

# Epidemiology and Toxicology of Arsenic Poisoning in Domestic Animals

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Arsenic poisoning is one of the more important causes of heavy metal poisoning in domestic animals. Two species—dogs and cattle—are intoxicated more frequently than other animals; yet sporadic instances of poisoning have been observed in cats, horses, and pigs. Cases observed by veterinary clinicians are either peracute, acute, or chronic intoxications. Frequently the initial and only indication that a severe problem exists with peracute poisoning in a cattle herd is dead animals. Chronic intoxications are also observed in cattle. Acute intoxication is the most common form of arsenic poisoning observed and documented in the dog. Also intoxicated dogs were younger, i.e., 2-6 months of age. Arsenic is a severe alimentary tract irritant in domestic animals, and treatment in most instances consists mainly of symptomatic and supportive treatment. The source of intoxication, when it can be determined, is usually dips, sprays, powders, or vegetation contaminated by pesticides containing arsenic.

## Introduction

Arsenic is second only to lead as a cause of heavy metal intoxication in domestic animals. Clinically, arsenic intoxication occurs as an acute or peracute intoxication, although chronic forms of the disease have been observed, especially in cattle. Intoxication results from consumption of the trivalent inorganic or organic forms of arsenic. Trivalent arsenic is the more toxic form of the element for domestic animals (1). Arsenic occurs in small amounts naturally in soil and native vegetation (2, 3). However, most instances of intoxication result from the consumption of soil, vegetation, or discarded materials that contain or are contaminated with high levels of arsenic. When the source of the intoxication can be found, it is usually herbicides or insecticides containing arsenic. Described in this report is a review

of the basic toxicology of arsenic intoxication in animals and an evaluation of the medical records from 13 North American veterinary colleges‡ for the 11-year period of 1964-1974. We also reviewed cases from the Missouri State Diagnostic Laboratory at Columbia, Missouri, as well as selected data collected by the authors in their field investigations of suspected intoxication outbreaks in cattle, later documented as arsenic intoxication.

## Background

Man and lower animals are highly susceptible to inorganic arsenic. But in the diagnostic laboratory, arsenic poisoning is most frequently encountered in the bovine and feline species resulting from contamination of their food supply. Occurrence of arsenical poisoning in these two species is closely followed in other forage-eating animals, such as the sheep and horse. Arsenical poisoning in most animals is usually manifested by an acute or subacute syndrome. Chronic poisoning, although it has been reported in animals, is seldom seen and has not been clearly documented. Experience with field cases of arsenic poisoning indicates that animals which are weak, debilitated and dehydrated are much more susceptible to arsenic poisoning than normal animals. This may be because of reduced excretion rate via the kidneys (4).

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Inorganic arsenic is found in nature and is synthesized in many complex and varied forms, having many uses from medicinal to forensic. In practice, the most dangerous arsenical preparations are dips, herbicides, and defoliants in which the arsenical is in a highly soluble trivalent form, usually trioxide or arsenite. Unfortunately, animals (such as dogs and calves) will frequently seek out and eat materials such as insulation, rodent baits, dirt, and foliage that have been contaminated with an inorganic arsenical.

Soluble forms of arsenic, such as sodium arsenite, are readily absorbed from all body surfaces. Arsenic trioxide and other less soluble arsenicals are poorly absorbed from the digestive tract and are largely excreted unchanged in the feces. Once absorbed, pentavalent arsenic is readily excreted by the kidneys, whereas trivalent arsenic is more readily excreted into the intestine via the bile. It is generally considered that regardless of whether an arsenical is introduced into the body as trivalent or pentavalent arsenic, all the major actions can be attributed to the trivalent form. Arsenicals are suspected of having a metabolic function (5) and ultimately, they exert their effects by reacting with sulfhydryl groups in cells (6).

While most textbooks report that arsenic is accumulated in the tissues and slowly excreted, this phenomenon appears to be true only in rats. Most species of livestock and pet animals apparently rapidly excrete arsenic (7). This phenomenon is very important when one considers arsenic levels in tissues as a means of confirming suspected poisoning.

Peracute and acute episodes of poisoning by inorganic arsenic are usually explosive with high morbidity and moderate mortality over a 2- to 3-day period. Symptoms are manifested by intense abdominal pain, staggering gait, extreme weakness, trembling, salivation, vomiting (in dogs, cats, pigs, and perhaps even cattle), diarrhea, fast, feeble pulse, prostration, rumen atony, normal to subnormal temperature, collapse, and death.

