is thus better determinable than the indistinctly limited latency which lasts weeks up to years.
5. Other persons simultaneously exposed within the same environment fall ill exhibiting similar symptoms.
6. The strength of the health effects correspond to that of a multitude of patients which have been exposed to a similar dose (dose-effect-relation).

2.2. Evaluation of individual complaint spectrum

The complex complaint spectrum of each patient was graphically reflected, so that it can be grasped 'at first sight' as an optical pattern (Müller-Mohnssen and Hahn, 1995). The answers of patients are creating the actual data material and they provide the first level of analysis. On the second level the 97 items are reduced to 14 functional groups. Each group refers to a disorder of one organ or organ system. Within the individual complaint spectrum the distinctly marked symptom groups are striking for the eyes as those areas, in which the symbols of high ratings are gathered together. Moreover, the profile was numerically evaluated by means of a computer program. A group will be accepted, if its average rating value is equal or higher than 2, corresponding to 'distinctly intense complaints', and if the dominant peaks and valleys of the *R*-profile were imitated by the individual profile (Müller-Mohnssen and Hahn, 1995).

The referring physician is then requested to focus the consecutive clinical examination on the distinctly marked symptom groups accepted in order to prove, whether the organ disorders inferred from the complaints are clinically detectable. The questionnaire analysis thus allows to select and rationalize the further diagnostic procedure necessary to encircle the diagnosis.

2.3. Pyrethroid reference profile

If the criteria of causal relationship (without criterion 2) are met by a patient, he or she is integrated within the pyrethroid reference collective (Müller-Mohnssen and Hahn, 1995). The 'clinical picture' of pyrethroid intoxication is represented by the pyrethroid reference profile which is the result of averaging the individual profiles of a multitude of exposed patients, i.e. of the members of the pyrethroid reference collective. The

individual clinical picture of each newly admitted patient is then compared with the reference profile in order to determine, whether the required similarity according to the second criterion of causal relationship is evident.

2.4. Validity of house dust samplings

To evaluate a tentative diagnosis of pyrethroid intoxication according to the first criterion of causal relationship, the dose of indoor pyrethroid exposure is generally estimated from measurements of the pyrethroid concentration in dust samples collected within the household environment of the respective patient (Schwabe et al., 1994). This could be performed for 92 patients of the pyrethroid reference collective, mainly for those suffering from chronic intoxication (see below). Above 10 mg pyrethroid/kg dust symptoms of intoxication appeared which forced the patients

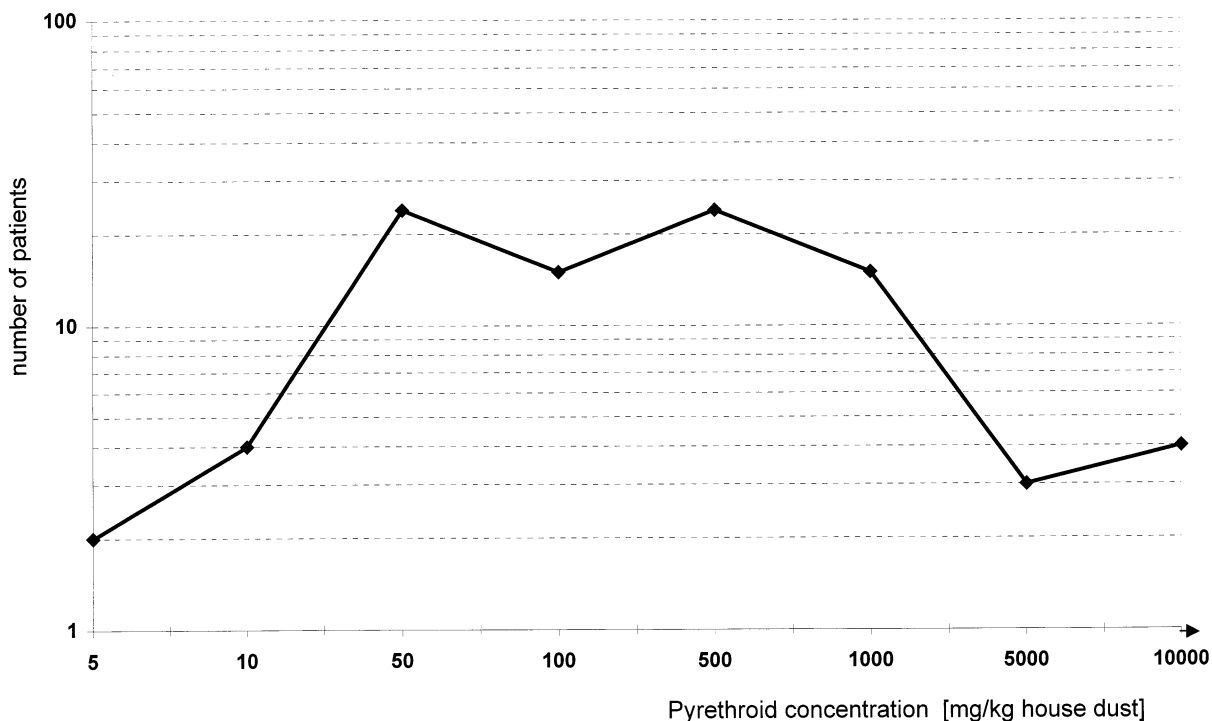


Fig. 1. Distribution of the number of adults having fallen ill during pyrethroid exposure (ordinate), versus house dust pyrethroid concentration of their households. Above 10 mg pyrethroid/kg dust the incidence of illness increases with increasing concentration. Average pyrethroid concentration in this collective: 587 mg/kg dust ($n = 92$). Reference value: 0.22 mg permethrin/kg dust for the households of average German population ($n = 1600$) (Friedrich, 1998).

to take medical advice (Müller-Mohnssen and Hahn, 1995) (Fig. 1). The average pyrethroid concentration in this collective amounts to 587 mg/kg dust. This value exceeds the mean of 0.22 mg permethrin/kg dust measured for the households of 1600 randomly selected adults representative for the average German population by a factor of 2000 (Friedrich, 1998).

