What levels of potentially toxic seed should be allowed in grains in South Africa? I. Background and pyrrolizidine alkaloid-containing plants

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The allowable levels of toxic seeds in agricultural grains vary considerably among countries. South Africa's much stricter regulatory levels result in possibly unwarranted downgrading of grain, which has caused difficulties in its importation and exportation. This paper offers a model for evaluating the level of toxic seed that would not be deleterious to human health and would not impose impossible restraints on grain producers. Contamination of grain with seeds of plants containing toxic pyrrolizidine alkaloids has caused serious intoxications worldwide. The background to pyrrolizidine alkaloid (PA) toxicity is discussed. Only some PAs are toxic, and there are large differences in toxicity of different species of the same genus. In South Africa, it would appear that the only serious threat of PA intoxication via grain is from *Crotalaria* species. For example, the model presented is applied to calculate the level of PA containing seed that should be allowed in grain in South Africa. The level found, using the strictest guidelines, is 10 *Crotalaria* seeds per 10 kg of grain product. This level is less restrictive than previously enforced levels. Assumptions made in the calculation, especially the possible chronic toxicity effects of other *Crotalaria* species that may be present in grain, however, will have to be tested to ensure that the recommendations are scientifically valid. As plants containing different toxins are present in other grain-exporting countries, different levels may have to be set, depending on the origin of grain imported.

Introduction

Seeds of toxic weeds that grow with grain crops may contaminate the grain during harvesting and pose a health risk if they cannot be removed adequately by grain processing. Many countries have legislation to determine the acceptable level of noxious seeds in grains. Contaminating seeds that are present in grains could be toxic to either humans and/or to animals or be unacceptable because of complications in the cleaning, milling or manufacturing processes. For the purpose of this review, only seeds that are toxic, that is, contain ingredients that are harmful to humans or animals, are considered.

There are major differences in the level of toxic seed allowed in grains by different countries. The levels proposed for grain in South Africa are generally more stringent than those in other countries. There may be valid reasons for this situation.

Several reports commissioned by different bodies were written on the levels of toxic seeds (Table 1). Unfortunately, marketing and legislative authorities' differences of opinion on the reports and acceptable levels have not been resolved. The report by Ybema[1] provides a valuable source of information. The Soybean and Sunflower Forum, which represents producers, processors and marketers of soybean, sunflower and canola commissioned one of us (J.N.E.) to write a review paper that should be subjected to peer review and be published in a scientific journal to ensure that the recommendations are based on evaluated scientific evidence and open to correction. The responsible officer in the Department of Health, T. van de Venter, agreed with this approach, especially since the responsible toxicologist, the deputy director: Chemical Safety (F.W.J.vR.) is a co-author. Other role players were invited to collaborate in this review, but some did not accept the invitation. We decided to look further than toxic seed currently included in the legislation. Although mycotoxins represent a major health concern for humans using contaminated grain, this important aspect is not covered in this review.

A literature review revealed that, with few exceptions [Damron[6] and work on *Crotalaria* species and pyrrolizidine alkaloid (PA)-containing plants], little has been published on this topic in readily accessible journals during the past decade. This may be because (a) it is not a problem as far as grain-exporting countries are concerned, (b) in many countries grain is produced mainly as an animal feed, or most likely, (c) levels were addressed by regulating authorities after commissioning reviews that did not lead to publications in scientific journals.

The problem is examined in two papers, the aim of which is is to review published and unpublished information on toxic seed that may contaminate grain crops, to make recommendations on acceptable levels, and to identify gaps in knowledge that may require additional research. We examined the literature as well as unpublished reports and correspondence. Correspondence with officials at the Department of Health and minutes of meetings held and stored in the National Herbarium and elsewhere, as well as discussions with people involved with toxic plants at Onderstepoort Veterinary Institute and the Veterinary Science Faculty of the University of Pretoria, yielded useful unpublished information. A recent report by the Australia and New Zealand Food Authority,[7] accessible on the Internet, was especially valuable.

In this paper, part I, the problem and general principles are discussed. The problems encountered with pyrrolizidine alkaloid-containing plants worldwide and the PA-containing genus *Crotalaria* in South Africa are also discussed here. In a companion paper, part 2, to be published in this journal, other plants are discussed, recommendations on acceptable legislative levels based on risk and eating patterns are made, and future research needs on other plants are identified.

We have found that almost all the reports published to date do not clearly state the assumptions on which their toxic seed level recommendations are based and cannot, therefore, be evaluated. The model proposed here is a logical one used internation-

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Table 1. Reports on toxic seed in grain in South Africa.

