



Severe pulmonary toxicity associated with inhalation of pyrethroid-based domestic insecticides (Bop/Sapolio): a case series and literature review

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Purpose of review

The current review focuses on serious pulmonary toxicity after inhalation of over the counter available pyrethroid-based insecticides. Pyrethroid is a synthetic product of pyrethrin, which in turn is the active ingredient of pyrethrum, a flower extract.

Recent findings

On the contrary, a large gap of knowledge exists in the association of interstitial lung disease (ILD) with pyrethroids. So far, two cases of ILD, one associated with pyrethrin and one associated with pyrethrum, were described. Existing literature on both other (pulmo)toxic effects of pyrethroids in human and animals is summarized.

Summary

We present three cases of severe pulmonary toxicity after inhalation of pyrethroid-based insecticides demanding hospitalization and oxygen therapy. One of these cases died. Although a causal relationship was hard to establish, these cases all demonstrated an obvious history of (repeated) pyrethroid exposure associated with ILD. Moreover, other causes of ILD as well as infections were excluded. Furthermore, studies in mammals as well as aquatic animals confirm (pulmonary) toxicity of pyrethroids. The occurrence of toxicity is dose-dependent but also associated with individual susceptibility. Therefore, we would like to acknowledge that awareness of potential hazards of commercially available insecticides containing pyrethroids to both medical physicians and the public is mandatory.

Keywords

herbicides, interstitial lung diseases, pesticides, pulmonary toxicity, pyrethrin, pyrethroid, pyrethrum

INTRODUCTION

Interstitial lung diseases (ILDs) are a heterogeneous group of diffuse parenchymal pulmonary diseases encompassing a large number of conditions, with a wide range of causes, clinical manifestations, and imaging and pathological features. ILDs related to environmental exposures, include pneumoconiosis due to inhalation of inorganic substances and hypersensitivity pneumonitis mostly related to inhalation of organic particles (e.g. domestic or occupational exposure) [1*,2].

ILD often present a diagnostic challenge and a multidisciplinary approach is warranted [1*].

Within 1 year (2019–2020), three cases of severe pulmonary toxicity after inhalation of pyrethroid-based insecticides Bop/Sapolio were admitted to the Department of Pulmonology of the Curaçao Medical Center, Dutch Antilles. A detailed description of these cases will follow. Bop is a widely available domestic insecticide used against flying and

crawling insects [3]. The active ingredients are tetramethrin, D-allethrin, cypermethrin, MGK and piperonyl butoxide [3–5]. It is claimed the number

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KEY POINTS

- This case series emphasizes the potential hazards of domestic pyrethroid-based insecticides and highlights the importance of a thorough exposure history for example, occupational and environmental exposures.
- As the mechanisms of chemicals like pesticides are comparable with drugs, drug-induced ILD could be expanded to xenobiotic-induced ILD.
- Awareness can avoid a diagnostic delay and in turn, a progressive course of the pulmonary toxicity.
- In future studies next to 'personalized medicine' also 'personalized toxicity' should be taken into account for diagnoses and treatment.

one brand in the Caribbean, also recently introduced in Latin-America and is soon to be released in the United States [3]. Sapolio roach killer is also a domestic insecticide spray used mainly against cockroaches and other crawling insects. Its vapors are claimed to penetrate corners where insects hide [5]. The ingredients are imiprotrin, D-cyphenothrin, coadjuvants and inerts [5]. These insecticides are difficult to use, because for safety measures rooms should be ventilated, but to be more efficient in killing insects the manufacturer of Bop advises to close all windows and doors [3].

The main ingredients of both domestic insecticides Bop and Sapolio belong to the group of pyrethroids, a synthetic form of pyrethrin. Pyrethrin is the active ingredient of pyrethrum, which is a natural extract of the African *Chrysanthemum cinerariaefolium* flower [6]. Pyrethroids are a class of highly effective, broad-spectrum biodegradable synthetic pesticides [7]. Pyrethroids have recently been linked to overall human toxicity [8^{***}]; however, severe pulmonary toxicity or associated ILD has not been described in humans. The safety datasheet of Bop only mentions allergic reactions, but no severe toxicity [9].