In subacute arsenic poisoning, animals may live for several days, exhibiting depression, anorexia, watery diarrhea, increased urination at first followed by anuria, dehydration, thirst, partial paralysis of the rear limbs, trembling, stupor, cold extremities, subnormal temperature, and death. The watery diarrhea may contain shreds of intestinal mucosa and blood. Convulsive seizures have been reported but are not an expected manifestation. Poisoning from arsenical dips usually results in some of the signs noted previously, in addition to blistering and edema of the skin followed by cracking and bleeding with associated secondary infection (4).

Characteristic gross lesions associated with inorganic arsenic poisoning include reddening of the gastric mucosa (abomasum in ruminants) which may be localized or general, reddening of the small intestinal mucosa (often limited to the first few feet of the duodenum), fluid gastrointestinal contents which are sometimes foul smelling, soft yellow liver and red, edematous lungs. In peracute cases of poisoning, occasionally no gross postmortem changes are noted. The inflammation is usually followed by edema, rupture of the blood vessels and necrosis of the mucosa and submucosa. Sometimes the necrosis progresses to perforation of either the stomach or intestine. The fluid gastrointestinal contents may contain blood and shreds of mucosa. Hemorrhages on all surfaces of the heart and on the peritoneum may occasionally be observed (4, 8).

Histopathologic changes include gastric and intestinal edema of the mucosa and submucosa, necrosis and sloughing of mucosal epithelium, renal tubular degeneration, hepatic fatty change and necrosis, and capillary degeneration in vascular beds of the gastrointestinal tract, skin, and other organs. In cases involving cutaneous exposure, a dry, cracked, leathery, peeling skin may be a prominent feature.

The urine of poisoned animals may contain protein, red blood cells and casts. The arsenic level in the urine varies with the form of arsenic, route of exposure and species but usually ranges from 2-10 ppm (4).

## Materials and Methods

Medical records in the Veterinary Medical Data Program (VMDP) for the years 1964-1974 were reviewed for cases with a diagnosis of arsenic intoxication. The VMDP is a data collection and storage registry sponsored by the National Cancer Institute, to which veterinary university hospitals/clinics submit standardized abstracts about each medical episode occurring at their facility. All diagnoses of arsenic poisoning were considered regardless of the diagnostic techniques used to arrive at a diagnosis. In a majority of instances the diagnosis of arsenic intoxication was based only on clinical observations. Also, because a majority of the intoxications occurred in two species—dogs and cattle—major considerations of the epidemiology and toxicology were confined to these two species. Furthermore, comparison with controls, i.e., cases presented to one of the clinics without arsenic intoxication, will be considered only for dogs as approximately 70% of the arsenic intoxicated animals observed in the 13 veterinary hospitals/clinics occurred in this species. The medical records in the VMDP registry were either compiled directly from a disk file or

they were abstracted onto computer cards and analyzed using the Statistical Package for the Social Sciences (SPSS) or the Statistical Analysis System (SAS) computer programs (9, 10).

The effects of the independent variables of age, breed and sex upon a diagnosis of arsenic poisoning were evaluated by estimating the relative risk of occurrence by Gart's method (11). Comparisons were made with a reference population drawn from the same medical facilities and study period as the case series. The reference population was tabulated by the patient-years-at-risk method.

In addition to reviewing the veterinary clinic records, the records of one of the diagnostic clinics in Missouri was reviewed for possible instances of arsenic intoxication. With these records, a majority of the instances of arsenic intoxication occurred in cattle. In some of these outbreaks one of the authors conducted field investigations and/or had analyzed tissues or feed for arsenic. "Typical" examples of these investigations will be presented to facilitate our discussion of the toxicology and epidemiology of arsenic intoxication in domestic animals.

## Results

Between June 1964 and July 1974 a total of 93 animals were diagnosed as having arsenic intoxication in the VMDP registry. Of these 93 animals shown in Table 1, 64 (69%) were dogs, 18 (19%) cattle, 5 (5%) cats, 4 (4%) pigs, and 2 (2%) were horses. Thirty-three (35%) of the cases were treated as outpatients. Of those animals hospitalized the median length of hospitalization was less than 2 days. Sixty-eight (73%) of the animals survived the initial intoxication experience. Approximately 10 patients with arsenic intoxication were diagnosed annually from 1968 to 1974, except 1970, when 21 animals were seen with arsenic intoxication. A majority of these animals were intoxicated cattle. This represents 44% of the total of cattle diagnosed with arsenic intoxication during our survey period.