3. Results

The house dust probe is an adequate measurement for the height of exposure for persons who are exposed exclusively to agents bound to the house dust. It is not relevant for persons exposed during spray application and who have inhaled the original pyrethroid containing preparation atomized within the air as in the following case.

3.1. Case report: example for progredient toxic eczema, bronchial asthma after inhalative intoxication

A woman (18 years, 70 kg, 169 cm) was accidentally hit in the face from the aerosol of an insecticide containing bioresmethrin and pyrethrines. Immediately after she wiped her face with a wet towel.

Four hours after exposure she suffered from burning sensations of eyes and face, painful irritation of oral and respiratory mucosa, severe coughing, vertigo and disturbed consciousness. The following morning she was somnolent, confused and even after hours difficult to address (comment: in this state of an acute pyrethroid intoxication often the tentative diagnosis of an acute encephalitis is given; see also Section 4.2). On day 4 a periocular eczema had developed, followed by edema of the lids and conjunctivitis with threatening corneal detachment. On day 40 she had to be hospitalized under emergency conditions due to the rapidly expanding contact eczema (Fig. 2c). After 50 days of local corticoid treatment the toxic eczema changed into postinflammatory hyperpigmentation. Due to the inhalation of the insecticide a chronic bronchitis and alveolitis had

developed. On day 67 an asthmatic crisis necessitates again emergency hospitalization.

After 8 months time the residuals of the contact eczema subsided but flamed up again after exposure to light and contact with water. In the morning she suffered from rheumatoid pain and impaired movability lasting for about 1 h. Insecurity of movement, however, endured with trembling, vertigo, and the sensation of falling sideways. She further developed bronchial asthma and suffered from depression, diminished intellectual ability, loss of hair and softening of nails which became pliable and translucent with a yellowish tinge. One molar fell out without causing pain. Her overall condition declined steadily including weight loss to a present 52 kg (Fig. 2d).

3.1.1. Clinical findings after 8 months

Leucocytosis 17 000/ μ l (67% lymphocytes, 27% neutrophils in the differential blood count). Sternal marrow biopsy: reactive peripheral leucocytosis as in chronic inflammation. Bronchial lavage: green alpha haemolitical streptococci, 100 000 germs/ml.

3.1.2. Clinical findings after 11 months

Elevated IgE (150–350 IU). Epicutantest strongly positive to pyrethrin, intracutantest positive to permethrin. She was sensitive to other antigens (acquired cross reactivity induced by the pyrethrine intoxication?). Inhibition of mitogen (PHA-) stimulated T-lymphocyte-proliferation; reduced interleucine production (IL-4), delayed and reduced production of immune interferone IFN gamma; [Diel et al. (1998a), Diel et al. (1998b), Varshneya (1992), Blaylock et al. (1995) for immunotoxic response on pyrethroid exposure reported by other authors].

At the time of exposure the patient was in good health; she had no chronic neurological or immunological illness, no asthma, no individual or family history of diseases.

3.1.3. The following residuals have been established 2 years after the accident

(1) Cellular and humoral immune deficiency. (2) Periocular hyperpigmentation and hypertrichosis in the face, chronic conjunctivitis, alopecia areata.



Fig. 2. Progreident toxic eczema following dermal contact with a sprayed insecticide containing bioresmethrin and pyrethrines; (a) 17 days before the accident; (b) 5 days; (c) 38 days; (d) 6 months after the accident.

(3) chronic purulent bronchitis and alveolitis, progreident severe bronchial asthma. Suspicion of peripheral and central nervous system involvement was rated secondary in importance and awaits further investigation.

For the time during and immediately after spraying, solely indoor air sampling would provide information on the extent of exposure. Because spray missions do not happen under conditions of

planned experiments, the quantities governing the pyrethroid concentration in the breathing air (distance of spray device from the head, duration of spraying, space and ventilation of the room a.s.o.) has to be determined in detail by statements from the patient, referring physician, pest controller, property management and the height of acute exposure and the intake during spray application calculated on the basis of model experiments.

3.2. Description of decrease of room air concentration after spraying in model experiments

Model experiments show, that the agents are transferred from the air to the solid components (Class and Kintrup, 1991; Willeke et al., 1993; Matoba et al., 1994; Walter et al., 1994; Miyamoto, 1995). The decrease of room air concentration c (Class and Kintrup, 1991) (Fig. 3) can per chance be subdivided into three phases, described by a series of three exponential functions with different decay constants similar to radioactive decomposition series [Fig. 3 derived from Class and Kintrup (1991), for principles of quantitative description see Willeke et al. (1993)].

General form of equation: $c = \exp(a + bt)$

a ; load constant, dependent on the starting con-

centration, b : decay constant dependent on sedimentation and elimination of the agents from the room by means of cleaning and airing; for the quasistationary phase the decay constant depends on the persistency of agents; t : time.

Application phase 0–60 min

$$c_1(t) = c_0 \exp(6.25 - 0.039t) \quad (t) \text{ min}, \quad c_0 = 1 \text{ } \mu\text{g}/\text{m}^3 \quad (1)$$

time constant ($1/b$) = 26 min, half value time HVT ($\ln 2/b$) = 18 min [regression with experimental data from Class and Kintrup, 1991].

