THE EFFECTS OF AGRI-CHEMICALS ON ANIMALS

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Domestic animals are raised in environments that can result in exposure to a wide variety of agricultural chemicals. Because of the desire to maximize agricultural yields, whether related to crops or to food-producing animals, there is extensive use of insecticides, herbicides, fungicides, and other chemicals to control economically significant pests. Exposure of animals to these types of chemicals may be intentional, such as the dermal application of various pesticides for control of insect and parasite infestation, or exposure may be accidental, such as the consumption of chemically-contaminated feed. In either situation, there are concerns. One concern is the potential deleterious effect of the chemical on the animal itself. A second concern, particularly to producers of food animals, is a commodity, whether it be meat, milk, or eggs, that is not contaminated with chemicals. While these concerns are not trivial, use of commercial pesticide formulations in accordance with the label, in general, poses minimal risks to animals and ultimately to the human consumer of food products derived from those animals.

However, loss of animals, whether they be domestic or wildlife species, through the use of pesticides and other agricultural chemicals does occur. For example, the most common causes of poisoning in cats and dogs are insecticides and rodenticides. Insecticides are the second most common cause of poisoning in cattle. When combined with other agricultural chemicals, insecticides, herbicides, and fungicides are among the most commonly cited sources of chemical toxicity in horses, swine, sheep, and goats. This information indicates that there are circumstances which can and do result in animal intoxication by agricultural chemicals, particularly pesticides.

The primary reason for domestic animal poisoning by pesticides and other agricultural chemicals is human error. For example, the miscalculation of concentrations for spraying and dipping procedures and for oral dosing preparations can result in animals being exposed to a chemical at a concentration several times higher than what it should be. Another common cause of poisoning is the use of insecticides not recommended for animals or the use of insecticide formulations designed for soil or crop application. For example, few of the chlorinated hydrocarbon insecticides are recommended for use on animals because of their high toxicity or because of their persistence in tissues. Wettable powders and emulsifiable concentrates intended for spraying on plants are not suitable for animal application because the particle size of these formulations is larger than the particle size for animal formulations. Thus, when a plant preparation is sprayed on an animal or used as a dip, there is a tendency for the heavy particles to

concentrate on the hair of the animal, resulting in excessive exposure and possible toxicity. The use of seed grain or other plant components which have been treated with pesticides such as heptachlor for animal feed has resulted in situations where large numbers of food producing animals have been exposed to toxic and persistent chemicals. The spraying of pesticides on crops or land has resulted in animal exposure either through direct contact with the spray or via consumption of treated vegetation. Improper storage of chemicals is a common cause of animal poisoning. Granular or powdered pesticide formulations, when stored with feed ingredients, can easily be mistaken for salt or mineral preparations and, as a result, be inadvertently mixed into animal feeds. Chemicals stored or disposed of in areas where animals have access to them is a potential problem because of their indiscriminating eating habits. Placing feed or water in containers which previously held chemicals can lead to poisoning if the containers are not properly decontaminated.

The previous examples of circumstances in which animals are inappropriately exposed to chemicals are preventable. The vast majority of pesticide problems in domestic animals results from ignorance or mismanagement. This carelessness can affect a few animals of a single producer or it can impact a whole industry. It is important to realize in the following description of agri-chemical effects on animals that, based on our present knowledge, these effects are not likely to occur in the field if the chemical is used and stored properly. The effects described are often the results of controlled experiments utilizing laboratory animals which have been administered doses of the chemical which exceed the concentration that an animal is likely to be exposed to in the field. It is also important to realize that there is a considerable degree of uncertainty in using toxicological data obtained in a very controlled and artificial laboratory situation to predict events in our environment which is considerably less controlled.

