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Health and Safety Guide No. 26

PYRROLIZIDINE ALKALOIDS
HEALTH AND SAFETY GUIDE

This is a companion volume to
Environmental Health Criteria 80: Pyrrolizidine Alkaloids

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INTRODUCTION

The Environmental Health Criteria (EHC) documents produced by the International Programme on Chemical Safety include an assessment of the effects on the environment and on human health of exposure to a chemical or combination of chemicals, or physical or biological agents. They also provide guidelines for setting exposure limits.

The purpose of a Health and Safety Guide is to facilitate the application of these guidelines in national chemical safety programmes. The first three sections of a Health and Safety Guide highlight the relevant technical information in the corresponding EHC. Section 4 includes advice on preventive and protective measures.

The target readership includes occupational health services, those in ministries, governmental agencies, industry, and trade unions who are involved in the safe use of chemicals and the avoidance of environmental health hazards, and those wanting more information on this topic. An attempt has been made to use only terms that will be familiar to the intended user. However, sections 1 and 2 inevitably contain some technical terms. Further background information on the subject of this Guide may be found in Environmental Health Criteria 80: Pyrrolizidine Alkaloids.

Revision of the information in this Guide will take place in due course, and the eventual aim is to use standardized terminology. Comments on any difficulties encountered in using the Guide would be very helpful and should be addressed to:

The Manager
International Programme on Chemical Safety
Division of Environmental Health
World Health Organization
1211 Geneva 27
Switzerland
THE INFORMATION IN THIS GUIDE SHOULD BE CONSIDERED AS A STARTING POINT TO A COMPREHENSIVE HEALTH AND SAFETY PROGRAMME
1. PRODUCT IDENTITY AND USES

1.1 Identity

The toxic pyrrolizidine alkaloids (PAs) are a large group of related compounds (about 160 are known) that occur in plants, mainly in species of *Crotalaria* (Leguminosae), *Senecio* and related genera (Compositae), *Heliotropium, Trichodesma, Symphytum, Echium*, and other genera of the Boraginaceae. The chemical structures of some alkaloids that are important in relation to human disease are shown below.

- **Heliotropine** $C_{16}H_{27}NO_5$
  CAS Registry No. 303-33-3

- **Monocrotaline** $C_{16}H_{23}NO_6$
  CAS Registry No. 315-22-0

- **Lasiocarpine** $C_{21}H_{33}NO_7$
  CAS Registry No. 303-34-4

- **Retrorsine** $C_{18}H_{25}NO_3$
  CAS Registry No. 480-54-6

- **Senecionine** $C_{18}H_{25}NO_5$
  CAS Registry No. 130-01-8
1.2 Physical and Chemical Properties

The pure alkaloids are mostly crystalline solids; some are gums or amorphous solids. Some are only slightly soluble in water, but all dissolve when neutralized with acid. They occur in the plants partly as N-oxides, which are water soluble. The alkaloids are fairly stable, but are subject to hydrolysis in alkaline solution and to enzymatic decomposition. The latter occurs in some plant species during wilting and drying. The stability of the alkaloids when the plants are cooked is not known.

1.3 Uses

One alkaloid, monocrotaline, is marketed commercially as a fine chemical for research purposes. Another, indicine N-oxide, is being tested as an antitumour drug in human beings.
2. SUMMARY AND CONCLUSIONS

2.1 Human Exposure to Pyrrolizidine Alkaloids

The contamination of cereal grains with seeds of PA-containing plants has caused epidemics of human poisoning in four countries. The plants involved were species of *Heliotropium*, *Trichodesma*, *Crotalaria*, and *Senecio*. Some of these plants thrive under arid conditions and their growth may be favoured by drought. Another important form of exposure is the use of PA-containing herbs as medicines, food, or beverages; this has resulted in occasional cases of human poisoning. The most important of such PA-containing plants are species of *Heliotropium*, *Crotalaria*, *Senecio*, and *Symphytum*. *Symphytum* species (comfrey) are also available in the form of ointments or as digestive aids in the form of capsules.

Low-level exposure may occur in some countries through the presence of PAs in foods, such as honey and milk, but no reports of human poisoning caused through these media are available.

2.2 Metabolism and Excretion

PAs are readily absorbed from the digestive tract and cause harmful effects only after undergoing activation in the liver to toxic metabolites. Effects include a variety of changes leading to permanent damage to genes and chromosomes, the ability of the cells to divide, or to the development of cancer, and even cell death. The alkaloids are quickly converted to harmless compounds and are largely cleared from the body within a few hours of absorption, so that no traces of the ingested PAs or their breakdown products are detectable in the body tissues and fluids. There are no indications that the alkaloids themselves accumulate in animal tissues, but their effects are cumulative, even at low rates of intake. The proportion excreted in urine varies according to the water solubility of the alkaloid. Estimates of the total intake over a long period can only be approximate.

