Reports of metaldehyde and iron phosphate exposures in animals and characterization of suspected iron toxicosis in dogs

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Objective—To describe reports of animals exposed to metaldehyde- and iron phosphate–containing molluscicides and characterize iron phosphate exposure incidents in dogs with clinical signs compatible with iron toxicosis.

Design—2-part retrospective case series.

Sample—1,500 reports of animals exposed to molluscicides containing metaldehyde (n = 1,285) or iron phosphate between 2001 and 2011 (n = 215; part 1) and a subset of 56 reports involving 61 dogs with suspected iron toxicosis (part 2).

Procedures—In part 1, a National Pesticide Information Center database was searched to identify reported exposures to metaldehyde- and iron phosphate–containing molluscicides before, during, and after a regulatory transition affecting metaldehyde product labeling beginning in 2006. Source of the report, number of animals, clinical signs, and deaths were evaluated. In part 2, reports involving potential iron toxicosis in dogs were additionally reviewed for signalment, circumstances of exposure, and product identification.

Results—Reports of metaldehyde exposures decreased each year between 2006 (n = 193) and 2011 (21), whereas reports of iron phosphate exposures increased between 2006 (n = 4) and 2010 (73); changes were not evaluated statistically. Animals had no clinical signs at the time of the call in 130 of 215 (60%) and 675 of 1,285 (53%) reports of iron phosphate and metaldehyde exposure, respectively. In dogs, 35 deaths were associated with metaldehyde exposure and no deaths were associated with iron phosphate exposure.

Conclusions and Clinical Relevance—Veterinary professionals should be aware of the potential for iron toxicosis following exposure to iron phosphate–containing molluscicides. (J Am Vet Med Assoc 2013;242:1244–1248)
dents involving animal exposures to metaldehyde or iron phosphate between October 1, 2000, and September 30, 2011. Study years were defined as the 12-month period from October 1 to September 30. For reports to be characterized as exposure incidents, reporters must have evidenced sufficient knowledge of the circumstances surrounding the exposure (ie, the reporter witnessed the exposure or the clinical signs personally) and the report had to be received within 2 years after the exposure event. Incidents lacking reasonable certainty about the product identity (ie, unknown molluscicide) were excluded.

Compilation of data from NPIC incident reports—Computerized records were searched for metaldehyde and iron phosphate exposure incidents during the study period. In the first part of the study, reports were evaluated for the caller's location (state), presence or absence of clinical signs in exposed animals, characterization of signs as compatible with or atypical for exposure to the reported substance, and deaths. In addition, the individual making the report was categorized as being a veterinary professional, being a member of the general public, or belonging to one of 19 other categories (eg, other medical professional, lawyer, or pest control professional). In the second part of the study, a more detailed review of reports involving iron phosphate exposure in dogs that had clinical signs compatible with toxicosis was completed. In addition to data compiled for part 1, records were evaluated to identify the circumstances of exposure (eg, access to the treated area or access to the product in storage), additional characteristics of exposed dogs (weight, age, breed, and sex), the product EPA registration number (a unique identifier for pesticide products that are marketed under a variety of brand names), and caller comments, if noted. Statistical analyses were not conducted to determine the significance of trends in exposure reports over time.

Classification of signs as compatible or atypical—At the time of data collection via telephone, pesticide specialists at the NPIC evaluate reported clinical signs and categorize these on the basis of available literature regarding the active ingredients involved. The NPIC maintains a library of case reports, peer-reviewed literature, books, and regulatory documents for most active ingredients. If, on the basis of the pesticide specialist's experience, reported signs vary substantially from those described in the literature, they are classified as atypical. Signs are considered compatible with exposure to the reported substance if the primary clinical sign or most of the clinical signs are consistent with those reported in the literature for the active ingredients involved and if the interval between exposure and onset of signs and the duration of signs are consistent with those described in case reports and other literature.

The NPIC staff members do not routinely evaluate the compatibility of clinical signs reported by veterinarians using the electronic reporting system; however, that analysis was necessary for purposes of the present study. Therefore, for study purposes, the criteria described for assessment of clinical signs in reports obtained via telephone were also used to classify signs in applicable reports received electronically.