Of the agricultural chemicals that animals can potentially be exposed to, insecticides are of primary concern. This can be attributed to the fact that insecticides can be applied to animals as well as plants and what makes a chemical toxic to insects can also make it toxic to other species of animals. The insecticides most commonly used are the organophosphates and carbamates. Examples of organophosphorus insecticides include chlorpyrifos (Dursban), isofenphos (Oftanol), trichlorfon (Proxol, Dylox), ethoprophos (Mocap), acephate (Orthene), isazofos (Triumph), and diazinon. Isazofos and diazinon are two examples of compounds that have restricted use because of harmful effects in the field which were not anticipated in the laboratory. Carbamates include carbaryl (Sevin) and bendiocarb (Turcam). The organophosphates were introduced as insecticides after World War II and eventually replaced most of the environmentally persistent organochlorine insecticides such as DDT. The carbamate carbaryl was introduced in 1957 and this class of insecticide has gained in popularity because the carbamates tend to be less acutely toxic than the organophosphates.

Organophosphate and carbamate chemicals have the same mechanism of action and thus have similar effects on animals. In order to understand how these insecticides affect an animal, it is necessary to have a general understanding of how a nerve cell works. A typical nerve cell (Figure 1) is comprised of a cell body and a single long axon. When a nerve cell fires:

1. An electrical impulse travels down the axon to the nerve terminal.
2. When the impulse reaches the nerve terminal, it causes a chemical called a neurotransmitter to be released. There are different neurotransmitters released by different types of nerve cells. In this case, the neurotransmitter of interest is called acetylcholine (ACh) and it is released by cholinergic nerve cells.
3. The acetylcholine molecule diffuses across a space called a synapse.
4. ACh binds to a receptor located on the surface of the adjacent cell. This adjacent cell (called a post-synaptic cell) may be another nerve cell, a skeletal (voluntary) muscle cell, a smooth muscle cell, or it may be a glandular cell.
5. When ACh binds to the receptor on the post-synaptic cell, it stimulates that cell to do whatever it's designed to do (if the cell is a nerve cell, it fires; if the cell is a muscle cell, it contracts; if the cell is a glandular cell, it secretes).
6. Once stimulation of the post-synaptic cell has occurred, the acetylcholine molecule is hydrolyzed (split in half) by an enzyme called acetylcholinesterase (AChE).

7. Once split, the neurotransmitter is no longer active. Thus, excitation of the post-synaptic cell stops and the process can begin again when needed.

Organophosphate and carbamate insecticides act by binding to acetylcholinesterase, thus preventing it from inactivating acetylcholine. As a result, acetylcholine molecules accumulate at the post-synaptic receptor causing excessive stimulation of:

1. Exocrine glands such as sweat glands and salivary glands,
2. Smooth muscles comprising a number of different tissues and organs,
3. Skeletal or voluntary muscles, and
4. Certain nerves in the brain and spinal cord.

Prolonged stimulation of these tissues produces a set of clinical signs that are very characteristic of poisoning by an organophosphate or carbamate insecticide. These signs are generally not apparent until normal acetylcholinesterase activity has been inhibited by 50% while severe poisoning is associated with 70% inhibition. The typical clinical signs observed include:

1. Tightness of the chest and wheezing expiration due to constriction of the bronchioles and excessive secretion of fluid within the lungs,
2. Increased salivation and lacrimation,
3. Increased sweating,
4. Increased contraction of the gastrointestinal tract which leads to nausea, vomiting, abdominal cramps, and diarrhea,
5. An initial decrease in heart rate followed by an increase in heart rate,
6. Involuntary and frequent urination due to contraction of the bladder,
7. Constriction of the pupil,
8. Twitching and stiffness of skeletal muscles,
9. Shallow breathing and cyanosis due to fatigue of respiratory muscles, and
10. Depression of the central nervous system.

If death occurs, it results from respiratory failure due to broncho-constriction and increased bronchial secretions, paralysis of respiratory muscles, and depression of the respiratory center located at the base of the brain.