We present three cases along with a comprehensive review of the current literature on (pulmonary) toxicity associated with pyrethroid inhalation.

CASE SERIES

Case A

A 55-year-old female patient was admitted to the pulmonary ward due to progressive dyspnea, chest tightness and a dry cough shortly after inhalation of the insecticide Bop. Her saturation on room air was 94% in rest, with a desaturation below 90% during exercise. Chest auscultation revealed bilateral crepitations. Lab work showed normal C-reactive protein

(CRP), autoimmune serology was negative, but blood eosinophils were $1.84 \times 10^9/l$ (normal range $0.02-0.55 \times 10^9/l$). She did not have a history of occupational or environmental exposure. Imaging on admission revealed reticulation, ground glass and consolidations classified as nonspecific interstitial pneumonia (NSIP)/organizing pneumonia pattern (Fig. 1a and b). Bronchoalveolar lavage fluid (BALF) cultures were negative and revealed an eosinophilia.

She was treated with prednisolone, 60 mg/day orally after which she experienced improvement of symptoms and could be discharged after 1 week with 30 mg prednisone/day and a tapering schedule. Within the next weeks the improvement continued, and, moreover, the high resolution computed tomography-scan showed substantial improvement (Fig. 1c).

Case B

A 64-year-old male patient was admitted to the emergency department (ED) due to subacute complaints of cough and dyspnea. At examination, he showed a peripheral oxygen saturation of 65% (95% with 15 l/min non rebreather mask) and Velcro crepitations on both lungs. As a pneumonia was suspected based on the presentation and chest radiograph (Fig. 2a) cefuroxime was started immediately. Due to respiratory deterioration, he was intubated one day later. A transthoracic echocardiogram revealed a normal left ventricular ejection fraction. A chest computed tomography (CT) revealed reticulation, consolidation and ground glass (Fig. 2b). His relatives reported that he very regularly used Bop together with Sapolio and stayed in the room after use without any protection. Cultures for both bacteria and viruses from blood, sputum and BALF remained negative. BALF revealed mild neutrophilia and some eosinophils. HIV and autoimmune serology were negative. Because of respiratory deterioration in the absence of infectious agents, we started pulse methylprednisolone 1000 mg/day for three consecutive days. Although a small clinical improvement was noticed, he developed a pneumothorax and multiple cerebral infarctions, and, finally, he deceased.

Case C

A 59-year-old female with a history of asthma was admitted to the ED due to progressive dyspnea and cough. A thorough anamnesis disclosed the recurrent use of Sapolio insecticide. Physical examination revealed a prolonged expirium and some rhonchi on auscultation, no fever, and an oxygen saturation of 68% on room air. CRP and leukocytes were normal.