Sedimentation phase 60–14 400 min (9 days)

$$c_2(t) = c_0 \exp(3.93 - 0.00027t) \quad (t) \text{ min}, \quad c_0 = 1 \text{ } \mu\text{g}/\text{m}^3 \quad (2)$$

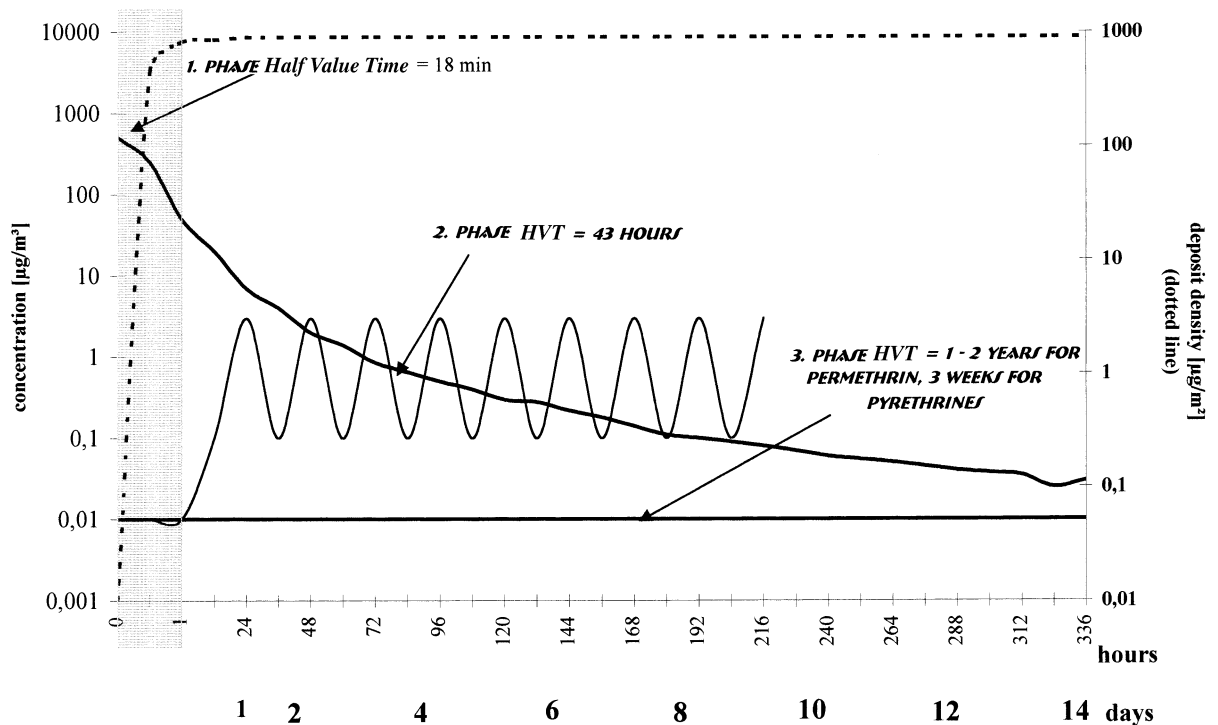


Fig. 3. Exchange transfer of agents between room air and solid components of the room after spray application. Solid curve: time course of decrease of room air concentration. Dotted curve: time course of increase of surface deposit density (schematically, the mirror inverted shape could be seen in linear plot only, for the application phase, first hour, the time scale is enlarged). The decrease of room air concentration during the quasi-stationary phase (half value time of up to 2 years for permethrin) is represented by the horizontal solid line which extends the curve for the time span of more than 2 weeks. Oscillating curve: average room air concentration due to nightly application of an electro evaporator (schematically).

time constant = 3704 min (62 h), HVT = 2567 min [43 h, regression with experimental data from class Class and Kintrup, 1991]. The correlation coefficient amounts to 0.99, indicating that the e -function is suitable to describe the curve measured for application and sedimentation phase.

Quasi-stationary phase > 14 400 min (> 10 days)

$$c_3(t) = c_0 \exp(-1.139 - 0.061t) \quad (t) \text{ months, } c_0 = 1 \text{ } \mu\text{g}/\text{m}^3 \quad (3)$$

time constant = 16.4 months, HVT = 11.4 months (example of a real case).

The values of decrease of room air concentration during the quasi-stationary phase are not derived from the above mentioned experimental results but from series of house dust probes from a real case. The values are calculated under the assumption that the load of airborne dust and that of deposited dust is the same and that the respective concentration values can be converted into each other. For a permethrin concentration of 10 mg/kg house dust and an airborne dust pollution of 1 mg/m³ the indoor air concentration amounts to 10 ng/m³.

The first 24 h after application are characterized by the highest room air concentrations. For reasons of estimation of patient exposure under real circumstances and diverging from the quantitative description, the first 24 h are summarized as initial phase and the sedimentation phase is counted as the time span from day 1–10. In the following the mechanisms underlying the decrease of room air concentration will be described qualitatively.

3.2.1. Initial phase of 24 h duration

In model experiments peaks of the space average pyrethroid concentration 'up to 300 µg/m³ and more' were found in the room air immediately after application of a cyfluthrin spray in a room of 20 m² floor and 50 m³ air volume (Class and Kintrup, 1991). The rooms in which the majority of our patients was exposed, were smaller (bedroom, kitchen, student hostel as well as lavatory and galley in air planes) and the distance between face and spray device frequently was less than 1 m (arm's length in case of self

application) and the pyrethroid concentration of the breathing air thus considerably higher than the average room air concentration. Therefore, the calculation was started with an initial inhaled air concentration estimated to 500 µg/m³. Due to sedimentation of the aerosol droplets, this initial concentration rapidly decreases to 50% in 18 min and falls below 10% after 1 h (Class and Kintrup, 1991, table 4).