Author	Date	Title	Commissioned by	Pages
T.W. Naudé and T.S.Kellerman[2]	1995	Natural toxins in commonly used human foods — a broad overview	Paper, 3rd International Conference on Community Health	10
C.J. Botha[3]	1994	Report on potential toxic seeds in grain	Department of Health, South Africa	20
F.W. Jansen van Rijssen[4]	1997	Evaluation of toxic seeds	Department of Health, South Africa	15
J.N. Eloff[5]	1999	Report on gradation regulations for toxic seeds in South African grains	Sunflower and Soybean Forum, South Africa	12
S.G. Ybema[1]	1999	An investigation into noxious-poisonous-toxic seeds with special reference to the Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972 as amended	Grain South Africa	103

ally by regulating bodies. We provide the assumptions underlying our calculations and recommendations so that it will be possible to update the recommended level of toxic seeds if and when there is new information. The model we use is illustrated in Fig. 1. We trust that this approach will lead to recommendations based on scientifically verifiable facts in a transparent process.

Plants to be considered

The Onderstepoort Veterinary Institute, in particular, has done much work in South Africa on toxic plants over many years. Several books have been published on toxic plants.[8–14] Any toxic plant growing in grain fields would cause concern for the health of the end user. Toxic plants have usually been identified after stock losses, and there are probably many toxic plant species that have not yet been discovered because animals avoid them.

In South Africa, the following plants are listed in the legislation:[15] *Convolvulus* species, *Crotalaria* species, *Datura* species, *Ipomoea purpurea, Lolium temulentum, Ricinus communis,* and *Xanthium* species. *Lolium temulentum* is probably listed due to bacterial galls that contain corynetoxin. *Ergot* sclerotia are also listed (Anon. 1990). There may be more plants that have to be considered, for example *Argemone* species. Several other plant species (see below) have also caused serious problems in grains in Asia and eastern Europe. This and other aspects are discussed in the second review paper.

History of South African legislation

The Department of Health published regulations governing tolerance of toxic seeds in grains in 1987.[15] However, the toxic seed regulations allowed tolerances (typically three seeds per 10 kg grain) to be determined by the marketing boards.[16] Consequently, the tolerances originally laid down by the Department of Health (typically one seed per 10 kg grain) were never applied. After the demise of the different boards in the early 1990s, the tolerances of the Department of Health were the only legal standards. It soon became apparent that the South African tolerances were more stringent than those of most other trading partners, for instance, Australia and the United States.[1] This situation could result in technical trade barriers. South Africa has, therefore, to revise these tolerances based on sound science according to a decision taken by officials of the departments of Health and Justice at a meeting attended by one of us (F.W.J.vR.).

At the end of 1999, a shipment of wheat was imported that contained *Convolvulus* species seed far in excess of local legislation, but within international standards.[1] Pressure from producers and importers and the result of the review undertaken in these two papers, led the Department of Health to change the regulations in 2002 to bring them in line with international levels.[17] Depending on the toxicity of weed seeds in different countries, the basis for recommended levels may differ from country to country. It is therefore important to have sound and justifiable scientific means to determine safe levels for toxic seeds.

Situation in other grain-exporting countries

There are major differences in the levels of toxic seed allowed in different countries as is discussed in part 2. Tolerances between different countries cannot readily be compared without any further work because different species may occur and there may be large differences in toxicity.

In an effort to address the situation, international guidelines were drawn up by the Codex Alimentarius Commission, a body under the joint auspices of the Food and Agriculture Organization (FAO) and the World Health Organization (WHO). The purpose of Codex Alimentarius is to guide governments on world food standards. These standards are based on scientifically verified data and should facilitate trade.[18] The World Trade Organization (WTO) accepts these standards. The Codex states 'The products covered by the provision of this standard shall be free from the following toxic or noxious seeds in amounts which may represent a hazard to human health'. The standard applies

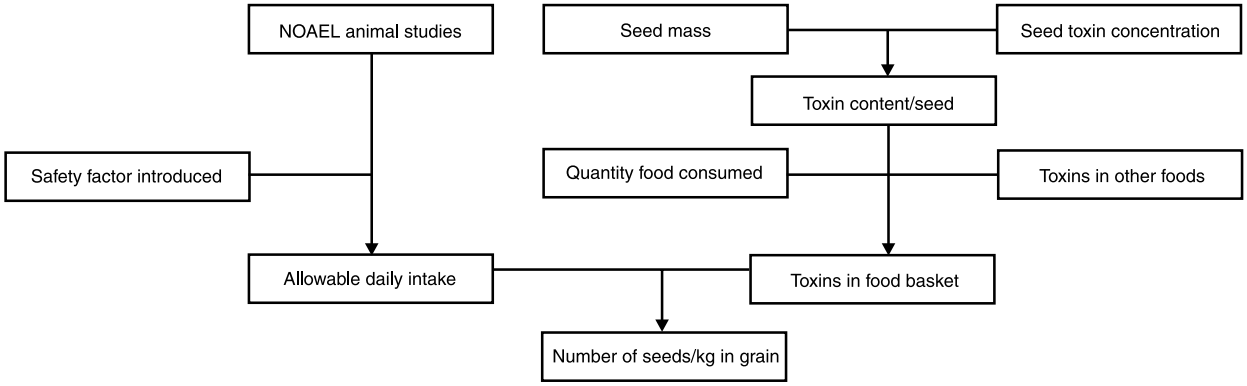

Fig. 1. Model for determining number of seeds allowed in agricultural products (NOAEL = no observed adverse effect level).

to commodities for human consumption, that is, ready for their intended use as human food, presented in packaged form or sold loose from the package directly to the consumer. The standard does not apply to food processed from these commodities. The commodities included here are: maize, oats, pulses (beans of *Phaseolus* species; lentils of *Lens culinaris*; peas of *Pisum sativum*; chickpeas of *Cicer arientinum*; field beans of *Vicia faba* L.; cowpeas of *Vigna unguiculata* (L.) and other cowpea species, sorghum grain, wheat and durum wheat. Rice and peanuts are not included in this Codex list of toxic seeds. No other grains are specified.