Results

Molluscicide exposure reports—The majority of reports (1,419/1,500 [95%]) evaluated in part 1 of the study came from members of the general public; most often, animal owners telephoned for information or crisis management assistance. Seventy-six (5%) reports were received from veterinary professionals, often seeking the same type of consultation. Three reports were received from other medical personnel, 1 from a lawyer, and 1 from an unclassified caller. The reporter's location was recorded for 1,485 of 1,500 (99%) reports; these were received from 45 states in the United States and Puerto Rico. Most reports (1,217/1,500 [81%]) were from West Coast states, including California (830 [55%]), Oregon (208 [14%]), and Washington (179 [12%]). Some reports involved multiple animals.

Between 2001 and 2011, the NPIC received 1,285 reports of metaldehyde exposure incidents in animals. Although not tested statistically, an apparent increase in the number of reports was observed each year between 2001 and 2003, followed by decreasing numbers each year thereafter (Figure 1). During the same 11-year period, 215 reports involving iron phosphate exposure incidents were received, and the majority of these (195 [91%]) involved dogs. Most reports (179 [85%]) reports of iron phosphate exposure were received between 2004 and 2011. During the study period, 33 deaths of dogs were associated with metaldehyde exposure. Iron phosphate exposures were not associated with any reported deaths of dogs.

When all animals (including dogs, cats, chickens, toads, rabbits, and goldfish) were considered, those exposed to iron phosphate had no clinical signs at the time of the call in 130 of 215 (60%) reports; animals exposed to metaldehyde had no clinical signs in 675 of 1,285 (53%) reports. When clinical signs were de-
described, at least 1 of the signs was consistent with published reports regarding the active ingredient in 549 of 610 (90%) reports following metaldehyde exposure and 59 of 85 (69%) reports following iron phosphate exposure. Whether clinical signs developed after the time of the report was not evaluated.

Among 85 reports in which animals had clinical signs following iron phosphate exposure, signs were classified as atypical in 26 (31%). Of the remaining 59 reports where signs were classified as compatible with iron phosphate exposure, 3 involved species other than dogs (2 reports of 1 cat each and 1 report of 2 chickens). The remaining 56 reports involving 61 dogs were analyzed in further detail.

Characterization of suspected iron toxicosis in dogs—Forty-three of 56 (77%) reports of iron phosphate exposure in dogs evaluated in part 2 of the study were received from the owners, and 13 (23%) were received from veterinary professionals. Location was recorded for all reports; these were received from 12 states in the United States and Puerto Rico. Most (44 [79%]) reports originated from West Coast states, including California (30 reports), Oregon (8 reports), and Washington (6 reports).

The product EPA registration number was available in 43 of 56 (77%) reports. Two formulations were involved in all reports with documented product information, and each product contained approximately 1% iron phosphate. In 8 of these reports, the person calling expressed concern about language on the label implying that the product could be safely used around animals.

The 56 reports involved 61 dogs. Median weight of the dogs was 7.3 kg (16.0 lb) and ranged from 1.4 to 40.9 kg (3 to 90 lb). Median age was 3.0 years (range, 3 months to 15 years). Thirty-three of the 61 (54%) dogs were female, 23 (38%) were male, and sex was not specified for the remaining dogs; neuter status was not evaluated. Twenty-six (43%) dogs were of toy breeds as classified by the person calling. A wide range of breeds was represented in the incident reports.

In more than half of reports (31/56 [55%] reports involving 34 dogs), the caller indicated that exposure occurred after the molluscicide product was applied to a surface, typically in a residential outdoor setting. In 11 (20%) reports involving 12 dogs, exposures occurred when the product was stored inside a home or garage. Callers described exposures that occurred during application or at the staging area for mixing or loading of the product in 5 (9%) reports involving 5 dogs. Exposure scenarios for the remaining 9 reports (10 dogs) were unspecified. In 2 reports involving 1 dog each, the caller estimated ingestions of up to 0.91 kg (2 lb) of product/dog.

Vomiting was the most commonly reported clinical sign (40/56 [71%] reports involving 43 dogs). Other frequently reported signs included diarrhea (24 [43%] reports involving 24 dogs) and lethargy (14 [25%] reports involving 13 dogs). These signs were reported in varying combinations in 21 (38%) reports involving 21 dogs. Detection of blood in vomit (n = 3) or diarrhea (4) was sometimes noted.

Other signs reported in connection with iron phosphate exposures included anorexia (n = 8 dogs); apparent gastrointestinal distress (6), dehydration (3), or fatigue (4); staggered, uncoordinated movements (2); and seizure (1). Nonspecific subjective observations (eg, characterization of a dog as not acting normally) were not quantified.