3.2.2. Sedimentation phase of approximately 9 days duration

During the following sedimentation phase the room air concentration further decreases from ≈ 10 µg/m³ to values corresponding to the respective pyrethroid concentration in the house dust, i.e. to ≈ 0.1 µg/m³ for 100 mg/kg and 1 mg/kg airborne dust pollution; the half value time amounts to 2 days (Fig. 3, solid curve). Mirror inverted to the decrease in room air concentration the surface concentration increases to 1000 µg/m² or even more (dotted curve, schematic). The sedimented aerosol droplets form opalescent precipitation layers on the surfaces of objects placed in the room. Therefore the wiping probe is relevant for the exposure during the sedimentation phase. From these layers the agents diffuse into permeable materials (textile, wood, paper, plastics, paints).

3.2.3. Quasi-stationary phase > 10 days

Cleaning of surfaces inverts the concentration gradient of the agents normal to the surfaces, so that they diffuse back from the interior of the material to the surfaces. From here they distribute over the room on two different ways: (1) by contaminating the deposited dust particles which directly contacts the surface. Whirled up these particles contribute to the airborne dust; (2) by vaporization the agents redistribute molecularly over the air and precipitate on surfaces of primarily uncontaminated materials. Because of their strong affinity to surfaces pyrethroids are eagerly accumulated, mainly by fibrous materials characterized by a high surface:volume ratio, by textile garments, for instance, from which a dermal intake is possible (Gebefügi, 1989; Gebefügi et al., 1992) and by dust particles, which can be inhaled.

Table 1
Average pyrethroid volume concentration of room air as function of time

Day	1	2	3	4	5	6	7	8	9	10
c_{av} ($\mu\text{g}/\text{m}^3$)	284 (First hour) 43 (23 h)	29	20	14	9	6	4	3	2	1.5

In spite of the vapor pressure being extremely low, the pyrethroid concentration of the secondarily contaminated materials can increase to the values known from house dust probes (Fig. 1). During this quasi-stationary phase the room air concentration decreases slowly with a half value time of up to 2 years for permethrin. This long half value time of elimination originates from the high persistency of pyrethroids. During the initial and sedimentation phase, however, the changes of concentration are governed by sedimentation processes so that the influence of persistency is negligibly small. For pyrethrines a half value time of 3 weeks can be derived from the values of Berger-Preiß (1997). Application of pyrethrines instead of pyrethroides is, therefore, of no advantage for persons who are exposed during initial and sedimentation phase.

3.3. Estimation of inhalative intake

To obtain an estimate of the pyrethroid dose received by an adult person via inhalation Eqs. (1) and (2) were applied to calculate average room air volume concentrations on the basis of the following assumptions: (1) respiratory rate = 20 l/min; (2) respiratory volume = 0.5 l/breath \Rightarrow 0.6 m^3/h (3) 100% resorption of the pyrethroids in the lung (excretion and metabolism neglected).

For each time interval considered the average volume concentration c_{av} was calculated as arithmetic mean of the concentrations at the begin and the end of this interval. With the exception of the first day the time intervals are taken as one day. The first day was bisected into the first hour (governed by Eq. (1)) and the remaining 23 h (governed by Eq. (2)). The results are listed in Table 1. Under the assumption that the inhalative intake of pyrethroids into the organism is proportional to the room air concentration and to time, the daily inhalative intake was obtained by multi-

plying these concentrations with the corresponding respiratory volumes as presented for 0.6 m^3/h in Table 2 (see Fig. 4 for the total inhalative intake as function of time). For an initial room air concentration of 500 $\mu\text{g}/\text{m}^3$ the intake for the first day amounts to 784 μg and then the daily intake decreases continuously. If the respiration is slightly enforced due to hard work the intake considerably increases (for instance to 1018 μg at 0.55 l/breath and 24/min \Rightarrow 0.8 m^3/h). After 3 weeks, i.e. during the stationary phase, the daily inhalative intake attains a nearly constant value. This value is calculated to be \approx 0.5 $\mu\text{g}/\text{day}$ for an adult of 60 kg body weight at a residual load of 100 mg/kg house dust (Fig. 4, lowest curve).

3.4. Dose-effect-relation

During the initial phase the intake per day is thus 1600–2000 times higher than during the stationary phase. A well defined parameter for the strength of the health effects is the latency period (the time interval from the beginning of the exposure till the effects exceed the threshold of perception), because its measurement requires only a yes/no decision from the patient. The latency of the intoxication disease increases with decreasing dose rate (dose/time).

3.4.1. Acute onset of symptoms

The shortest latency periods (minutes up to a few hours) and the most severe intoxication symptoms have been observed after an inhalative exposure during self application or presence during spraying pyrethroid-containing insecticides without protection of respiratory tract and skin.

3.4.2. Subacute intoxication

Subacute intoxication due to medium exposure during the sedimentation phase is characterized by a silent 'incubation period' of 3 days on the

average and an acute polyneuritis as the primary disease [chronic intoxication after exposure during quasi-stationary phase is described elsewhere (Müller-Mohnssen and Hahn, 1995)].

Subacute intoxication has been observed: (1) in persons, who enter rooms within two days after a spray mission if not aired and especially in persons who cleaned the furnishings from the sedimentation film of insecticide agent without protection of respiratory tract and skin (see casuistic number 3); (2) in persons who have used electro-evaporators in distances less than 50 cm from the face so that the pyrethroid concentration of the breathing air is considerably higher than the average room air concentration.

3.5. Case report: example for neurological residuals after subacute intoxication

A 48-year-old internal specialist (77 kg, 182 cm) used electric evaporators with bioallethrin as active agent at night in distances of 3 m during the summer of 2 years. During one night in July 1992 the distance between device and face was only 50 cm.