Standards for edible oils do not include possible contamination with toxic substances from plants.

The toxic seeds that are named by the Codex are those of *Crotalaria (Crotalaria* species), corn cockle (*Agrostemma githago* L.), castor bean (*Ricinus communis* L.), and Jimson weed (*Datura* species). The Codex includes a general statement that reads, 'other seeds that are commonly recognized as harmful to health'.

The Codex thus does not resolve the problem of levels because only a general statement is made and the list of toxic species is open ended.

Principles

Acute toxicity

The most common published indicator of acute toxicity is the LD_{50} value, that is, the statistically determined concentration that causes the death of 50% of the animals tested (usually rats). This is the value usually found in the literature and is frequently the only available tool to screen the toxicity of substances present in plants and their seeds. LD_{50} values are relatively reproducible, but the LD_0 value, which is closer to what is required for risk assessment, cannot be deduced from the LD_{50} value because the gradient of concentration effect is generally not given. Because of ethical considerations, LD_{50} determinations are not generally performed any more. Nevertheless, in some instances LD_{50} values are still required. The lowest dosage indicating toxicity is now accepted as a more humane way of evaluating toxicity. Signs and the severity of the signs of acute toxicity would also be considered in assessing the risk associated with toxins.

Chronic toxicity

Unfortunately, with some compounds, there can be a cumulative effect, and sub-lethal doses can lead to chronic toxicity. The exposure levels at which chronic signs become detectable are usually much lower than required levels for acute toxic effects. Chronic toxic effects are difficult to detect, require long-term or epidemiological studies, and may be more important than acute toxicity. Natural toxins with acute toxicity should be investigated in greater depth on aspects such as mutagenicity, teratogenicity, oncogenicity, as well as chronic exposure studies. Because there are many uncertainties, a safety factor extrapolation to humans is usually built into the recommendation, depending on the kind and severity of the toxic effects. The no-observed-effect-level (NOEL) is defined as the highest dose administered that does not produce any effects. Similarly, a no-observable-adverse-effect-level (NOAEL) can be determined. We prefer the NOAEL criterion because a compound causing a positive effect at a certain level should not be disqualified at that level. An additional safety factor of 10 is usually introduced to compensate for inter-individual variation among humans.

Extrapolating from animals to humans

It is easier to make recommendations on grain used for animals because experiments on toxicity have been conducted on animals. Where humans are concerned, case studies have to be taken into account or epidemiological studies have to be carried out. In the rare instances where the toxin is also used pharmacologically, for example, atropine present in *Datura* species, useful pharmacological data on humans using these toxic compounds under supervision can help to determine toxicity and assess risk. If one considers that the cost of clinical trials to get one medicine approved was approximately US$231 million in 1990 and takes twelve years to complete,[19] it is clear why data on human toxicity are based more on incidents or case studies than on sound controlled studies.

The toxicity of a single substance varies considerably among different animals. In ruminants, in particular, detoxification by microorganisms in the rumen flora is well known.[11] Single-stomach animal species, such as man, dog, pig and horse, are generally more susceptible to toxins.

If studies are only carried out on animals, an additional safety factor of 10–100 is incorporated to compensate for inter-specific differences. Obviously the closer the test organism is related to man, the smaller this factor could be.

When chemicals for which no reliable chronic exposure data in animals are available, an uncertainty or safety factor of 1000 has been used.[20] Responsible regulatory authorities would not easily allow the release of pesticides with such a high risk or uncertainty. This is unavoidable where little scientific information is available for contaminants such as toxic seeds in grains.

The primary purpose of safety factors is to protect human health. It does not mean that exposure to doses higher than the 'safe' level (NOAEL/safety factor) would have a toxic effect.[20] It is clear that insufficient knowledge necessarily leads to a large safety factor.

Daily intake levels

From the NOAEL, an Acceptable Daily Intake (ADI) value for the chemical substance (in this instance, in the seed) can be calculated. The daily intake level should also consider the possible cumulative effect of deleterious compounds present in other parts of the diet (Fig. 1). This is specially the case if the same or similar toxicological mechanisms of action are involved, or where the same organs are targeted. The exposure to the same toxicant in different food commodities obtained from contaminants in different agricultural products, for example, canola, maize, wheat, soybeans, sorghum, sunflower seeds, and so on, would result in a possible market-basket effect. Not only the same or related toxins, but also other toxins may increase the toxicity. PA may act synergistically with aflatoxin (a fungus-derived toxin present in several agricultural products) in causing cirrhosis and hepatoma in primates.[21]

Ideally, the presence of contaminating toxins in processed food consumed by the South African population, particularly children, would be the only justifiable indicator for determining the acceptable tolerance in grains and other food commodities.