In general, clinical signs appear within minutes to six hours in cases of oral exposure. If an animal is exposed dermally, clinical signs may not be apparent until one to four days after exposure. The duration of signs may be as short as a few minutes to a few hours (carbamates) or as prolonged as several hours to a few days (organophosphates).

As mentioned previously, the carbamates are considered to be less acutely toxic than the organophosphate compounds. This is because the carbamates are temporary inhibitors of acetylcholinesterase, meaning that they come off the enzyme in a matter of hours. Conversely, the organo-phosphate insecticides are considered to be permanent inhibitors of acetylcholinesterase because they come off the enzyme very slowly, if at all. Because inhibition of acetylcholinesterase by organophosphates is essentially permanent, repeated exposure of animals to these insecticides is a concern because of cumulative effects.

Some organophosphate compounds cause a condition that is not related to the inhibition of acetylcholinesterase. This condition is called organophosphorus-induced delayed neurotoxicity (OPIDN). OPIDN is characterized by incoordination and eventual paralysis of the hindlimbs which is not apparent until seven to 14 days after initial exposure. These clinical signs are due to degeneration of nerve cell axons in certain peripheral nerves and in specific areas of the brain and spinal cord. Chlorpyrifos has been implicated as a delayed neurotoxicant in chickens and cats but the doses required to cause OPIDN were considerably higher than the doses which cause death in these two species.

A third class of insecticide is represented by fluvalinate (Mavrik) which is a pyrethroid. Pyrethroids are synthetic variants of pyrethrins which are derived from chyrsanthemums. These chemicals affect nerve membrane sodium channels and thus function like DDT. When a nerve cell is not firing, the concentration of sodium ions on the inside of the axon is low while the concentration of sodium ions on the outside of the axon is high. This is because the pores or channels through which sodium ions enter the axon are closed. When the nerve cell is stimulated, the sodium channels open, allowing sodium ions to rush into

the axon. This initiates the electrical impulse which travels down the axon as sodium pores continue to open up. Almost as soon as they open, the pores close again and the sodium ions are pumped back out of the axon so the nerve can fire again in an orderly fashion. The pyrethroids act by keeping the sodium channels open. As a result, the nerve continues to fire causing excessive stimulation of the post-synaptic cell.

The clinical signs observed are varied and depend upon the chemical structure of the compound. Type I pyrethroids result in the simplest poisoning syndrome which is similar to that produced by DDT. It involves progressive development of fine whole-body tremors, uncoordinated twitching of dorsal muscles, hyperexcitability, and death. Death is due to an increase in metabolic rate which in turn leads to hyperthermia and metabolic exhaustion. Type II pyrethroid compounds act on a wider variety of tissues and thus produce a more complex set of clinical signs. In rats, there is progressive development of nosing and exaggerated jaw opening, profuse salivation, increasing extensor tone in the hindlimbs causing a rolling gait, incoordination progressing to very coarse tremors, writhing spasms, tonic seizures, respiratory arrest, and death. In general, mammals are relatively resistant to pyrethroids because of their ability to rapidly metabolize the compounds.

The yearly production of herbicides in the United States is more than double the production of insecticides. Simply from the standpoint of annual consumption, potential exposure of animals to herbicides is worthy of concern. However, because of marked differences between plants and animals, it is not surprising that many of the herbicides are highly toxic to plants but are relatively non-toxic to mammals. Nevertheless, some herbicides affect the same basic function in both plants and animals and thus are toxic to both while some herbicides are toxic to both animals and plants but through different mechanisms. As with the insecticides, the majority of animal toxicity problems are associated with human error. Poisoning is not likely to result if proper application rates and withholding times are observed.