After a symptom-free interval of 3 days, tingling, sensations of burning and numbness on fingers and toes appeared, spreading within a few days over hands and feet to distal lower leg and forearm. The sensibility disorder was so grave, that the patient feared becoming incapable of work. Movement disorders surfaced, and while trying to catch a bus the patient stumbled and fell. Pronounced tiredness, exhaustion were attributed to overwork. Neurographic and myographic findings of an university hospital verified a sensomotoric polyneuritis (neurographic: reduced velocity of nerve conduction, myographic: neurogenous transformation, deficit of activation). After 3–5 weeks the complaints started to alleviate. During August 1994 the patient tried to

use a pyrethroid electro evaporator again within a distance of 3 m. After one night application perception disorders reappeared similar to the intoxication symptomatic in strength and extension but without the movement disorder. These disturbances disappeared within 2 days.

3.5.1. Residuals after 6 years

Intermittent paresthesia in ulnar area of forearm bilateral and par- and hyperesthesia in the plantar area of the toes: ‘walking like on cotton wool’. Neurographic and myographic controls performed by the same hospital revealed unchanged pathological values and led to the diagnosis of a sensomotoric PNP with axon involvement. Numbness, hyperaesthesia and spontaneous pain in the affected region increased during the last 2 years and represent a noticeable handicap (Besch, 1996).

4. Discussion

4.1. Acquired non-specific intolerance to chemicals (AIC)

Since January 1995 the problem of ‘multiple chemical sensitivity’ has been discussed in Germany (Altenkirch, 1995; Lohmann et al., 1996). In the cases of the author’s observations this disease began with a high-dose exposure to pyrethroid insecticides with clinical signs of intoxication (Müller-Mohnssen, 1996). In most of these cases the neurotoxic syndrome is followed by an intolerance of chemicals with an interval of 2–4 months and reaches a maximum when the neurologic symptoms are either no longer electrophysiologically present or when they have reached the stationary level of defect healing and then the intolerance subsides very slowly.

Table 2
Daily intake µg/person of pyrethroids by inhalation

Day	1	2	3	4	5	6	7	8	9	10
Intake (µg)	784	418	288	202	130	86	58	43	29	22

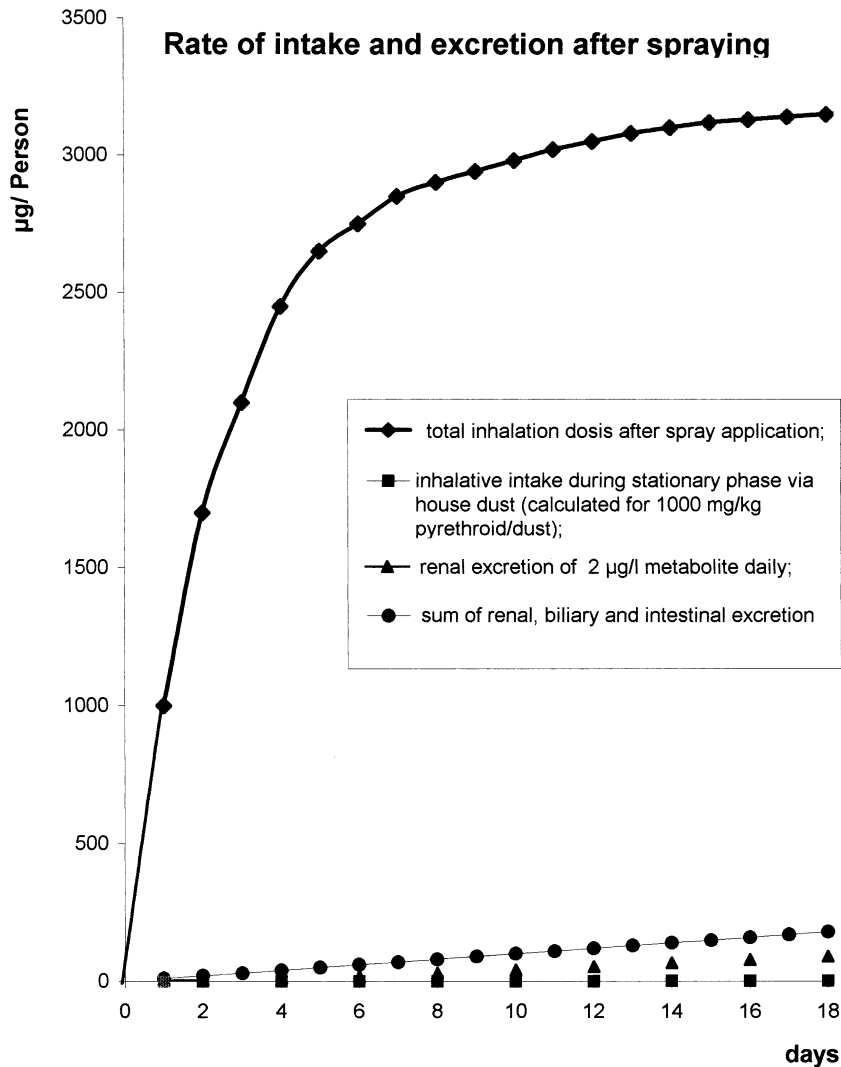


Fig. 4. Rate of inhalative intake during the initial and sedimentation phase after spray application calculated on the base of Eqs. (1)–(3) (uppermost curve; see text for further explanation).