Genetic toxicity

Toxins that affect the composition of the human genome are especially dangerous because even a single molecule that changes a gene can theoretically cause a toxic effect. This genetic change, or mutation, can be transferred to cells subsequently formed from the DNA template. The toxin may be a carcinogen or a teratogen, which affects offspring. There is no NOAEL value because even a single molecule has the potential to change the genetic composition of cells. Although the mutation is usually not lethal, or may affect only somatic cells, the effect can be irreversible. With genotoxic compounds, such as aflatoxins,

occurring on maize and groundnuts and other compounds present in the environment, the ALARA (as low as reasonably achievable) level of contamination is specified.

More than 200 mutagen assays are used to determine genetic toxicity. The predictive value of many of these assays is uncertain.[22] Any toxic seed probably containing such a genotoxic compound must obviously be avoided.

Information required to make a reliable recommendation.

If the final recommendation is to be in terms of number of seeds allowed per mass or volume unit of grain, information on many different aspects is required (Fig. 1)

Mass and toxin content of the seed

Data are frequently expressed as the number of seeds that has a toxic effect. This is the most practical way to enforce legislation at farm, silo or depot level to prevent the toxin from entering the food chain. The value that is actually required is the LD_0, that is, the highest dose at which no test organisms are killed by the toxic compound or, preferably, the NOAEL. Unfortunately, this information is hardly ever available for humans and infrequently for animals. LD_{50} values are commonly the only available information. To calculate the quantity of toxin present in a single seed, the mass of the seed and the toxin concentration are required. From the toxin content of a single seed and the NOAEL or LD_0, and applying safety factors, the number of seeds that would not cause an adverse effect can be calculated. These values have to be expressed on a per kilogram bodyweight basis because the mass of the person ingesting the seed is directly related to the dose that can be tolerated.

Variability of toxin content

The toxins present are usually secondary plant compounds and there can be a wide genetic variation in concentration, even within the same species. Generally, one would expect with weeds that are frequently cosmopolitan and good competitors (and therefore not as prone to evolutionary pressure), that the variation may not be as high as in many other plants. In some cases, different species of a genus may contain the same secondary compound at similar concentrations, such as novel amino acids in *Dichapetalum* species,[23] but in other cases, there are major variations. One of us (T.W.N., unpubl. data), however, has found great variation of tropane alkaloids in *Datura stramonium* growing in the same field. To extrapolate from different species of the same genus is therefore totally unacceptable unless research has indicated that there are not large differences. It is also well known that different parts of the same plant may vary in concentration of secondary compounds and consequently also in toxicity. Furthermore, seasonal and climatic factors may also have a large effect on the concentration of toxins.

It is important, therefore, to know exactly which species are the contaminants of grain, which species are toxic and how variable the toxicity is within the same species, and finally how seasonal and climatic factors influence toxin concentrations.

Stability and/or extractability of the toxin(s) during processing

If the identity of the toxic principle is known, then existing knowledge on, for instance, the LD_{50}, can be applied if the concentration is also known. The important parameter, however, is not how toxic the contaminating seeds are, but rather how toxic the final edible product is. If the toxic principle is a protein or peptide, it may be destroyed by heat during processing or digestion. If the toxic principle is non-polar, only a small portion may dissolve in water if this is used to prepare the final edible product, and such substances may also absorb slowly from the gastrointestinal tract. On the other hand, if the toxin is water-soluble, most of it will be extracted into water if the product is cooked and the water discarded. Similarly low concentrations of polar toxins will be present in oil extracted from the produce.

Effect of the diet

It is important to realize that toxicity (with the possible exception of chronic and genotoxic toxins) is dose-related and that almost any compound is toxic if the dose is high enough. The difference between toxic and non-toxic components is therefore quantitative and not qualitative. Many components of our normal diet, such as sodium chloride, are toxic if the dose is high enough. On the other hand, table-ready food may contain only traces of a toxin incompletely removed during processing, manufacturing, and preparation of the comestibles.

The quantity of the final edible product consumed is therefore important. If it contains toxic compounds below the threshold value, it would have no effect. In order to calculate the dose ingested with maize porridge we assume that 100 g of maize meal (yielding 400 g of porridge) is the daily intake. For sunflower seed oil we assume oil content of 38% of the seed, a density of 0.92 and an average daily intake of 10 ml of sunflower seed oil. The daily intake of sunflower seed oil is therefore equivalent to approximately 25 g of sunflower seed ($10 \times 0.92 \times 1/0.38$). The daily intake of sunflower seed oil is thus about a quarter of that of maize and the number of toxic seeds can be four times as high to give the same exposure of the toxic compound. The daily intake for soybean may be even lower than that of sunflower oil, leading to an even higher tolerance level. The cumulative effects of different parts of the diet must be taken into account if the deleterious compounds present in the diet have an additive effect.

