Ethylene Glycol
(Conventional Radiator Antifreeze)

Synonyms - Ethylene glycol, 1,2 ethanediol

Sources

- The primary ethylene glycol source that results in toxicosis is conventional automotive permanent antifreeze, which is approximately 95% ethylene glycol. Other heat exchange fluids, such as those used in solar collectors, ice rink freezing equipment, some brake and transmission fluids and diethylene glycol used in color film processing, may also serve as sources.

Structure

HO-CH2-CH2-OH

Susceptible Species

- Both birds and mammals are susceptible to ethylene glycol poisoning.
- Toxicosis is most common in young male dogs and cats. Cats are especially sensitive.
- Most poisonings occur between late fall and early spring. Animals consume ethylene glycol voluntarily, even when water is available.
- Due to delays in presentation and diagnosis and due to therapeutic limitations, a high death rate (78%) has been reported in dogs and cats. Poisoned animals are often presented without a history of exposure and are diagnosed postmortem or after damage has occurred.
Toxicity

<table>
<thead>
<tr>
<th>Species</th>
<th>Lethal Dose Undiluted (95%)</th>
<th>Approximate Fatal Amount (50:50 - Antifreeze:Water)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feline</td>
<td>As low as 1.5 ml/kg BW</td>
<td>A 5-kg cat would have to drink about 15 ml (1 tbsp) of diluted antifreeze</td>
</tr>
<tr>
<td>Canine</td>
<td>Minimum lethal dose of 6.6 ml/kg BW</td>
<td>Using a dose of 13.2 ml/kg diluted antifreeze, a 10-kg dog would have to drink about 132 ml or 4 1/2 oz of diluted antifreeze</td>
</tr>
<tr>
<td>Poultry</td>
<td>7 - 8 ml/kg BW</td>
<td></td>
</tr>
<tr>
<td>Cattle</td>
<td>2 - 10 ml/kg BW (younger animals appear to be more susceptible)</td>
<td></td>
</tr>
</tbody>
</table>

Absorption, Distribution, Metabolism and Excretion (ADME) and Pathogenesis

- Unmetabolized ethylene glycol has about the same toxicity as ethanol, and it is rapidly absorbed.
- Peak blood concentrations occur in dogs from less than 1 - 4 hours postexposure.
- At low doses, the plasma half-life of the parent compound ethylene glycol is 2.5 - 3.5 hours in the dog.
- Significant portions of ethylene glycol are excreted unchanged in the urine, especially during the first 4 hours, continuing for up to 24 hours.
- A knowledge of the metabolism of ethylene glycol is critical in understanding intoxication and making therapeutic choices.
- Metabolism occurs in the liver beginning with oxidation by alcohol dehydrogenase to glycoaldehyde. This step is the first of 2 important rate-limiting steps in the metabolism of ethylene glycol. Glycoaldehyde is more toxic than ethylene glycol, but it doesn't accumulate because it is readily metabolized to glycolic acid.
- The severe metabolic acidosis associated with ethylene glycol toxicosis in dogs is believed to result primarily from glycolic acid, which is more toxic than ethylene glycol. Urinary glycolate concentrations correlate with clinical signs, including mortality.
- The next step in metabolism, the conversion of glycolic acid to glyoxylic acid, is the other rate-limiting reaction. The slow degradation of glycolic acid allows time for it to cause acidosis and probably nephrosis. Glyoxylic acid is more toxic than any of the other metabolites, but its half-life is so short that the concentrations reached are probably too low to cause toxic effects. Glyoxylic acid can be converted to formic acid and carbon dioxide, and in some species the conversion to CO₂ is a major pathway. Glyoxylic acid may also be metabolized to glycine and serine, which enter the pool of amino acids via steps requiring pyridoxine as a cofactor. Some of the glycine reacts with benzoic acid to form hippuric acid. Glyoxylic acid may also be conjugated to produce oxalomalate, hydroxyketo glutarate and, using thiamine pyrophosphate, to hydroxy-keto adipate.
- Another pathway of glyoxylic acid metabolism is oxidation to oxalic acid. It is estimated that between 0.25 - 3.7% of an ingested dose of ethylene glycol is converted to oxalate. Most oxalic acid is excreted in the urine, but some combines with calcium to form calcium oxalate crystals, a portion of which are precipitated in the renal tubules and to a lesser degree in the vasculature of the brain and other tissues. Nervous system effects of ethylene glycol toxicosis, however, do not correlate well with the presence of oxalate crystals, and in surviving animals complete recovery of the central nervous system (CNS) function is the rule.