2.3 Effects on Experimental Animals

The acute toxicity of PAs varies widely. The rat LD₅₀s of most alkaloids known to be significant for human health are in the range of 34–300 mg/kg, though some approach 1000 mg/kg. When ingested, the toxicity of the *N*-oxide of an alkaloid is similar to that of the parent alkaloid.
PAs are toxic for a wide variety of domestic, laboratory, and farm animals, pigs and poultry being the most sensitive of farm animals followed by horses and cattle, and sheep and goats, which are the most resistant; sheep and goats are affected only after extended periods of exposure.

The toxic effects of most PAs occur primarily and mainly in the liver. Some PAs are particularly prone to cause damage in the lungs, principally to the blood vessels, resulting in a rise in blood pressure in the lungs, which leads to secondary effects on the functioning of the right side of the heart. The kidneys and some other organs are less commonly affected. The brain is the principal target organ of one or two PAs.

The effects of PAs in animals may be acute or chronic, depending on the dose level and the period of survival after exposure. In acute poisoning, death occurs within about 7 days, due to severe liver damage. Chronic liver damage may follow administration of a single sublethal dose or of repeated low doses.

PAs produce aberrations in the chromosomes in plant and mammalian cells and induce changes in genes that are perpetuated in subsequent cell divisions in mutagenesis test systems. Several PAs have been shown to be capable of producing cancer, chiefly in the liver in rats.

**2.4 Effects on Human Health**

Although all age groups are affected, children are particularly vulnerable to the effects of PAs. The symptoms, which are generally acute in onset, are characterized by upper abdominal discomfort that develops rapidly and progresses to swelling of the abdomen resulting in increased girth, sometimes accompanied by a reduction in the quantity of urine excreted and swelling of the feet. The disease is called veno-occlusive disease (VOD) because of the characteristic obstruction of the small venous blood channels that carry blood from the liver back to the heart. The disease often progresses rapidly and mortality is high. There may be vomiting of blood in advanced stages of the disease. While many patients recover, the disease may continue for a long time in others resulting in a severely scarred liver—a condition called cirrhosis. Some patients may have only vague symptoms and the only sign of the disease may be persistent enlargement of the liver.
The liver is usually the target organ but, in an epidemic caused by contamination of the staple cereal with the seeds of *Trichodesma*, the brain and the nervous system were mainly affected.

Chromosome aberrations have been reported in the blood cells of children affected by VOD but, as yet, there is no evidence pointing to an increased incidence of cancer of the liver or other organs or congenital anomalies in the newborn offspring of patients exposed to PAs.

### 2.5 Effects on the Environment

Plants containing PAs are likely to grow as weeds among staple food crops and pastures, especially following drought, and consumption of such crops can cause large scale outbreaks of toxic disease in both man and farm animals. Little is known about the effects on wildlife but, in one report, the death of deer was ascribed to their grazing on toxic plants.

PAs are believed to be biodegradable so that water supplies are not suspect.
No-observed-adverse-effect levels have not been established in experimental animal studies with PAs. Estimates of intakes causing toxic effects in human beings indicate that they are more sensitive than rats and domestic animals. Rats dosed with lasiocarpine at a rate equivalent to 0.2 mg/kg body weight per day (equivalent to about 2 mg/kg in the diet) developed tumours. Pigs fed monocrotaline at 1.8 mg/kg of feed (equivalent to about 0.08 mg/kg body weight per day) developed chronic liver damage in several months. The lowest intake rate causing VOD in a human being was estimated to be 0.015 mg/kg body weight per day, and was the result of self-medication with a comfrey preparation. In view of the established ability of some PAs to produce cancer in rats, plant products containing them should not be eaten or drunk.
4. PREVENTIVE MEASURES AND MEDICAL ADVICE

4.1 Main Hazards for Man and the Environment

Consumption of contaminated grain or the use of PA-containing plants as herbal medicines, beverages, or food by man, or grazing on contaminated pastures by animals, may cause acute or chronic disease. The principal target organ in man and most animals is the liver, resulting in collection of fluid in the abdomen and swelling of feet, etc. In experimental animals, administration of PAs has been known to produce cancer. Though there is no proof yet of cancer developing in man, such a possibility cannot be entirely ruled out.

4.2 Prevention of PA Poisoning

Prevention of exposure is the only effective method of limiting toxicity due to PAs. Even low doses over a period of time may present a health risk and exposure should be avoided or minimized as far as possible. Measures are required at several action points.

4.3 Advice to Physicians

Occurrence of symptoms of rapidly increasing swelling of the abdomen accompanied by dragging discomfort in the right upper abdomen, particularly if affecting more than one member of the family or several members of a community over a limited period and geographical area, should arouse suspicion. The diet of such persons should be examined for possible contamination with the seeds of toxic plants and the affected persons should be questioned regarding the possible intake of herbal preparations. If any such history is positive, the suspected toxic seeds/herbs should be analysed for the presence of PAs using a simple field test, which can be carried out in a not too highly specialized chemical laboratory.

Examination of the liver by needle biopsy in patients or at post-mortem examination is most likely to provide the crucial clue. Haemorrhagic centrilobular necrosis and occlusion of the hepatic vein radicles in the liver are the hallmarks of the disease, if found in patients with the symptoms
described above. Needle biopsy of the liver should be performed only in a properly equipped hospital with facilities for blood transfusion.