Data available on PAs and *Crotalaria* species

Presence of PAs in plants

PAs are the leading plant toxins associated with disease in animals in the world.[24] Over 200 PAs have been identified in 300 species of 13 plant families. It is estimated that up to 3% of the flowering plant species contain toxic PAs.[25] These toxic alkaloids are found mainly in three genera, *Senecio* (Asteraceae, 142 PAs), *Crotalaria* (Fabaceae, 60 PAs) and *Heliotropium* (Boraginaceae, 25 PAs).[26] In South Africa, there are approximately 250 *Senecio* species.[27] Some species, such as *S. tetrorsus* and *S. latifolius,* contain toxic PAs, which are the third most important cause of livestock poisoning in South Africa.[11] *Crotalaria spartioides, C. dura, C globifera, C. juncea* and *C. burkeana* also poison many animals every year.[28] *C. spectabilis* contains monocrotaline that causes pulmonary vascular disorders in chickens. Although there are 19 *Heliotropium* species in South Africa,[27] intoxication in stock has not been attributed to them to date.

Many *Symphytum* species, including comfrey (*S. officinale*), the widely used herbal medicine, also contain toxic PAs. PAs are also present in several other herbal medicines such as agrimony, alkanna, alpine ragwort, borage, colt's foot, dusty miller, golden ragwort, groundsel, gravel root, hound's tongue, hemp, petasties and tansy ragwort.[30] The accidental inclusion of an *Aristolochia* species, which contains toxic PAs, in a Chinese herbal medicine has led to development of kidney cancer in many people in Belgium.[31] At least 13 PA-containing plant species are also used as food. They include four *Crotalaria* species, mainly used in Asia and East Africa,[26] as well as three *Senecio* species used as a spinach in South Africa.[32]

Chemistry of PAs

Mattocks[33] provided an excellent account of many aspects of PAs. This includes trivial names and structures of 186 PAs. Generally, PAs are esters of hydroxylated 1-methyl pyrrolizidines; the amino alcohols are called necines and the acid moieties necic acids. Some PAs are toxic and others not. Hepatotoxicity requires an unsaturated 3-pyrroline ring, one or two hydroxyl groups attached to the pyrroline ring, one or two esterified groups, and the presence of a branched chain on the acid moiety.[24] Without these structural features, the PAs are not changed to a toxic metabolite. It appears that the majority of PAs are not toxic.

Toxicity of PAs

Acute toxicity. An excellent summary of the information available up to 1986 is presented in a book published by the United Nations Environment Programme and the WHO.[26] This 226-page publication is based on the work of a WHO task group on Environmental Health Criteria for Pyrrolizidine Alkaloids in 1988. This publication is also available on the Internet at http://www.inchem.org/documents/ehc/ehc/ehc80.htm

The first recorded instance of PA intoxication in humans was in South Africa, when many people in the Western Cape suffered from liver cirrhosis after eating bread made with wheat contaminated with *Senecio burchellii*.[34] Mattocks[26] lists human intoxications occurring before 1986. *Heliotropium* species caused fatalities in Afghanistan, Hong Kong, India and the USSR. *Senecio* species caused intoxication in South Africa and U.S.A. *Crotalaria* species caused intoxication in Ecuador, India and the West Indies. In the majority of cases, the intoxication was caused because the plants were used as a medicine. At least nine major intoxications have occurred thus far.[7] In 1993, a *Heliotropium* species in grain affected 3906 people, representing 0.4% of the population, in Tajikistan.[35]

Monocrotaline is the most important PA in *Crotalaria* species. The LD_{50} for monocrotaline for acute intoxication in rats is 109–230 mg/kg.[33] The hepatotoxicity for the oral route is generally slightly lower than for the intraperitoneal route.[33] Apparently no incidences of acute *Crotalaria* toxicity to humans have been found in South Africa. *Crotalaria* species used as medicine have, however, caused toxicity in East Africa (*C. brevidens, C. incana, C. laburnifolia, C. mucronata, C. recta, C. retusa*), in Jamaica (*C. brevidens*), Asia (*C. laburnifolia, C. retusa*), and Sri Lanka (*C. verrucosa*).[26]

Acute toxicity with *Crotalaria* species may not be as serious a cause for concern if the required levels of toxic seeds in grain are calculated. Major differences in species susceptibility, and because apparently no tests on primates have been done, make this a dangerous assumption.

Chronic toxicity. A more important concern, however, is chronic toxicity. Because physicians examining patients with liver disease do not generally consider PA intoxication, many cases of intoxication are probably missed.[36] It has been calculated that the 0.1% tolerance for *Heliotropium lasiocarpum* seeds allowed in the former USSR could result in 1820 μg PAs per kg grain, and wheat contained 26 mg/kg of three PAs from *Heliotropium europaeum*.[37] In Australia the PA content of grains varied from <50 to >6000 μg/kg.[7]

Human PA intoxication can also occur via milk, honey, eggs or tea made from toxic plants.