![Ethylene glycol metabolism diagram](image)

Ethylene glycol metabolism. Different species favor different metabolic pathways.
Clinical Pathology

- Mild mature lymphopenia and mild mature neutrophilia (stress leukogram) may occur. Hemoconcentration as reflected by increased packed cell volume (PCV) and total protein often occurs in clinically dehydrated animals.
- As the syndrome progresses, increases in blood urea nitrogen (BUN), creatinine and phosphorus are quite common, and in most dogs and cats hyperglycemia and hypocalemia may occur. Hypocalcemia may contribute to hyperglycemia by inhibiting insulin secretion. Hyperglycemia may also be due to the effects of aldehydes on inhibition of glycolysis and the Krebs cycle due to the severe depletion of NAD+ brought about by the metabolism of ethylene glycol.
- Hyperkalemia attributable to renal failure and/or acidosis may also be present.
- Hypochloremia and low blood bicarbonate concentrations often develop.
- The overall blood gas picture reflects a metabolic acidosis. Hypocalcemia occurs in many acidotic states due to competitive displacement of calcium from serum albumin by hydrogen ions. The displaced calcium diffuses into the cells or is eliminated, lowering the total blood calcium. This apparently occurs in ethylene glycol toxicosis. Oxalic acid may also lower blood calcium due to precipitation of calcium oxalate in tissues and excretion in the urine. Serum calcium declines while urinary calcium greatly increases.
- It is uncertain whether the hypocalcemia in ethylene glycol toxicosis is responsible for CNS or cardiac malfunction since the ionized (active) calcium of the blood is maintained even as the albumin-bound calcium declines.
- Increased anion gap and osmolar gap are often present and are used as diagnostic aids in ethylene glycol toxicosis. The combination of a severe, high anion-gap metabolic acidosis with a high osmolar gap also occurs in methanol toxicoses; but only with ethylene glycol are oxalate and hippurate crystalluria prominent.
- The anion gap is computed as the serum sodium plus potassium minus the sum of serum chloride and bicarbonate ([Na+] + [K+] - ([Cl-] + [HCO3-])). The normal anion gap is about 10 - 15 mEq/L. A value of greater than 25 mEq/L is assumed to represent an excess accumulation of unmeasured anions (ethylene glycol metabolites). It may be noted that ketoacidosis, renal failure, lactic acidosis, administration of amino acids with sorbitol, and salicylate and paraldehyde toxicoses may also cause a high anion gap.
- Osmolality is a measure of the number of molecules in a solution. The osmolar gap is the difference between the measured and calculated serum osmolality. The molecules which contribute most to serum osmolality are sodium, chloride, bicarbonate, glucose and
urea. Most laboratories express electrolytes as mEq/L (same as mmol/L for monovalent anions) and the usual units for glucose and urea are mg/dl. Dividing glucose by 18 and BUN by 2.8 as shown in the formula below equilibrates the laboratory values to equivalent mmol/L values:

\[
\text{Calculated Serum Osmolality in mOsm/L} = 1.86 \left( \frac{\text{Na} + \text{K}}{2} \text{ in mEq/L} \right) + \frac{\text{Glucose in mg/dl}}{18} + \frac{\text{BUN in mg/dl}}{2.8} + 8.6
\]

The constant 8.6 is added as an estimate of normal, osmotically active solutes, e.g., calcium, phosphate, and creatinine.

- Plasma osmolality may also be measured directly using freezing point depression (1.86 °C for every osmol of solute). In the normal animal the calculated serum osmolality is within 5 - 10 mOsm/L of the measured osmolality. When measured osmolality is more than 10 mOsm/L greater than the calculated osmolality, an osmolar gap is said to exist. If the measured osmolality is not lowered by the presence of water-insoluble molecules such as lipids, the gap represents large numbers of other molecules, such as ethylene glycol and its metabolites. Ethylene glycol increases the measured osmolality by depressing the melting point of the plasma. Since its presence is not accounted for in the formula above, it also increases the osmolar gap. Normal osmolality for dogs and cats is 280 - 310 mOsm/L, and measured values in early ethylene glycol toxicosis may be increased by as much as 60 mOsm/L.

**Note** - In the later stages of ethylene glycol toxicosis, no osmolar gap may be present. Other causes of an increased osmolar gap include ethanol, methanol, isopropanol, acetone, mannitol, sorbitol and diatrizoate (IVP dye). Ethyl ether and trichloroethane may cause an increase in osmolar gap but not metabolic acidosis. Isopropanol toxicosis may also cause ketosis and depression of the CNS but not metabolic acidosis.

- Most urine specific gravities are in the isothenuric range (1.008 - 1.012); and the others are frequently dilute (1.013 - 1.025) in spite of dehydration. Acid urine, hematuria, proteinuria and glucosuria are frequently observed. Cats often develop coffee-colored urine.

- Urine sediments often contain red and white blood cells, renal epithelial cells, casts and calcium oxalate and especially hippuric acid crystals. Both types of crystals are similar in shape, and both are highly birefringent. To identify birefringence, two polarized lenses (as in a pair of polarized sunglasses) are laid over one another either above or below the stage of the microscope and one is rotated so as to darken the field of view. Crystals which stand out as strikingly bright against the dark background are birefringent. The same technique is used to examine kidney biopsies, impression smears and histologic sections (see Diagnosis).