4.2. Case report: example for neurological residuals after subacute intoxication with development of AIC

The apartment of a physician (male, 38 years, 64 kg, 186 cm) was treated by pest controller with an insecticide containing pyrethrum and permethrin. After 36 h the patient cleaned his premise without protection of skin and respiratory tract. After a period of 8 days he experienced 'pins and

needles', tingling and burning sensations in the feet, followed by rheumatgia-like pain in the extremities, especially in the calves. After further 3 days the symptoms subsided, but after a silent period of 1 week (15th day after exposure), they recurred. The much more pronounced par- and hyperaesthesia starting in the toes and extending to the hips over a period of three days were accompanied by fasciculations, muscle cramps and violent pains in the legs. Similar symptoms

appeared on the hands and fore arms though not as distinct as at the lower extremities. The general condition was disturbed by dizziness, inability to sleep, outbreak of sweat, depressive mood in connection with anxiety attacks never experienced before, accommodation disorders lasting several seconds, strong perspiration, sensibility to cold, tachycardia, dry mouth, and occasional perioral paraesthesia. After an exposure period of 4 weeks the patient became unfit to work. On the order of a colleague who supposed a causal relationship between the insecticide exposure and the occurrence of the symptoms the household dust of the apartment was investigated; it contained 470 mg/kg permethrin. A neurological university hospital established the diagnosis of a 'neurographically ascertained insecticide triggered intoxication'. The patient became stationary; subjectively the symptoms got better and the neurographic condition improved. After a period of 4 months and 1 week, the patient experienced his first attack of acquired intolerance of chemicals (AIC): 15 min after a 20 min stay in a carpet shop, the symptoms of initial disease suddenly recurred in the same strength. After 1 week the patient had recovered.

One year after intoxication, the sequelae were lowered to a 20% level with a tendency to further improvement and the AIC reactions became less frequent and severe. After 2 years the residuals of polyneuropathy (sock-shaped hyperesthesia) had attained a constant level, but beside a slight intolerance of alcoholic drinks the patient could ignore the danger to meet AIC attacks.

4.2.1. Residues after 4 years

Following an 8 day stay in a vacation domicile the patient was suddenly hit by strong pain and hyperesthesia in the lower and upper extremities combined with the symptoms of the original intoxication disease and the feeling of severe illness. Next day he found a device continuously evaporating dichlorvos. Ten days after this AIC episode he had recovered.

In the majority of the authors own cases this abortive and compensated form of acquired intolerance of chemicals (AIC) could be observed. Only in three cases did the decompensated form appear. Because the AIC is phase-shifted to neu-

rologic symptoms, the physician can easily miss the toxic genesis when confronted with a patient showing the full clinical picture of AIC. Definitions like: 'the hypersensitivity is triggered by minute levels of threshold concentrations which do not cause any sensations in the general population' (Altenkirch, 1995), can lead the physician to an erroneous evaluation of the situation:

1. The acquired chemical intolerance (AIC) could be mistaken for a pre-existing hypersensitivity in the usual literally sense of the word as a tendency to overreact to weak stimuli as observed for instance in allergic persons. In accordance with the observations of other authors the author's allergic patients regularly succumbed earlier and more severely to intoxication symptoms than their non-allergic relatives and colleagues after the same exposure to insecticides (Diel et al., 1998a). The same holds true for persons with lower than average weight and other inborn or acquired deficiencies in their resistance, like condition after neurologic injuries (brain damage), neurologic diseases (epilepsy), and infection diseases during exposure and preload through other biocides. If these groups are included, the number of 'hypersensitive' persons adds up to over half of the urban population in Germany.
2. From this pre-existing hypersensitivity the acquired nonspecific intolerance of chemicals (AIC) following, but not preceding, an intoxication with insecticides has to be strictly discriminated. Apart from the symptoms of a chemical intolerance, neurological symptoms are often to be found as residues of a neurotoxic damage, indicating that in these cases the intolerance reactions should not be interpreted as an independent disease but as accompanying symptoms expressing an intoxication through neurotoxic substances. Therefore, the AIC is to be distinguished, moreover, from MCS analog to the suggestion of Fukada to reserve the term chronic fatigue immunodysfunction syndrome (CFS) to cases in which this syndrome appear idiopathically and not as side effect of neurotoxic diseases or of exhaustion (Fukada and Strauss, 1994).

The pathophysiological mechanisms by which a minute amount of chemicals differing widely in their chemical composition can trigger an AIC reaction are a cause of controversy. Talking to patients who are themselves physicians, one is reminded of an analogy which probably can help understanding the genesis and therapy of the AIC and which in itself is compatible with other hypotheses. Many individuals who have suffered from fish poisoning, for instance, know that the symptoms of the endured intoxication like blood congestion in the head, vertigo, tachycardia, sudden perspiration, nausea, and vomiting can be provoked even years after the initial event by, for example the smell of train oil or other stimuli reminiscent of the circumstances of the initial poisoning. The organism seems to develop a connection of highly sensitive sense organs with peripheral effector organs so that a conditioning takes place in which certain chemical stimuli provoke reflectorily an attack of intolerance, coded as a new poisoning event (Shusterman et al., 1988; Müller-Mohnssen, 1996). For patients exhibiting hyperosmy, olfactory stimuli are made responsible; prodromal symptoms, however, also often consists in burning sensations of the skin and in these cases dermal stimuli might be considered. The shortness of duration of an AIC attack (minutes up to few hours) show, that the symptoms of the AIC are no expression of organ injury triggered by a repeated intoxication but that they are an intrinsic warning signal against a renewed organ injury.

An AIC attack is such a threatening event for the patients that their first step is to avoid all situations which remind him/her of the circumstances of the intoxication accident. Only then as a second step they try to find the best acceptable middle way between avoidance and regain of his/her usual habitat. According to our own observations, however, the probability of not suffering

from an AIC attack under expected provocative situations is much higher than the contrary and the patient could avoid further exposure after experiencing prodromal symptoms. This is the chance for the patient to test environment and to regain step by step his original habitat. The patient will 'forget' the chemical intolerance similar to a vanishing conditioned reflex.