Grain contaminated with *Heliotropium europaeum* eaten by chickens led to PA concentrations of 26 ppm (0.0026%) of three PAs in eggs.[37] In Australian honey from bees feeding on *Echium plantagineum* flowers, toxic PAs up to 1000 μg/kg were found. This plant is a common weed in South Africa, but no evidence of stock loss has yet been reported. The annual stock loss cost in Australia amounts to A$30 million (Annual report, CSIRO Entomology, http://www.ento.csiro.au/research/rr95-97/weedm_tempweeds.html). Honey made from *Senecio jacobaea* contained up to 3200 μg/kg PAs.[37] Eggs contained levels of 5–168 μg/kg, and the levels in different grain commodities in Australia ranged from <50 to >6000 μg/kg.[7] There are currently no data on whether PAs occur in oilseed crops. From the levels attained in different food sources described above, and the fact that many acute intoxications have taken place, it is very likely that many people may be at risk of chronic intoxication by PAs.

After considering many intoxications that have taken place, and considering the differing toxicity of various PAs, the WHO task group[26] conclude that a daily intake of 10 μg/kg of heliotropine may lead to disease in humans. They also state that humans are sometimes markedly more susceptible to acute and chronic effects of PA than rats.

The Australia and New Zealand Food Authority has accepted a NOEL value of 1 $\mu g\ kg^{-1}\ day^{-1}$.[7] This is probably based on a case study where veno-occlusive disease was diagnosed in a woman who regularly used ground comfrey root. Ridker[38] calculated that her diet included 15 $\mu g\ kg^{-1}\ day^{-1}$ of PA. The Australia New Zealand Food Authority[7] incorporated a safety factor to allow inter-individual differences to reach the level of 1 $\mu g\ kg^{-1}\ day^{-1}$.

Carcinogenicity

In addition to hepatotoxic effects, some PAs are carcinogenic. The LD_{50} for rats varies between 34 and 400 mg/kg for different PAs.[33] A dose of 5 mg/kg of monocrotaline fed to rats over an extended period led to liver cancer in 17 of 60 rats.[39] To date, PA metabolites have been shown to cause cancer only in rodents. No conclusive evidence for cancer in humans has been shown. Follow-up studies on survivors of large-scale human toxic outbreaks have not indicated abnormal cancer incidence in these populations.[7] It has been proposed that human liver repairs DNA more efficiently than liver of rodents.[24]

Monocrotaline, the hepatoxic PA occurring in *Crotalaria* species, had a high mutagenic activity in the *Drosophila melanogaster* assay.[40] It is possible that the high rate of liver cancer and cirrhosis in Africa and Asia could be associated with long-term exposure to toxic PAs, especially since aflatoxins that occur in grain products in Africa may increase the sensitivity to PAs in primates.[27]

Teratogenicity

Some PAs can also pass the placenta in rats and lead to embryo toxicity. Although young animals seem to be more resistant than adult animals, ingestion of PAs may lead to embryo toxicity in the pregnant females. Veno-occlusive disease has been reported in an infant born from a mother taking a herbal tea made from *Tussilago farfara* (coltsfoot), which contained 0.6 mg/kg senecionine.[41]

Possible genotoxicity

The German Federal Health Bureau established regulations that placed a limit of 0.1 μg hepatotoxic PA and their *N*-oxides in a daily dose of herbal medicines. If prescription is limited to 6 weeks per year, the maximum daily dose is 1 μg per day.[37] The basis for this stringent level could not be assessed. It may be because some PAs may be genotoxic and a single molecule of a genotoxic carcinogen has the potential to induce a fatal genetic change.[33,35] Eggs, honey and milk may contain levels up to 1000 times these levels. The validity of the German levels formulated

for prescribed phytomedicines, which are under strict control, will have to be confirmed by more research before it is extrapolated to food.

This, and the preliminary results indicating the possible genotoxic carcinogenicity, has led to a clamp-down on allowable levels of PAs in Europe to 0.1 μg per day for herbs that have proven efficacy.

Calculated from the Australian data,[7] a teaspoon of porridge made from the most contaminated grain encountered would exceed the Europe levels approximately 100-fold, and a teaspoon of the most contaminated honey encountered would exceed the value about 100–300-fold.

Susceptibility of different organisms to PAs

There are wide differences in the toxicity of different PAs for the same species. There are also large differences in susceptibility of different species to PAs. Factors such as sex, age, biochemical, physiological and nutritional status all affect the toxicity.[42] Some moths and butterflies and at least one grasshopper can accumulate PAs, which may act as a defence against predators.[43]

Pigs and poultry are most sensitive to PAs, followed by horses and cattle, while sheep and goats are most resistant. Sheep can consume up to three times their body weight of certain PA-containing toxic plants without any measurable abnormalities.[44] Because animals with a rumen are more resistant to PAs, Lanigan[45] investigated rumen bacteria and isolated *Peptostreptococcus heliotrinreducens,* which could break down toxic PAs to non-toxic metabolites. This work has since then been continued.[46] The difference in sensitivity is not only caused by the metabolism to non-toxic metabolites, but also by the rate of metabolism to the lethal product. Part of the PAs absorbed is also excreted if the rate of change to the toxic metabolite is not high enough.