Discussion

New precautionary language for metaldehyde product labels, required by the US EPA beginning in 2006 and 2007, may have contributed to the apparent decrease in the number of exposure incidents reported to NPIC beginning in 2006. For products containing metaldehyde intended for use in residential settings, schools, and similar locations, labels must now include language on the front panel that indicates children and pets to be excluded from the treated areas until the applied product is no longer visible.

According to the original reregistration decision made by the EPA, registrants of technical grade metaldehyde increased the amount of denatonium benzoate from 30 to 300 µg/g in late 2003. Denatonium benzoate is a bittering agent, intended to deter children and pets from eating a product. However, metaldehyde exposure incidents were reported to the NPIC in increasing numbers until 2006. If the new formulation for metaldehyde-containing molluscicides dominated the marketplace rapidly in 2004, the apparent increase in exposure reports in subsequent years may suggest that 300 µg/g denatonium benzoate was not completely effective in overcoming the attraction of these products for dogs. It is also possible that individuals purchased molluscicides in 2003 or earlier that were stored for long periods of time.

After conducting an assessment of alternatives to metaldehyde for control of slugs and snails, the EPA concluded that nonchemical control measures and products containing iron phosphate were available for residential uses. Nonchemical control methods include watering in the morning, rather than the evening, and removing plant debris and other items used as shelter by slugs and snails, which are sensitive to desiccation during the day.

In other studies, most cases of iron toxicosis reported in dogs involved ingestion of dietary vitamin supplements, followed in frequency by exposure to iron-fortified fertilizers. To date, only 1 clinical report, describing 5 cases of iron toxicosis in dogs, has been published in relation to iron-containing baits for slugs and snails. In that report, the dogs ingested bait containing iron EDTA, rather than iron phosphate. It has been shown that the bioavailability of iron in foods is increased 3-fold when administered at a molar ratio (EDTA:Fe) of 0.5:1. Although it is not required to be identified on the product label, EDTA appears to be included in multiple iron phosphate–containing molluscicides.

Dogs’ indiscriminate eating habits have been cited as the reason why acute iron poisoning occurs primarily in dogs, rather than cats. Cats are susceptible to adverse effects from large doses of iron, but to our knowledge, no case reports in cats have been identified.
Homeostatic regulation of iron is very complex; it is achieved by modulating iron absorption rates in response to physiologic needs. Iron absorption from the diet is limited under normal conditions, with typical absorption rates from the gastrointestinal tract ranging from 5% to 15%. This rate can double in the presence of iron deficiency. Conditions in the gastrointestinal tract, the presence of chelating agents, and other components of the diet can also enhance or reduce iron absorption.

There is no natural mechanism for actively eliminating excess iron from the body. Once absorbed, iron is vigorously maintained and recycled. Iron lost from hemoglobin is bound to transferrin and transported to the bone marrow. Primary routes of elimination include iron loss through gastrointestinal epithelial cell sloughing and blood loss. Therefore, iron loss typically occurs at a fairly constant rate and is unchanged even after large doses of iron have been absorbed.

During absorption from the gastrointestinal tract, iron is bound to ferritin within gastric mucosal cells and to transferrin in the serum. When ferritin and transferrin become saturated, as in acute iron overload, free, unbound iron can enter the systemic circulation and damage cells via redox cycling. This results in the formation of free radicals and reactive oxygen species. Reactive oxygen species are destructive to DNA and to lipids required for cell membrane integrity; these also inhibit mechanisms involved in cellular repair. Four stages of iron toxicosis have been reported (Appendix). This progression has been described in detail for humans exposed to iron via the oral route, and clinical presentation in animals is very similar. If no clinical signs develop for 8 hours following a single ingestion, the prognosis is good for an exposed dog. In cases where clinical signs are mild or moderate, most dogs do not progress to the third stage of iron toxicosis.

Minimum toxic or lethal doses for iron phosphate have not been clearly established for any animal species. The rate of ingestion appears to be as important as the amount of iron absorbed, making it difficult to establish a minimum toxic dose. Other ingredients in formulated bait products, such as EDTA, can increase iron absorption substantially. Even chronic exposure to low doses of iron can result in clinical signs. Moreover, various forms of iron are absorbed and distributed at different rates.