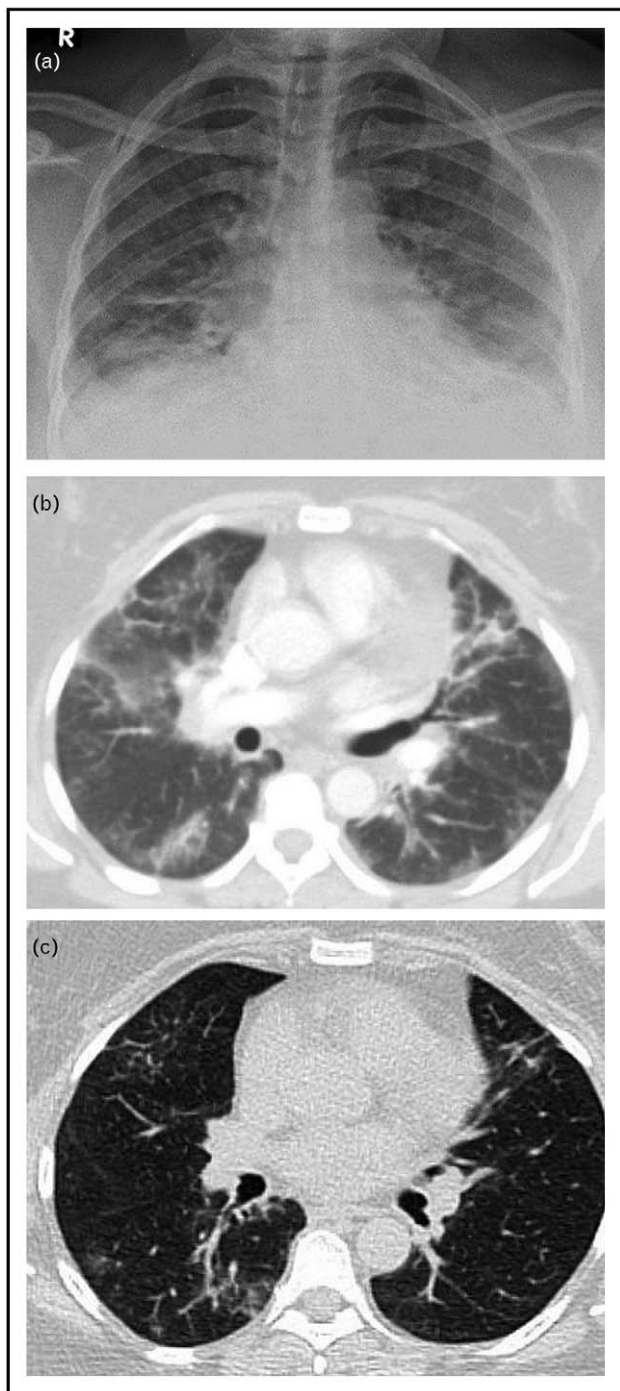


FIGURE 1. Radiologic exams of patient A. (a) Chest radiograph on admission showing bilateral consolidations in the middle and lower zones. (b) Chest computed tomography before therapy showing a reticular pattern, ground glass and consolidations. (c) Chest HRCT after steroid therapy with regression of consolidations.

SARS-CoV-2 PCR, HIV and autoimmune serology were negative. Chest radiograph and chest CT at admission revealed a reticular pattern and ground glass consolidations (Fig. 3a and b).

She was admitted to the pulmonary ward and treated with antibiotics and 6 mg dexamethasone. Chest radiograph after 1 week of treatment showed substantial improvement and she was discharged home in good clinical condition.

LITERATURE REVIEW AND DISCUSSION

According to the WHO pesticides and herbicides are considered as a special class of chemical compounds used to kill a wide range of pests that include insects, weeds and rodents. Pesticides are considered potentially dangerous to human health and their consumption needs to be carefully monitored. Gaseous pesticides tend to pose immense risk to individuals on inhalation. Furthermore, absorption through the respiratory tract is rapid and tends to affect multiple regions of the body. It can exhibit serious effects on lungs, throat and nose tissue [10[¶]].

PYRETHROIDS

Pyrethroids are a group of very effective biodegradable synthetic pesticides derived from the pyrethrum flower (Fig. 4). In Japan, pyrethrum seeds and their insecticidal activity was already recognized around 1880. An overview of the discovery and development of pyrethroid insecticides is given by Matsuo [11^{¶¶}]. Pyrethroids largely replaced previous classes of pesticides, mainly organophosphates, in the 1980s and are thought to be less dangerous to mammals [12]. Besides potential hazards, the world relies profoundly on pyrethroids for the control of vector-borne diseases, including malaria. Over the past 20 years, large progress has been made in malaria control primarily using pyrethroid-treated mosquito nets [13].

Pyrethroids act mainly by inhibiting voltage-gated sodium channels in insects. However, some mammalian voltage-gated sodium channel isoforms are also susceptible to pyrethroid exposure, albeit with lower sensitivity [14]. Due to the extremely wide application of pyrethroids, problems such as toxicity to mammals and aquatic organisms can occur [7]. Cypermethrin is one of the most studied pyrethroids [15]. Toxicity can be tested *in vivo* in fish models to detect toxicity to aquatic animals and in rat/mouse models to detect toxicity to mammals. Furthermore, cytotoxicity can be tested with in-vitro models [16[¶]].