Situation in South Africa

Fortunately, species that cause major problems overseas, such as *Heliotropium popovii,*[47] do not occur in South Africa, although 19 other species do grow here.[27] *Senecio madagascarensis* introduced into Australia has spread over vast regions of southeast Queensland and has caused toxicity problems.[24] It is interesting that *Echium plantagineum* (Patterson's curse), a major problem plant in Australia, does not cause problems in South Africa. It is not clear whether this is due to genetic or environmental factors. Obviously, care has to be taken that weed seed is not introduced into South Africa.

Many of the more than 300 *Crotalaria* (rattle pod) species occurring worldwide contain PAs.[33] Monocrotaline is the most important PA in this genus. In South Africa 71 species occur.[27] Mattocks[33] lists 43 *Crotalaria* species with unsaturated PAs, including *C. juncea, C. dura, C. globifera* and *C. spartioides,* occurring in South Africa.

Twelve of the *Crotalaria* species investigated up to 1981 contain only esters of saturated necines, that is, PAs that are not hepatotoxic.[25] *C. juncea* contains such low concentrations of PA that it is used as a cattle fodder without any negative effects.[48]

However, the seed has been shown to be pneumotoxic to horses.[49]

In South Africa *C. spartioides* (duinebos) leaves and stems results in typical veno-occlusive hepatic damage in cattle.[11] Similarly *C. dura* and *C. globifera* (jaagsiektebos) material causes a chronic fatal pneumotoxic syndrome known as 'jaagsiekte' in horses.[11] *C. juncea* leads to the same syndrome and additionally results in the loss of wool in sheep.[11] *C. burkeana, C. barkae,* possibly *C. rhodesiae, C. steudneri* and other annual species result in transient laminitis, colloquially known as 'stywesiekte', in cattle and equines. This is associated with liver pathology in equines, but not in cattle. This toxic principle has not yet been determined.

C. sphaerocarpa (maize crotalaria) is the *Crotalaria* species most likely to contaminate grain in southern Africa. *C. sphaerocarpa* has apparently not been analysed chemically. According to the minutes of a meeting held between different role players in 1985, the Bothaville district has the highest incidence of *Crotalaria* occurring in maize crops. Of 590 loads of maize, eight had to be returned. It was not certain, however, if this was due to the occurrence of *Crotalaria* or for another reason.

No evidence of acute toxicity has yet been found for *C. sphaerocarpa.* Several unpublished experiments carried out at Onderstepoort could not show that *C. sphaerocarpa* is acutely toxic to stock. *C. sphaerocarpa* is, however, included in the poisonous plant database of the U.S. Food and Drug Administration, Centre for Food Safety & Applied Nutrition Data (http://vm.cfsan.fda.gov/~djw/plantnam.html). No tests for chronic toxicity have yet been carried out on *C. sphaerocarpa.*

The individual seed dimensions (*c.* 2 × 3 mm) should allow easy removal by normal sieving. The seedpods (2–3 × 4–6 mm) containing two seeds may not be removed that easily. If the seedpod is dry the individual seeds are, however, readily released by handling.

Calculation of level of toxic seed allowed

Acute intoxication

Present information, which has to be confirmed, indicates that *Crotalaria* intoxication of humans via grain is not a serious problem in South Africa due to the low seed mass of *C. sphaerocarpa* and suspected low toxicity. Indirect intoxication via eggs, honey or milk may be a problem if contaminated feed is provided to animals or if bees feed on more toxic plants.

A 5 mg/kg per day dose of monocrotaline to rats led to long-term chronic effects in approximately a third of the animals.[39] A 10-fold decrease to approximate a non-toxic concentration, coupled to a 100-fold decrease to make up for species differences, means that a dose of 5 μg/kg per day would probably be equivalent to a NOAEL for humans.

Toxin content of seed

Marais[50] recovered 0.27% and 0.18% of the toxic PA dicrotaline from crude extracts of *C. dura* and *C. globifera.* If the crude extract removed 20% of the dry mass of the seed of *C. dura* and *C. globifera,* that means that seeds contain about 0.05% of dicrotaline. We have determined that a single bean-shaped seed of *C. sphaerocarpa,* with average diameters of *c.* 2 × 3 mm, weighs 3.6 mg (n = 100). Based on the assumption that 0.05% of the mass of the seed represents dicrotaline, a single seed would therefore contain 1.8 μg of dicrotaline. If dicrotaline has the same toxicity in rats as monocrotaline, a 70-kg person would have to ingest the equivalent of 70 × 5/1.8, that is, 194 seeds per day to have a dose of 5 μg/kg per day calculated from the rat data, with safety factors. In the case of maize, 500 g dry meal provides two meals per day. This means that 500 g of maize should not contain more than 194 seeds; and 10 kg should not contain more than 3880 seeds for acute toxicity. This is more than three orders of magnitude higher than present regulatory levels.