Though the concepts of therapy of the AIC on one hand and the therapy of neurological, immunological or other organic manifestations of the intoxication on the other differ, the elucidation of the toxicological base of the event is a prerequisite for both. (1) Identification and elimination of the causative agents is the basic therapy. (2) The elucidation of the suspicion of a possible toxicological genesis has a soothing effect on the patient. He regains clarity and is able to act rationally (decontamination of the premise and therapy of the basic disease). However, if the physician considers him to be simulating disease or hunting after pension without checking out the possibility of a basic intoxication, in short, if he accuses him of deception, he proscribes him in society, he hurts him personally and, since the cause of the AIC left unclear, he provokes anxiety. Such circumstances inhibit the regain of the habitat. To alarm the patient against a life 'ruined by poison' is also likely to perpetuate the conditioning of an AIC. If not hindered by such interferences, most of the patients are able to lead a life largely free of AIC symptoms 2 years after the initial intoxication.

4.3. Indication of dermal intake

According to the phase of a persons exposure pyrethroids produce diseases of different latency, clinical picture and degree of severity. During each of the phases following the application the agents are distributed differently over the gaseous

Fig. 5. Compartment syndrome with toxic necrosis within 12 h after dermal contact of a permethrin-containing wood protective: (a) primary compartment syndrome, state of the right foot on emergency admission (puncture prick of pressure measurement above ankle joint); (b) site after operative pressure release and necrectomy of colliquative, sludgy disintegrated muscle, fatty and tendinous tissue of the tibialis anterior compartment (site of lancing of the tibial ridge compartment is not shown); (c) surgical wound in the region of extensor compartment of the left forearm 1 week after covering the gaping wound by means of mesh grafts from the right thigh; (d) local residues after 2 years.



Fig. 5.

and solid constituents of the room and, consequently, enter the organism at different sites in quantities depending on the respective bioavailability.

In persons exposed to pyrethroids a renal excretion of pyrethroid metabolites was detected analytically with a lower limit of determination ranging between 0.5 and 1.0 $\mu\text{g/l}$ urine (Hoppe, 1994; Leng et al., 1996a,b). Excretion measurements showed, that local application of pediculicides induces a dermal intake of up to 10% (Butte, personal communication). In many patients exposed to a load of more than 100 mg/kg house dust during the stationary phase a continuous renal elimination of pyrethroid metabolites found in concentrations of larger than 1.5 $\mu\text{g/l}$ urine (Hoppe, 1994). For a metabolite concentration of 2 $\mu\text{g/l}$ and 1.5 l urine per day the renal excretion of metabolites attains 3.0 $\mu\text{g/day}$ compared to 0.5 μg inhalative intake (Fig. 4). Because metabolites like chrysanthemum acid represent only one half of the complete pyrethroid molecule the daily renal elimination corresponds to 6.0 $\mu\text{g/l}$ pyrethroids. Considering that beside of renal also biliary and intestinal excretion of nearly the same order of magnitude takes place, a renal elimination of 2 $\mu\text{g/l}$ metabolites indicates a total elimination of about 10 μg pyrethroides per day (Fig. 4). This value is a factor of 20 greater than the inhalative intake (0.5 μg) suggesting, that under the low exposure during the stationary phase a dermal intake takes place, presumably by secondarily contaminated textile garments (Gebefügi, 1989; Gebefügi et al., 1992).

These results suggest, moreover, that a contact with heavily contaminated surfaces during the initial or sedimentation phase induces a high dermal intake, particularly if the persons use cleaning agents and fat or oil containing cosmetics. Detergents and fat may enhance the dermal bioavailability of high lipophilic agents similar to that of oral bioavailability. By an acute pyrethroid exposure the skin is frequently injured (Section 3.1), so that its barrier function may be impaired and the dermal intake expected to be still higher. Consequences of high dermal perfusion without visible skin injuries will be demonstrated by the following case report.

4.4. Case report: example for toxic myonecrosis with irreparable residues after local permethrin contact

A woman (37 years, 63 kg, 160 cm) accidentally spilled a permethrin-containing wood protective over her left forearm and hand as well as over her right lower leg and foot. She washed the agent off and took a medical oil bath with soybean oil as additive.

Next morning she woke up due to unbearable pain in the contaminated regions. She was disorientated, confused, became giddy and collapsed while she dragged herself to the neighbour for help. Findings on emergency admission: somnolent, agitated patient, memory gap for the period around the accident (somnolency lasted 2 weeks), severe pain and pain on pressure with extensive swelling of the regions contacted with the insecticide, i.e. back of the hand, spreading to the forearm as well as back of the foot spreading to the lower leg (Fig. 5a). Pressure of 70 mm mercury of the tibialis anterior compartment combined with acute renal failure (Crush syndrome) led to the diagnosis of a toxic necrosis with accompanying primary compartment syndrome. Operative pressure release was made at once by spacious lancing also of the tibial ridge compartment (Fig. 5b) and of the extensor compartment of the left forearm (Fig. 5c). Postoperatively the necrotic histolysis progressed under further swelling and violent attacks of pain. Necrectomy of colliquative, sludgy disintegrated muscle, fatty and tendinous tissue required a series of operative interventions during the following days. Up to present 12 plastic operations were performed to cover the gaping wounds by means of mesh grafts from the right thigh and to sustain a minimal mobility by detaching the adhesions between skin, sinews and bones.

4.4.1. Local residues after 2 years

The left hand is almost immobilized. Only wagging motions of the right foot are possible (Fig. 5c). General residues: impaired memory, persistent headache, disequilibrium, blurred vision due to disturbances of accommodation, inability to work up to now.