PULMONARY TOXICITY OF PYRETHROIDS IN HUMANS

No previous cases of ILD or severe pulmonary toxicity related to pyrethroids have been described in English literature. However, one case of the

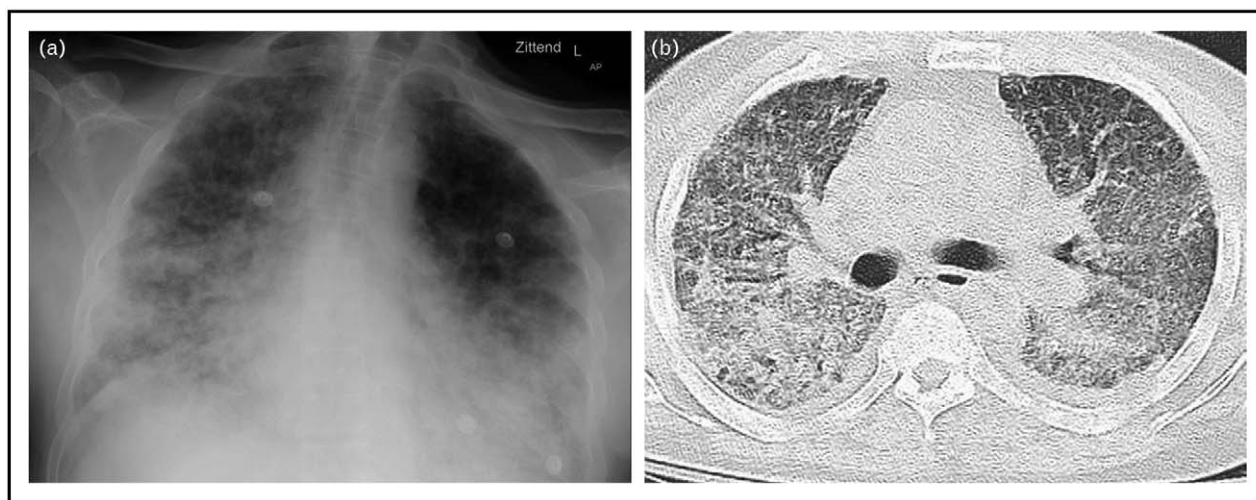


FIGURE 2. (a) Chest radiograph and (b) chest computed tomography on intensive care of patient B showing a reticular pattern, consolidation and ground glass.

originator pyrethrin-related pulmonary toxicity was described in a case of pet groomer presenting as hypersensitivity pneumonitis [6]. An NSIP pattern was seen and BALF-analysis and open lung biopsy results were consistent with hypersensitivity pneumonitis [17]. Avoidance of exposure led to clinical improvement. This novel occupation-related hypersensitivity pneumonitis was called a ‘Pet Groomer’s Lung’ [6]. Furthermore, the original natural extract pyrethrum was associated with one case of hypersensitivity pneumonitis in 1977 [18] and has been suggested as an etiological factor of asthma when it was more widely used in 1930 [19].

In 2001, several patients presented with dyspnea, cough, wheezing and blood eosinophilia after inhalation of 2% cypermethrin diluted in diesel in Manaus in Northern Brazil, which was used as prophylaxis for Dengue. Most of them were women and children who stayed at home after the insecticide was sprayed there, whereas men who left home to work outside seldom presented any symptoms (http://bvsm.sau.gov.br/bvs/periodicos/boletim_eletronico_epi_ano02_n07.pdf). In Europe, a similar widely used pyrethrum and piperonylbutoxide-based product is VAPONA [20]. We remember a 65-year-old male who was exposed to VAPONA after spraying his caravan interior without ventilating. Three days later, he was admitted with respiratory distress due to severe ILD comparable with the cases presented in this article (unpublished data).