Table 1. Incidence of arsenic intoxication by species: Veterinary Medical Data Program, 1964-1974.

Species	Frequency	Percentage
Dogs	64	68.7
Cattle	18	19.4
Cats	5	5.4
Pigs	4	4.3
Horses	2	2.2
Total	93	100.0

Table 2 presents a comparison of selected variables for dogs ( $N = 64$ ) and Cattle ( $N = 18$ ). Approximately twice as many dogs as cattle were treated as outpatients, and for those animals hospitalized the median number of days that they were hospitalized was half as long for dogs as it was for cattle. Another contrasting variable was that 83% of the dogs were discharged alive, where only 50% of the cattle were discharged alive from the clinics. Concerning clinical procedures, 53% of the dogs were diagnosed strictly on clinical findings, whereas only 22% of the cattle were diagnosed with the same criteria. Figure 1 gives the percentage distribution by month of arsenic poisoning diagnosed in dogs and cattle for the complete study period. The month which was the mode in most species was June. The fluctuation in this particular chart for cattle percentages may be due in part to the small number of animals observed.

Table 2. Comparison between dog and cattle arsenic intoxication for selected variables: Veterinary Medical Data Program 1964-1974.

Variable	Average value	
	Dogs ( $N = 64$ )	Cattle ( $N = 18$ )
Treated as outpatients, %	33	17
Median time of hospitalization for inpatients, days	1.3	3.5
Female, %	56	56
Discharge status	83% alive	50% alive
Median age, months	9	12
Clinical procedures		
Clinical diagnosis only, %	53	22
Gross pathology, %	14	33
Histopathology, %	14	28

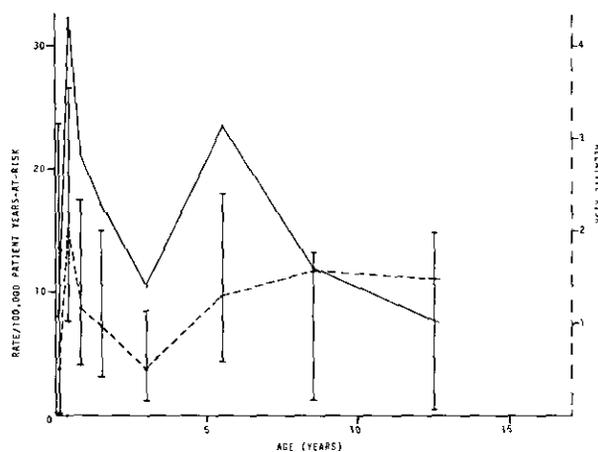


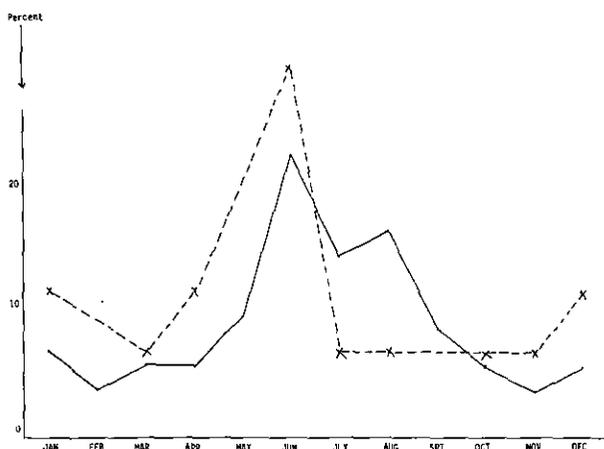
FIGURE 1. Percent distribution, by month, of arsenic poisoning diagnosed (●) in dogs ( $N = 64$ ) and (×) in cattle ( $N = 18$ ) by Veterinary Medical Data Program (VMDP) participants through 1975 (FY).