The chlorophenoxy herbicides, represented by 2,4-D, MCPA, and MCPP, are not as popular today as they once were. Part of this may be attributed to toxicological problems associated with this class of compounds, such as contamination of several chlorophenoxy herbicides with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Poisoning of animals is almost entirely due to accidental ingestion of concentrates or sprays. This class of compounds is slightly to moderately toxic. In ruminants, typical clinical signs include anorexia, depression, rumen atony, muscle weakness, and diarrhea. Ulceration of the oral mucosa may result from prolonged exposure. There may be an accumulation of fluid around the heart, swelling of the liver, and congestion of the kidneys. In addition to toxicity induced by the chlorophenoxy compounds themselves, these herbicides can indirectly affect animals through their action as plant growth regulators. As such, they alter the metabolism of the plant. A side effect of altered growth is that treated plants may accumulate high concentrations of nitrates or cyanide which in turn can be toxic to grazing animals. Also, many toxic weeds may become more palatable and thus more likely to be consumed.

Similar in chemical structure to the chlorophenoxy herbicides are dicamba, chlorthal (Dacthal), and chlorfenecol. These compounds range in acute toxicity from practically non-toxic (chlorfenecol) to moderately toxic (dicamba and chlorthal). Toxic effects are similar to those caused by chlorophenoxy herbicides in addition to muscle spasms, frequent urination, dizziness, and cyanosis.

The triazines are the second largest group of herbicides sold in the United States. A member of this class, atrazine, is the second largest selling herbicide in the U.S. Atrazine has moderate acute toxicity based on the oral LD50 value for rats. Clinical signs include anorexia, depression, muscular spasms, shallow breathing, weakness, and uncoordinated gait. Limited studies with rats and mice suggest that atrazine might be a carcinogen.

MSMA (Daconate) is an organoarsenic compound which is slightly toxic to rats. Acute over-exposure results in severe gastroenteritis. It has been noted that exposure to MSMA can result in symmetrical peri-pheral nerve damage which is typical of arsenic intoxication.

Benefin (Benfluralin, Balan), trifluralin (Treflan), and pendimethalin (Prowl, Stomp, Herbadox) are classified as dinitroanilines. As a class, the dinitroanilines are compounds of low acute and chronic toxicity.

Siduron (Tupersan) is a urea compound which has slight acute toxicity. Bromoxynil (Buctril) is classified as a nitrile compound and is moderately toxic to rats based on the oral LD50 value. Only a few

organophosphate pesticides are useful as herbicides. These compounds tend to be weak inhibitors of acetylcholinesterase and thus have a low acute toxicity. Bensulide (Betasan, Pre-San, Betamec) is an example of such a compound.

In general, adverse effects resulting from herbicide exposure are difficult to substantiate in the field. Most of the clinical signs are non-specific (gastrointestinal irritation, reduced feed efficiency, reduced growth rate, and depression of normal activity). There is no conclusive evidence that chronic exposure of domestic animals or wildlife species to herbicides that have been properly applied will result in reproductive, teratogenic, or carcinogenic effects.

The use patterns of fungicides, the restrictions on their use, and their generally low toxicity makes poisoning by this type of pesticide relatively rare. However, a number of common fungicides are typically used on home gardens and thus careless use poses a potential hazard to pets and livestock.

Dithiocarbamates are metal salts of dithiocarbamic acid. Thiram is a dimethyldithiocarbamate which is slightly toxic. Large doses in rats cause ataxia and hyperactivity, followed by inactivity, loss of muscle tone, labored breathing, and clonic convulsions. The ataxia is due to degeneration of spinal cord neurons and degeneration and demyelination of the sciatic nerve. Thiram has been shown to be teratogenic in mice and hamsters, but only at very high doses. Mancozeb is an ethylene bisdithiocarbamate which is practically non-toxic. However, mancozeb can be metabolized to ethylene thiourea which is a suspected liver and thyroid carcinogen.