OVERALL TOXICITY OF PYRETHROIDS IN HUMANS

Bao *et al.* [8^{***}] recently studied overall mortality in relation to exposure to pyrethroid insecticides in the

general US-adult population. A large cohort with a total of 2016 adults were screened for urine metabolites of pyrethroids (3-phenoxybenzoic acids) at baseline and followed from 1999 to 2015. Participants with higher urinary 3-phenoxybenzoic acid levels were at a higher risk of all-cause and cardiovascular-related mortality during the follow-up period. The underlying mechanism cannot be derived from this study.

In 2017, Han *et al.* analyzed pyrethroid metabolites in urine and studied the association with cardiovascular risk in a case-control study including 72 coronary heart disease (CHD) patients and 136 healthy controls. High concentrations of urinary pyrethroid metabolites were associated with an increased risk of CHD compared with the lowest concentrations suggesting a potential causal relation [21]. A wide variety of symptoms have been described associated with ingestion of cypermethrin even a case of suicidal poisoning [22].

Pyrethroids are known endocrine disruptors, as they interfere with endocrine signaling by blocking, imitating or synergizing endogenous hormones through direct receptor interactions, and secondarily via upstream signaling pathways [23]. Increased urinary pyrethroid metabolites were correlated with increased serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations in men and decreased semen quality [24]. Furthermore, pyrethroid exposure during puberty was linked to increased LH and FSH concentrations, earlier pubertal development in boys, and delayed puberty in girls [24]. One recent study found an inverse relationship between urinary 3-phenoxybenzoic acid, a pyrethroid metabolite, and serum free T3 concentrations during the third trimester