Taking the analysis a step further, Table 3 presents the crude attack rate per 100,000 patient-years-at-risk for the 64 dogs observed with arsenic poisoning. This distribution appears bimodal with two peaks, one in 1970, one in 1972 respectively. However, in pursuing this type of analysis further,

**Table 3. Arsenic poisoning in 64 dogs seen by participants, Veterinary Medical Data Program.**

Year	Number of cases	Crude rate/100,000 patient years-at-risk
1964-1969	15	14.72
1970	10	24.56
1971	8	18.20
1972	12	24.10
1973	9	15.88
1974	10	16.60

Figure 2 presents the attack rate per 100,000 patient-years-at-risk adjusted by age and sex, as well as the relative risk, for dogs with arsenic poisoning. This adjusted attack rate was again bimodal, with the highest peak in dogs 2-6 months of age and second highest peak occurring in dogs 4-6 years of age. However, the age risk values indicate 2-6 months of age as the time of life of significant risk in dogs. Finally, the last comparison made with the clinical data was a breed risk for dogs. Risk values calculated for breeds represented by six or more cases among the series by sex are shown in Table 4. No significant association was detected



**FIGURE 2.** Rate/100,000 patient years-at-risk adjusted for sex by age and relative risk by age (the vertical lines represent 95% confidence intervals). The data represent 64 dogs with arsenic poisoning.

( $p \leq 0.05$ ) between arsenic poisoning and these patient characteristics.

We then turned our attention to an evaluation of the Veterinary Medical Diagnostic Laboratory rec-

**Table 4. Estimated relative risk { of arsenic poisoning by breed and sex in dogs reported to the VM DP, 3/64-12/74.**

	Observed	R <sup>a</sup>	95% confidence interval <sup>b</sup>
<b>Breed</b>			
Dachshund	6	2.0	0.83-5.14
German shepherd dog	6	1.3	0.54-2.96
Poodle, miniature and toy	7	1.2	0.52-2.82
All breeds combined	64	1	
Mix breed	14	0.9	0.43-1.53
<b>Sex</b>			
Female	36	1.3	0.75-2.12
Male	28	1	

<sup>a</sup>Adjustment made for sex in determining breed risk; for breed in determining sex risk.

<sup>b</sup>When confidence interval includes 1, R is not significantly different from that among the reference group at  $p < 0.05$ .

ords at the University of Missouri-Columbia for the period January 1970-December 1975, i.e., the period during which records were available. A total of 26 cases of arsenic toxicosis were diagnosed in livestock at this diagnostic laboratory. A comparison of the number of instances of intoxication by species by year is presented in Table 5. The major-

**Table 5. Frequency of arsenic intoxication observed by species and year at the Veterinary Diagnostic Laboratory, Columbia, Missouri.**

Year	Cattle	Swine	Equine	Cat	Dog
1970	4	—	—	—	—
1971	4	—	—	—	—
1972	3	1	—	—	1
1973	5	1	—	—	1
1974	2	—	—	—	—
1975	2	2	—	—	—
1976 (to July)	4	—	—	1	1
Total	24	4	—	1	3

ity of those that were diagnosed in this laboratory were cattle. Taking this analysis a step further, the records that were available between 1970-1975 were then examined to try to determine the number of animals in the herd, number of animals affected, i.e., primarily those that died from the intoxication, possible case fatality rate, as well as the source of the arsenic intoxication. These results for some 12 outbreaks are summarized in Table 6. As shown in Table 6, in 58% of the outbreaks the source of intoxication was determined. To give a better appreciation of the difficulties involved in documenting field outbreaks of arsenic intoxication, the following examples are presented.

**Outbreak A.** Weeds were sprayed with a herbicide containing sodium arsenite as part of the maintenance program on a defense establishment in west central Missouri. The person applying the

Table 6. Number in herd, mortality, case fatality ratio and possible source of intoxication for cattle with arsenic poisoning, University of Missouri Veterinary Clinic—Columbia.

Farm ID	Number in herd	Number dead	Case/fatality rate	Source of arsenic
1	26	24	0.92	Herbicide
2	79	8	0.10	Herbicide or grasshopper bait
3	16	6	0.38	Cattle had access to an old house; were found eating a white powder in the house.
4	100	1	0.01	None determined
5	95	1	0.01	None determined
6	200	11	0.06	None determined
7	10	5	0.50	Access to trash, refuse, etc.
8	60	5	0.08	Road fence sprayed with brush killer 55.8% sodium arsenite
9	38	2	0.05	None determined
10	30	3	0.10	Powder containing 18,750 ppm arsenic
11	25	2	0.08	None determined
12	30	2	0.07	None determined (Liver 150 ppm arsenic)
13	30	8	0.27	Fence row sprayed with brush killer
14	25	18	0.72	Mixed in feed from unmarked container 40% sodium arsenite
15	36	11	0.31	Herbicide 40% sodium arsenite
Totals	800	107	0.13	60% suggested source of arsenic intoxication

weedkiller sprayed through the fence, covering weeds for a yard or so outside the defense station fence, and 24 of 26 young cattle in this adjacent pasture died of arsenic poisoning. Field observations and a history suggested that the cattle appeared to be attracted to foliage which had been sprayed with arsenical herbicide.