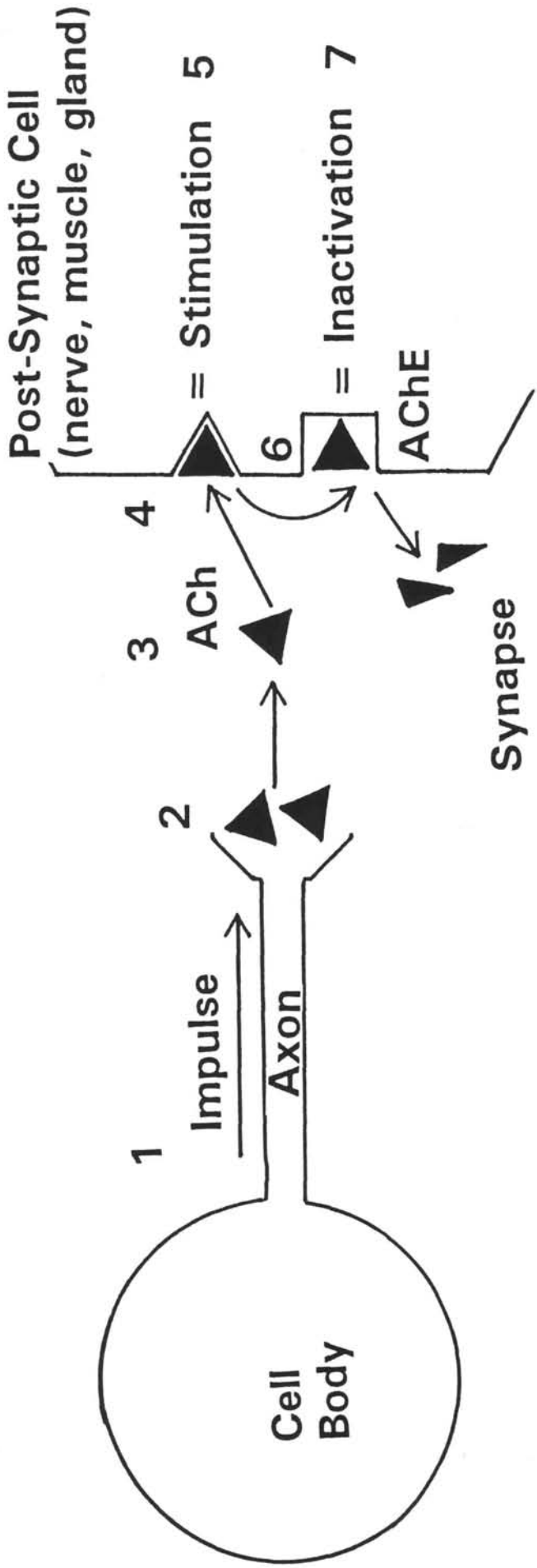
Quintozene or pentachloronitrobenzene is a nitrobenzenoid fungicide. As a class, these fungicides convert hemoglobin to methemoglobin thus decreasing the blood's capacity to transport oxygen. Quintozene is slightly toxic to rats based on the oral LD50 value.

Chlorothalonil (Daconil) is practically non-toxic when administered orally or dermally, but it is highly toxic when administered by the respiratory route.

Benomyl and thiophanate-methyl are benzimidazoles. Benomyl is practically non-toxic when administered acutely but it has been shown to be teratogenic in rats. Thiophenate-methyl has been demonstrated to be practically non-toxic in acute studies, while chronic exposure resulted in only slight growth retardation.

As with the herbicides, exposure to fungicides is difficult to define. While exposure of laboratory animals to high doses of these compounds may result in deleterious effects, exposure of domestic animals in the field may result in only mild gastrointestinal irritation.

In summary, the use of agri-chemicals should pose minimal risk to animals. However, human carelessness can result in situations where animals are exposed to quantities of these chemicals which can result in toxicity. Insecticides are the chemicals which cause the greatest concern because of their use patterns and because their mechanisms of action are relevant to animals.


Post-Synaptic Cell
(nerve, muscle, gland)
= Stimulation 5
= Inactivation 7
AChE
6
4
3
ACh
2
Synapse
1
Impulse
Axon
Cell
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