The development of the compartment syndrome in this patient can be explained as follows. Due to the oil additive and further supported by the heat of the bath the transport of the lipophilic permethrin into the subjacent muscle tissue was presumably highly increased. One of the immediate local effects of pyrethroids, a vasospasm (Class and Kintrup, 1991), is followed by an ischemia, which is known to produce a compartment syndrome. Pyrethroids are membrane poisons acting on membranes of all cells. Permethrin in particular enhances the passive influx of sodium ions (Na^+) into the resting cell similar to veratridine as shown by membrane depolarisation of Ranvier nodes of isolated nerve fibres (author's results, unpublished). In attempting to compensate the enhanced passive Na^+ influx the cell elevates the active outward transport of Na^+ . This can lead to a break down of the cell metabolism already imbalanced by the ischemia and finally to necrosis (cell damage resulting from the enhanced Na^+ influx was the reason to discard the use of veratridine as local anesthetic). In the forearm and the lower leg particularly an edematous swelling, preceding the ischemic necrosis of the muscle tissue, enhances the pressure within the facial space and increases the ischemia by vascular compression in a vicious circle. The severity of the injuries in this patient is ultimately a consequence of the particular localization of the pyrethroid contact as well of the oil bath enhancing the dermal bioavailability.

References

- Butte, W. Personal communication.
- Altenkirch, H., 1995. Multiple chemical sensitivity (MCS) syndrome. *Gesundh. Wes.* 57, 661–666.
- Berger-Priß, U.A., 1997. The behaviour of pyrethroids indoors: a model study. *Indoor Air* 7, 248–261.
- Besch, W., 1996. Polyneuropathie und Pyrethroide: gibt es einen Zusammenhang? *Oekologisches Ärzteblatt* 2 + 3, 114–117. siehe auch Gegendarstellung und Schlußwort in 4, 141 (1996).
- Blaylock, B.L., et al., 1995. Suppression of immune response in BALB/c mice following oral exposure of permethrin. *Bull. Environ. Contam. Toxicol.* 54, 768–774.
- Class, T., Kintrup, J., 1991. Pyrethroide als Haushaltsinsektizide; Analyse, Innenraumbelastung, Persistenz. *Fres. Zschr. Anal. Chemie.* 340, 446–453.
- Diel, F.M., Detscher, M., Schock, E.M., 1998a. In vitro effects of the pyrethroid S-bioallethrin on lymphocytes and basophiles from atopic and nonatopic subjects. *Allergy* 53, 1–8.
- Diel, F., Detscher, M., et al., 1998b. Effects of permethrin on human basophils and lymphocytes in vitro. *Inflamm. Res.* 47 (Suppl. 1), 11–12.
- Friedrich, K., 1998. Pyrethroide im Hausstaub der deutschen Wohnbevölkerung Ergebnisse zweier bundesweiter Querschnittsstudien. *Gesundheitswesen* 60, 95–101.
- Fukada, K., Strauss, S.E., 1994. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann. Int. Med.* 121, 953–959.
- Gebefügi, I., et al., 1992. Anreicherung von Bioziden in Innenräumen; in: *Schadstoffbelastung in Innenräumen, Kommission Reinhaltung der Luft im VDI und DIN 19, 229–233.*
- Gebefügi, I., 1989. Chemical exposure in enclosed environments. *Toxikol. Environ. Chem.* 20–21, 121–127.
- He, F., Wang, S., Liu, L., Chen, S., Zhang, Z., Sun, S., 1989. Clinical manifestations and diagnosis of acute pyrethroid poisoning. *Arch. Toxicol.* 63, 54–58.
- Hoppe, H.W., 1994. Biomonitoring bei Pyrethroid-Exposition, Nachweis von Pyrethroid-Metaboliten im Harn; in R. Schwabe u.a.: *Pyrethroide im Hausstaub, WABOLU-Heft 3, 103–111.*
- Leng, G., Kühn, K.H., Dunemann, L., Idel, H., 1996a. Gaschromatische und massenspektrometrische Methode zum Nachweis ausgewählter Pyrethroidmetabolite im Urin. *Zbl. Hyg.* 198, 443–451.
- Leng, G., Kühn, K.H., Idel, H., 1996b. Biological monitoring of pyrethroid metabolites in urine of pest control operators. *Toxicol. Lett.* 88, 215–220.
- Lohmann, K., Pröhl, A., Schwarz, E., 1996. Vielfache Chemikalienunverträglichkeit (Multiple Chemical Sensitivity Disorder) bei Patienten mit neurotoxischen Gesundheitsstörungen. *Gesundh. Wes.* 57, 322–331.
- Matoba, Y., Hirota, T., et al., 1994. An indoor simulation of the behaviour of insecticides supplied by an electric vaporizer, *Chemosphere* 28, 435–451 (1994).
- Miyamoto, J., 1995. Chemistry, Efficacy, Uses, Risk/Benefit relationship; Presentation in Toxicology forum. Oxford, 21.3.
- Müller-Mohnssen, H., Hahn, K., 1995. Über eine Methode zur Früherkennung neurotoxischer Erkrankungen (am Beispiel der Pyrethroid-Intoxikation). *Gesundh. Wes.* 57, 214–222.
- Müller-Mohnssen, H., 1996. Leserbrief in *Gesundh. Wes.* 58, 415–416 zu H. Altenkirch: 1995. Multiple chemical sensitivity (MCS) Syndrom. *Gesundh. Wes.* 57, 661–666.
- Schwabe, R. et al. 1994. Pyrethroide im Hausstaub, Eine Übersicht im Auftrag des Umweltbundesamtes. *WABOLU-Heft 3.*

- Shusterman, D., Balmer, J., Cone, J., 1988. Behavioral sensitization to irritants/odorants after acute overexposure. *J. Occup. Med.* 30, 565–567.
- Varshneya, C., 1992. Immunotoxic responses of cypermethrin, a synthetic pyrethroid insecticide in rats. *Ind. J. Physiol. Pharmacol.* 36, 123–126.
- Walter, G., Keller, R., Beckert, J., Butte, W., 1994. Anreicherung von Bioziden in Innenräumen am Beispiel der Pyrethroide. *Zbl. Hyg.* 195, 450–456.
- Willeke, K.K., Baron, P.A. (Ed.), 1993. *Aerosol Measurement, Principles, Techniques and Applications*, New York.