In the present study, many of the signs of iron toxicosis were reported following exposure to molluscsides containing iron phosphate. These included signs of damage to the gastric mucosa such as abdominal pain, lethargy, vomiting, and diarrhea. However, no deaths of dogs were reported to NPIC following exposure to these products, and a higher proportion of animals exposed to iron phosphate had no clinical signs at the time of the call (130/215 [60%]), compared with those exposed to metaldehyde (673/1,285 [53%]).

In many of the reports in the present study, it was not possible to estimate the amount of molluscside product ingested by dogs, particularly in the 31 of 56 (55%) reports in which dogs had access to a molluscside-treated area. In a few of the stored product exposures, the caller estimated ingestions of up to 0.91 kg of product/dog.

Because iron toxicosis occurs when the ability to bind free iron is exceeded, the circulating iron concentration is a confounding factor in determining the dose at which iron ingestion would result in adverse effects. Dogs with iron-rich diets may have a lower tolerance for an increase in iron intake, compared with dogs that consume low-iron diets. Among the 61 dogs with potential iron toxicosis in the study reported here, dogs typically weighed < 9.1 kg (20 lb).

Generally, iron toxicosis is dependent on the total soluble concentration of elemental iron; currently available pesticide products contain about 1% iron phosphate, and iron phosphate contains 37% elemental iron. Estimation of elemental iron can thus be calculated as follows:

\[
\text{amount of formulated bait ingested (mg)} \times 0.01 = \text{amount of iron phosphate ingested (mg)}
\]

Hall indicated that elemental iron doses of 20 to 60 mg/kg (9.1 to 27.3 mg/lb) can have mild or moderate toxic effects, and doses > 60 mg/kg may cause severe intoxication. In dogs, doses > 100 mg/kg can be fatal without early intervention.

It is recommended that serum iron concentration and TIBC be measured 4 to 6 hours after ingestion. If the iron concentration is near the TIBC, testing should be repeated 2 to 4 hours later. When the iron concentration exceeds the TIBC, signs of iron toxicosis may be expected. Treatment of acute ingestion of large amounts of iron phosphate in animals without clinical signs of toxicosis involves gastric decontamination with emetics. Treatment of animals that have clinical signs involves fluid therapy and chelation with desferoxamine as an IV infusion. Activated charcoal does not bind iron. Treatment of iron toxicosis often requires 2 to 3 days of chelation therapy, which should continue until serum iron concentrations are less than the TIBC, or 300 µg/dl, whichever is lower.

None of the information reported to NPIC in the present study was verified by independent investigation, laboratory analysis, or any other means. Veterinarians who reported incidents to NPIC did not include results of laboratory analysis. Because incidents may have been reported immediately or up to 2 years after the exposure, these reports should be viewed as cross-sectional in time. The NPIC does not conduct follow-up investigations; therefore, clinical signs that may have developed or resolved and deaths that may have occurred after the report was received were not reflected in the data.

Statistical analyses were not conducted to determine if apparent trends in incident reports over time were significant. However, between 2006, when products containing iron phosphate began to dominate the residential molluscside market, and the end of the study in 2011, the overall number of reports involving molluscside exposure in animals received by the NPIC appeared to decline consistently. Although no deaths of dogs were reported following iron phosphate exposure in the present study and clinical signs were reported less...
commonly in animals exposed to iron phosphate than in those exposed to metaldehyde, pet owners and veterinary professionals should be aware of the potential for iron toxicosis from this type of exposure. In dogs, the clinical signs reported appeared similar to those described following more common iron exposures from dietary supplements and fertilizers.

References

Appendix

Stages of iron toxicosis in animals.10,11,15

<table>
<thead>
<tr>
<th>Stage</th>
<th>Approximate time after ingestion</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0–6 hours</td>
<td>Damage to the gastric mucosa, signs of depression, abdominal pain, and vomiting and diarrhea (which may or may not contain blood)</td>
</tr>
<tr>
<td>2</td>
<td>6–24 hours</td>
<td>Apparent recovery and increased alertness</td>
</tr>
<tr>
<td>3</td>
<td>12–96 hours</td>
<td>Return of GI signs, weakness, shock, GI hemorrhage, tachycardia, cardiovascular collapse, coagulation disorders, and possibly death</td>
</tr>
<tr>
<td>4</td>
<td>2–6 weeks</td>
<td>Repair of GI injury results in obstruction secondary to fibrosis; does not occur as commonly as stages 1–3</td>
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GI = Gastrointestinal.