**Outbreak B.** An owner uncovered a metal drum in a corner of a combination machinery shed and hay barn. The container was so old that any original labels were lost or had become illegible. He thought the drum contained a molasses supplement, so he mixed the contents with feed which was then fed to feeder calves. The cattle became seriously ill within a few hours and many died. Necropsy of the dead cattle revealed evidence of arsenical poisoning. Tests for arsenic on tissue and contents of the digestive tract were positive for arsenic. The remains of the material in the drum which the owner thought was molasses proved to contain 40% sodium arsenite, undoubtedly a weed killer and not a molasses supplement! The owner lost 18 of 25 calves.

**Outbreak C.** A rancher stated that his cattle were "eating dirt," and it was poisoning them. He submitted a dead animal to necropsy after his local veterinarian had made a tentative diagnosis of arsenic poisoning. The soil sample, as well as tissues from the dead animal, contained high levels of arse-

nic. Search of the site where the cattle were seen to be "eating dirt" revealed that the cattle had unearthed an old metal drum, buried many years ago along with other trash. Time and erosion had exposed the arsenic container, and the cattle finished uncovering it. As in outbreak A, cattle seemed to be attracted to discarded material or soil containing arsenical compounds.

## Discussion

The clinical and toxicological signs of arsenic intoxication in domestic animals have been the same since the disease was first reported. Arsenic is not highly corrosive; it does, nevertheless, cause severe inflammation, eventual edema, and subsequent necrosis of the gastrointestinal mucosa and submucosa, if the animal survives the peracute phase. Thus, the major clinical sign seen is a severe gastroenteritis, primarily a diarrhea.

If one counts specimens sent to the diagnostic laboratory with a request that the specimen be analyzed for arsenic, one would include a majority of the diarrheas of unknown etiology. What is presented herein are the confirmed cases of arsenic intoxication in domestic animals; as such, they represent only a small portion of the true incidence. The incidence of arsenic intoxication reported to our diagnostic laboratory agrees with the observa-

tions of Hatch and Funnell, who reported 21 positive diagnoses of arsenic poisoning in cattle during an 8-year period in Ontario, Canada (12).

Common sources of arsenic, when the source could be determined (Table 6), included sprays, dips, and powders used as insecticides or herbicides. In a majority of the intoxicated cattle this material was consumed voluntarily from such sources as feed, contaminated soil, materials left on trash piles, in vegetation along fence rows, or around buildings that had been sprayed with a weed killer. In approximately 80% of the dogs intoxicated with arsenic, the source was found to be ant or roach bait containing arsenic, e.g., a sodium-arsenate compound. In these instances, the dogs were presented to the clinic with a history of vomiting and some muscular weakness and muscular trembling. Subsequent interview with the owner suggested that in a majority of cases an insecticide containing arsenic had been used in the area where the dog was housed or allowed to roam free. Many times owners of poisoned animals are not aware that an arsenical compound was available; that is, they do not realize that ant bait may contain arsenic.

In many cases of arsenic intoxication in large animals, no source of arsenic was detected. Often considerable effort is required on the part of the clinician or diagnostician to assist owners in finding the source. It is characteristic that the owner will "look harder" when a positive diagnosis of arsenic intoxication has been confirmed or suggested. A positive clinical diagnosis of arsenic intoxication stimulates owners to help detect the source of the compound. In the instance of intoxication in large animals, often a field trip is an invaluable aid to the clinician and toxicologist in defining the location of the source of the compound, since the owner may not be aware of what to look for (e.g., signs of eating treated foliage, remains of containers or powders) as a source. Cattle owners used the compound frequently as a weed killer, and it was only on subsequent investigation that it was documented that such compounds were the cause of the intoxication. One statement we have made to owners in the past on field investigations is: "You and I have been searching this pasture for an hour looking for the source of the intoxication. These calves have been present in this pasture for approximately 3 to 10 days, and they have been more successful in locating the source for consumption and intoxication." It sometimes appears that animals, especially cattle, develop an increased desire to consume weeds sprayed with an arsenic weed killer, not because of a change in palatability of the plant but possibly because arsenic compounds tend to taste salty, and thus attractive, to the animals.