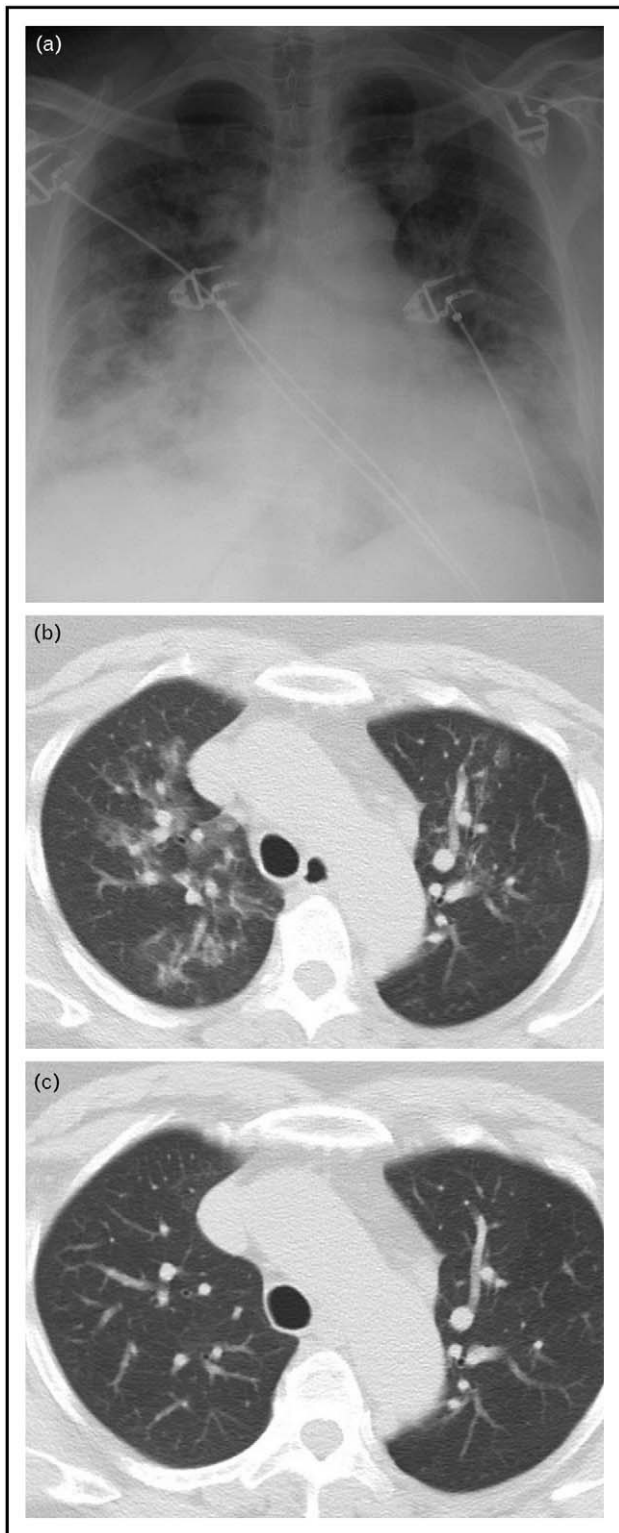


FIGURE 3. (a) Chest radiograph at admission showing diffuse infiltrates/consolidation. (b) Chest computed tomography showing diffuse consolidations on both lungs with central distribution. (c) Chest computed tomography 3 months later showing substantial improvement.



FIGURE 4. The *Tanacetum cinerariifolium* (cinerariifolium flower) is a species of flowering plant in the aster family, *Asteraceae*, and formerly part of the genus *Pyrethrum*, but now placed in the genus *Chrysanthemum*, or the genus *Tanacetum* by some biologists. Source: [http://commons.wikimedia.org/wiki/User: KENPEI](http://commons.wikimedia.org/wiki/User:KENPEI).

[25]. Another study in 717 pregnant women also found increased concentrations of neonatal thyroid-stimulating hormone as a function of maternal 3-phenoxybenzoic acid exposure [26].

PULMONARY TOXICITY OF PYRETHROIDS IN ANIMALS

Few animal studies investigating-specific pulmonary toxicity of pyrethroids were found. A study in 25 pyrethroid exposed rats showed similar histological lung changes with thickening of the connective tissue stroma, congestion of intervening blood vessels, presence of mixed inflammatory cells infiltrates and lung injuries [27]. Another study in rats ($n=32$) exposed to alpha cypermethrin (α -CYP) with or without *N*-acetyl cysteine (NAC) revealed that α -CYP significantly increased serum lactate dehydrogenase (LDH) and pulmonary malondialdehyde levels [28]. Histopathological changes of the pulmonary parenchyma included congestion, cellular infiltration, necrotic changes and thickening of inter-alveolar septa. NAC showed antioxidant, anti-inflammatory and antifibrotic effects on lung tissues [28]. Another study in 80 mice investigated the lung hyperresponsiveness after aerosolization of cypermethrin with or without diesel. The sample exposed to diesel in combination with cypermethrin showed higher respiratory system resistance, lower compliance and increased blood and lung eosinophils and neutrophils compared with diesel or cypermethrin alone [29]. Furthermore, a study in 16 mice showed that inhalation of cypermethrin resulted in

significant pulmonary edema, alveolitis, and pulmonary fibrosis by the deposition of collagen. The latter was also time/exposition dose dependent [30]. A study with deltamethrin nebulized rats showed similar results with dose-dependent changes to lung parenchyma including perivascular edema, lymphoplasmocytic infiltration with focal NSIP, foamy alveolar macrophage accumulation, emphysema and focal hemorrhage. Alveolar lining cells showed mild degeneration and a slight hyperplasia in reactive type II pneumocytes (RP2) and increase in collagen formation [31]. Presence of RP2 in BALF specimens was previously associated with the presence of foamy alveolar macrophages, alveolar hemorrhage, hypersensitivity pneumonitis and mainly with conditions of acute lung injury in humans [32]. A study in pigeons exposed to increasing doses of cypermethrin revealed that in all cases pathological changes in the lungs were found, mostly emphysema and congestion, some with foamy alveolar macrophages [33].