4.4 Precautionary Measures to Protect the Environment and to Prevent Disease

(a) Toxic PA-containing flora growing in the region, particularly those that may contaminate cereal grain crops, and those that are used locally as herbal foods, beverages, or medicines, whether grown locally or imported, should be identified.

(b) Appropriate agrotechnical practices should be followed for the prevention/control of the growth of PA-containing plants among cereal food crops and pastures.

(c) Appropriate systems should be developed for the routine monitoring of seed grain and harvested grain crops to detect the presence of PA-containing plants and seeds.

(d) If the crop is found to be contaminated, immediate steps should be taken to remove the toxic plants from the fields and to rid the domestic and commercial cereal grain stores of the toxic seeds by sieving or winnowing and destroying the toxic seeds/plants.

(e) The suspected contaminant and its toxic PAs should be identified in specialized laboratories.

(f) Public awareness of the risks arising from the consumption of grain contaminated by seeds, and the use of herbal preparations containing PAs as food or medicines, should be created through the media.

(g) The import and sale of seeds, herbs, and herbal preparations containing PAs should be restricted.

(h) In the event of an outbreak, epidemiological investigations of the affected population should be carried out, and plans made for long-term follow-up.

(i) Cases of PA poisoning should be recorded and surveillance organized by Poison Control Centres or other appropriate agencies of the government.
4.5 First Aid

Immediate first aid measures are rarely possible for an acute exposure but may be required in the management of emergencies, such as vomiting of blood from bleeding blood vessels in the oesophagus.

No specific antidote is known for PA-induced toxic effects. The only immediate valuable measure is to:

— identify the source of the PA and
— STOP any continued exposure.

4.6 Medical Management

No specific antidote or therapy for PA toxicity is known. Treatment is supportive.
### 5. CURRENT REGULATIONS, GUIDELINES AND STANDARDS

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>RESTRICTED ITEM</th>
<th>NATURE OF RESTRICTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td><em>Symphytum</em> (comfrey) (Any part of the dried plant and its extracts or preparations for human internal use)</td>
<td>Scheduled as a poison, effectively preventing sale for medicinal purposes</td>
</tr>
<tr>
<td>Austria</td>
<td><em>Senecio numorensis</em> <em>Symphytum officinale</em> <em>Petasites officinalis</em> <em>Tussilago farfara</em> <em>Pulmonaria officinalis</em> (used as medicinal preparations)</td>
<td>Medicinal preparation must be registered with the Federal Ministry of Health and Environmental Protection and sold only in pharmacies</td>
</tr>
<tr>
<td>Canada</td>
<td><em>Senecio jacobaea</em> (ragwort) <em>Symphytum asperum</em> Lepech (prickly comfrey) <em>Symphytum officinale</em> L. root (common comfrey) <em>Symphytum × uplandicum</em> Nym. (Russian comfrey)</td>
<td>Proposed for inclusion in the list of adulterants, thus prohibiting sale of such compounds in or as food (Section B.01.046 of the Canadian Food and Drug Regulations)</td>
</tr>
<tr>
<td></td>
<td>Echimidine or any of its salts or any of the following plant species or extracts or tinctures thereof:</td>
<td>Proposed for inclusion in the list of adulterants, thus prohibiting sale of these substances in or as drugs (Section C.01.038 of the Canadian Food and Drug Regulations)</td>
</tr>
<tr>
<td></td>
<td>(i) <em>Symphytum asperum</em> (ii) <em>Symphytum × uplandicum</em> (iii) Any other plant species containing echimidine</td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td><em>Symphytum officinale</em> L. or its parts either fresh or dried</td>
<td>Dispensaries and drug stores not allowed to prepare, sell, or advertise it</td>
</tr>
</tbody>
</table>
## CURRENT REGULATIONS, GUIDELINES AND STANDARDS

<table>
<thead>
<tr>
<th>Location</th>
<th>Species/Compounds</th>
<th>Regulations</th>
</tr>
</thead>
</table>
| **USA**  | *Crotalaria spectabilis*  
*Crotalaria sagittalis*  
*Crotalaria striata*   | Compliance policy guidelines require that the presence of an average of at least one whole seed per pound of product represents the criterion for direct reference seizure to the office of regulatory affairs (ORA) HFC-25 and for direct citation by the district offices (OB/01/82) |
|          | Lasiocarpine      | Any solid waste (except domestic) containing lasiocarpine must be listed as hazardous waste (subject to regulation and notification requirements); where lasiocarpine is a principal organic hazardous constituent in the EPA permit, incineration must achieve a destruction and removal efficiency of 99.99% |
| **USSR** | Stored grain:  
*Heliotropium lasiocarpum*  
--- Seed  
*Trichodesma incanum*  
--- Seed  
--- Seed grain | Contamination limit  
0.1%  
0%  
Contamination with both species is prohibited |

(Note: Besides the above, a number of countries have regulatory proposals under development and several others enforce administrative or compliance guidelines based on general prohibitory provisions for the basic food and drug products; studies are being carried out to further evaluate the risk.)
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