In diagnosis of arsenic intoxication, wet chemistry tests, such as the Reinsch test (13), are used as a screening tool; and, if positive, then more definitive chemical analysis must be used to quantitate the levels of arsenic; e.g., arsine evolution (14). A positive test does not conclusively confirm arsenic intoxication, for this test is sensitive to as little as 2 ppm of arsenic. In Missouri, for example, the geometric mean of arsenic found in soil varied from 13 ppm in the glaciated prairies portion of the state to approximately 7 ppm in the oak-hickory-pine area. In every sample of soil that was analyzed for arsenic, the inorganic form of the element was detected in all of the major vegetation-type areas (3).

If we contrast the epidemiology of arsenic intoxication in the major species that were presented to our diagnostic laboratory and 13 veterinary clinics, we see quite a different view. A majority of the small animals, dogs and cats, are admitted to the veterinary clinic; whereas a greater majority of cattle cases are submitted to the diagnostic laboratory or seen on ambulatory service. The picture of arsenic intoxication by species is in part related to the type of animal population that these two facilities observe during the year. Dogs are more apt to be treated as outpatients than cattle. Also dogs were hospitalized a shorter period of time and more of them survive the intoxication, possibly not because of greater resistance to the arsenic, but rather because of a lower degree of exposure. In addition, most intoxications in dogs were diagnosed solely on a clinical examination and history. Younger animals are more likely to be intoxicated with arsenic. For example, in calculating the rate of arsenic poisoning for 100,000 dog-years-at-risk, adjusting for sex and age (see Fig. 2), there was a threefold increase for dogs 2-6 months of age compared to dogs under 2 months of age. Our initial impression before adjusting for age and sex was that possibly younger animals were being exposed to arsenic in the dam's milk; this is not the case. Further evaluation of the clinical records, however, did not support this hypothesis.

It has also been suggested that Thiacetarsamide, a trivalent organic arsenical and the only drug that has consistently been found to kill adult canine heartworms that infect dogs (15), might cause arsenic intoxication. Recent work by a number of clinicians shows that an animal treated for heartworms with the arsenical treatment schedule does have a temporary rise in some liver function tests and in some instances animals will die shortly after treatment, suggesting a reaction to the arsenical drug (16, 17). Yet, overt arsenic intoxication has not been confirmed as the cause of death.

Finally, in an earlier report we were concerned with the potential public health aspects of arsenic

intoxication, primarily in cattle and other food-producing animals (18). Depending on the form of the compound, arsenic may be excreted in the feces without absorption, with minimal absorption, or, if absorbed, it is primarily excreted through urine and the half-life is found to be fairly rapid, being a number of hours rather than days or weeks, compared to many other chemical compounds. The potential public health risks in cattle were felt to be minimal, if nonexistent. Preslaughter withdrawal after a single, acute exposure was recommended at 14 days; with multiple exposure 6 weeks withdrawal. In contrast, in the dog, the second species in which greater numbers of cases occurred, arsenic generally is consumed by a younger dog who is active, playful and inquisitive. The potential public health risk relative to dogs is not from a food-producing standpoint, but rather for children who are exposed to the same area as the pet. There is also a potential public health risk that has been associated with another domestic animal; i.e., sheep. It has been recognized that arsenic can cause skin and lung cancer, especially in sheep dip workers (19). Monitoring domestic animals with a history of arsenic intoxication may offer clues to environmental hazards yet unknown to humans.

## Addendum

According to information received from Bencko (20), excessive contamination of the environment by arsenic has resulted in the extinction of bees' colonies up to 30 km in the direction of the prevailing winds from the Novaky power plant in Czechoslovakia. Examination of soil and vegetation in the exposed area showed a relationship between arsenic in the soil and vegetation. The quantity of nitrogen in the soil was diminished with increasing quantity of arsenic. Also, soil samples containing approximately 165 ppm of arsenic showed diminished quantities of bacteria as well as protozoa, and no worms were found in samples containing arsenic in values about 150 ppm.

Influence of arsenic on the reproductive functions of domestic animals was encountered in this area. In a village near the power plant, there was a pig-breeding farm specializing in large-scale production of piglets. After the power plant went into operation, the incidence of abortions among sows increased with time to the point where it was necessary to close the farm and move it away from the power plant. Arsenic is known to be a capillary-toxic poison. Due to environmental pollution, the pregnant sows received in their forage sufficient doses of arsenic to damage the placental blood

capillaries to the extent that abortions began to occur. Abortion rates also increased among cattle in this area but did not reach epidemic proportions.

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