OVERALL PYRETHROID TOXICITY IN ANIMALS

In mammals, pyrethroids can have adverse effects on the cardiovascular system. In a recent study in rats, increased exposure to α -CYP induced higher plasma concentrations of cardiac markers (LDH, Creatine Kinase myocardial band and troponin-T) and elevated cardiac oxidative stress. The harmful effect was histologically confirmed [33]. Furthermore, pyrethroids also disrupt cardiac sodium channels, induce arrhythmia and modulate other voltage and ligand-gated ion channel currents in rats [14].

A recent original article by Zhu *et al.* examined photodegradation of deltamethrin, permethrin and other pyrethroids [7,8²²,23]. They discovered that pyrethroids, and, most of their photodegradation products, were toxic to fish, daphnid and green algae [7]. Another recent aquatic animal study found that under chronic exposure to cypermethrin, growth and reproduction rate of aquatic invertebrates were severely affected. Furthermore, temporal-mRNA expression profile showed modulations in antioxidant-related genes in response to cypermethrin suggesting the underlying toxic mechanism being oxidative stress [34]. The photochemical behavior of household pyrethroids was previously studied, and some of the photoproducts are lethal to fish [34,35].

DISCUSSION

In line with our observation, potential hazards of pyrethroids have been described in both humans and animals. In humans, pyrethroid pulmonary toxicity has not been studied, although a recent study

did show potential cardiovascular risk and furthermore endocrinological effects are beyond dispute [8²²,23].

Animal studies, mostly in rodents, demonstrated dose-dependent cytotoxic and genotoxic effects, as well as increased oxidative stress. This could explain why case B with highly likely the highest exposition had an unfavorable course. Various pyrethroids have a different chemical structure, multiple isomers can therefore differ in metabolic processing and toxicity both *in vivo* and *in vitro* [23]. Cypermethrin and deltamethrin are often tested in animal studies. It is unknown whether the two pyrethroid-based insecticides used in the three presented cases are equally pneumotoxic in humans.

In addition, often pyrethroid-based pesticides are combined with piperonyl butoxide, which increases efficacy by inhibiting insect cytochrome P450 monooxygenases [36]. *In vitro*, piperonyl butoxide prevented Hedgehog signaling, a pathway important for neurological development [36]. Moreover, it has been shown that in rats pyrethroids significantly induce hepatic CYP enzymes after prenatal exposition [37]. Species-specific differences in metabolism may result in variable detoxification of pyrethroids, which in turn may result in divergent toxic outcomes. Many pesticides are also subjected to metabolic biotransformation by CYP enzymes, which implies involvement of the CYP system (phase I reactions) in the detoxification of pesticides. Significantly, in humans, polymorphisms of cytochrome P450 genes have an effect on the metabolic activity of the subsequent enzymes, which may in turn lead to tissue damage in for instance lung tissue [38,39]. This might be another explanation for susceptibility and interpatient disease variability. A case report by de Raadt *et al.* [40] described the possible association of glyphosate-surfactant associated pulmonary toxicity with reduced metabolic capacity of CYP enzymes.

One experimental study in rats showed potential benefit on pulmonary toxicity of the pyrethroid α -CYP when treated with NAC [28]. No other studies have investigated treatment after pyrethroids lung toxicity. Two out of three cases improved after treatment with steroids, but this was uncontrolled.

There is a clear need for more studies evaluating human toxicity to develop appropriate guidelines how to use it safely.

CONCLUSION

We presented three cases of severe pulmonary toxicity associated with inhalation of pyrethroid-based insecticides. Although a causal relationship was hard to prove, the strong history of repeated

pyrethroid exposure with exclusion of other causes made the association highly likely.

Although literature on pulmonary pyrethroid toxicity in humans is lacking, toxicity reports of pyrethrin and pyrethrum combined with findings of overall pyrethroid toxicity in both humans and animals underline the toxic abilities of these compounds.

We urge for more awareness of potential hazards of commercially available insecticides containing pyrethroids to both users and caregivers. Furthermore, we would like to stress that a thorough interview exploring exposure to potential triggers in unexplained cases is warranted to avoid harmful damage in the future.

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Conflicts of interest

There are no conflicts of interest.

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