Chronic toxicity

If we accept the Australia and New Zealand Food Authority level of 1 μg kg^{-1} day^{-1}, and one seed contains 1.8 μg of toxic PAs, if

a 70-kg person eats 500 g of maize per day, the number of seeds per 10 kg of maize is reduced to 777.

Genotoxicity

If we accept the extremely strict European value of 0.1 μg PAs per day, the levels drops to 11 seeds per 10 kg.

Discussion

An assessment of the exposure to these toxic seeds in food and feed is an essential part in characterizing the risk. In large-scale commercial farming the application of herbicides may largely eliminate weeds that produce toxic seed. In some cases, such as *Datura* and *Xanthium* species, however, if herbicides are used early, fresh weeds germinate later and grow and mature fast enough to ripen with grains such as maize. The cost of 100% control of weeds is high and has to be evaluated in the overall benefit-cost to the producer and consumer.

Food produced in subsistence farming may pose a greater risk because of less-sophisticated agricultural practices. Legislation on toxic or potentially toxic contaminating seed will have little effect on mitigating this risk. Rather, communities should be informed of the risk associated with certain seed. Removing weeds producing toxic seed by hand would be feasible as the grain is mainly hand-cropped.

It is difficult to generalize about PAs because of the large differences between individual compounds and even between individual hepatotoxic PAs. The difference in susceptibility of species is caused by complicated factors governing detoxification, excretion and biotransformation to the toxic metabolites. Based on the assumptions listed and on our present knowledge, 10 seeds of *Crotalaria sphaerocarpa* per 10 kg of grain should be a safe level. This is higher than the 1 seed per 10 kg required by the 1987 regulations[15] or the 3 seeds per 10 kg previously enforced by agricultural board.[16] In the latest development,[17] the Department of Health has changed the level to 10 *Crotalaria* seeds per 10 kg grain as an interim measure until research confirms the validity of the assumptions we make in this paper.

One or two changes may, however, have a serious effect on the level recommended. If, for example, the level of PA in *C. sphaerocarpa* seed is the same as the 1.89% of monocrotaline in *C. retusa*[51] as quoted,[10] instead of the 0.05% inferred for *C sphaerocarpa* by Marais,[50] the recommended level based on the European standard falls to 0.25 seed per 10 kg grain. Other *Crotalaria* species apparently have much heavier seed. A 10-fold increase in seed mass will lead to a 10-fold decrease in allowable seed levels This may explain why Australia does not allow any *Crotalaria* seed per 500 ml of grain.[1] On the other hand, in the United States two *Crotalaria* seeds are allowed per kg of grain.[1] The differences may be based on differing toxicities of *Crotalaria* species in different countries. Once again, this emphasizes the importance of obtaining trustworthy information on *Crotalaria* toxicity.

Apparently, the only *Crotalaria* species growing in association with cultivated grain in South Africa is *C. sphaerocarpa,* the maize crotalaria. No other possibly PA-containing plants seem to be so connected. There is consequently little chance of PAs contained in other foods adding to the food-basket effect.

To ensure scientifically acceptable levels, the following questions need to be answered:

- Does *C. sphaerocarpa* contain toxic PAs at acute or chronic levels?
- Is there a difference in PA levels of *C. sphaerocarpa* in different populations or growing under different environmental conditions?
- Do any other *Crotalaria* species occur in cultivated grain lands?
- How toxic are other *Crotalaria* species occurring in South Africa that may contaminate grain, and which PAs occur in different populations of these species?
- What is the mass and toxin content of seed of these other species and how serious is the potential hazard?
- To what level are PAs removed by processing of the different grains?
- Can the evidence for a genotoxic effect for toxic PAs occurring in *Crotalaria* species be confirmed?
- Can a method sensitive enough be devised to determine the levels of toxic PAs in food ready for human consumption?
- Should government regulate the concentration levels of the active ingredient of the toxic seed in food or regulate toxic seeds levels in grain as a preventative measure?
- What is the threat to South African consumers of grain products imported from grain producers containing more toxic PA contaminants, and can different levels of PA-containing seed be justified for local and imported grain?
- Is it possible to develop a technique that would assess the toxic PA content and the toxicity directly instead of counting seed, which varies so much in toxicity?

The research required could be expensive because it includes animal studies. The latest preliminary levels accepted by the Department of Health based on our research findings are acceptable to the grain industry. Whereas it was willing to support research on toxic seed in grain before the regulations were changed, the grain industry is not interested in financing further research. We stress that our conclusions are based on certain assumptions and that these assumptions have to be tested. The question remains, who should be responsible for financing research on a potential public health hazard? Especially in South Africa, where substantial aflatoxin-related liver toxicity occurs, the possibility of PA-enhanced liver disease[27] should not be taken lightly. Owing to the possible genotoxic effect of hepatotoxic PAs, the guideline of ALARA levels should be enforced in staple food such as maize, especially since Australia allows no *Crotalaria* seeds at all in grain.

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