**Gross Lesions**

- Some dogs have severe dehydration.

- Hyperemia of the gastrointestinal tract, swollen kidneys, and pulmonary edema may occur.

- If the animal lives long enough to become uremic, there may be significant weight loss, oral ulcers and hemorrhagic gastritis.

**Microscopic Lesions**

- Calcium oxalate or hippurate crystals can usually be seen in renal impression smears and especially histologic sections. Blood vessels of the brain and muscle may occasionally have crystals present as well.

- In ethylene glycol nephrosis, renal tubules are usually very dilated, but the tubular pathology is not always accompanied by oxalate crystals.

- There is generally little reaction to the crystals, and healing occurs despite their presence. In surviving animals, the renal lesions generally resolve, but in a few cases chronic fibrosing renal damage occurs.

**Diagnosis**

- Diagnosis of ethylene glycol toxicosis often requires a known or suspected exposure history, appropriate clinical signs (most commonly ataxia, depression, vomiting, hypothermia, anuria, or oliguria), alterations in the serum chemical profile (azotemia, hyperphosphatemia, hypocalcemia, and hyperglycemia), and urinalysis (isothenuria, calcium oxalate, and possibly hippurate crystalluria). The oxalate crystals may take the appearance in urine of 6-sided prisms, dumbbell, "hempseeds", or 6-sided prism with 4-sided crystals budding from their surfaces.

- Analysis for ethylene glycol in blood or urine is a specific test but, due to metabolism, is practical only in the early stages (first 12 - 24 hours) of toxicosis. In ethanol-treated animals, inhibition of metabolism of the parent compound may prolong the presence of ethylene glycol in blood and urine.

- Colorimetric kits are on the market for in-house analysis. Their sensitivity should allow them to be useful if the poisoning has occurred within 24 hours.

- Analysis of serum for glycolic acid may be preferable since detection is possible from 3 - 60 hours after ethylene glycol ingestion.

- High hippurate concentrations also occur in the urine of ethylene glycol-poisoned dogs.
Unfortunately, ethylene glycol, glycolic acid and hippurate analyses are not rapidly available to most practitioners.

Ethylene glycol is not identified in some coma screens which may include some other alcohols, barbiturates, nonbarbiturate hypnotics, tranquilizers, salicylates and carbon monoxide.

These obstacles and the availability of electrolyte, blood gas and serum chemistry assays in clinical pathology laboratories make it such that serum anion and osmolar gaps may be more immediately useful in diagnosis.

Kidney calcium concentrations tend to be very high-often between 1,000 and 10,000 parts per million as compared to control values in the range of 100 parts per million.

Prognosis

- Dogs with very low blood pH, severe base deficit and high venous PO2 (associated with increased respiratory rate and decreased activity) are less likely to respond to treatment.
- At 30 hours after exposure, persistence of hypothermia, hypocalcemia and elevations of phosphorus, BUN and creatinine all indicate a poorer prognosis.
- Some dogs presented in a coma after ethylene glycol ingestion should be given a poor prognosis since they are frequently in a terminal state of either acute intoxication or renal failure with uremia.

Treatment

- Animals allowed to eat and drink during all courses of therapy.
- A few hours delay before specific treatment is instituted can make a grave difference.
- In very early cases, when coordination and postural and gag reflexes are intact, emetics should be given.
- Despite some suggestions that it may not bind ethylene glycol, activated charcoal (1 - 2 grams/kg) and a saline cathartic (250 mg/kg), such as a magnesium or sodium sulfate solution, may be given by stomach tube when animals are presented within the first 3 hours of ingestion. If an emetic is used, the charcoal and saline cathartic are given after vomiting has subsided.
- The use of ethanol and bicarbonate with fluid therapy is widely accepted. Ethanol competitively inhibits alcohol dehydrogenase, allowing more unmetabolized ethylene glycol to exit via the urine. The development of acidosis is thereby reduced.
- Sodium bicarbonate is used to correct the metabolic acidosis and to ion-trap metabolites, thereby reducing their diffusion into the cells and enhancing their removal in the urine.

**Note** - Treatment with ethanol or 4-methylpyrazole is not indicated in patients that are already in oliguric renal failure. In these patients, fluid, electrolyte, and acid-base abnormalities should be corrected.

Treatment results are not ideal. Problems with ethanol-bicarbonate therapy include:

- Animals that may already be depressed are given another CNS depressant.
- To allow for ethylene glycol excretion, it is necessary to maintain a blood level of ethanol for up to 72 hours.
- In dogs, ethanol may fail to prevent death when ethylene glycol at 10 ml/kg is ingested and treatment is started as early as 1 hour thereafter.
- When animals are first presented 18 or more hours after exposure, fluid therapy with sodium bicarbonate is strongly indicated but ethanol, if started at this point in time, would usually do more harm than good, since it is assumed that almost all the ethylene glycol would be past the first metabolic step. This assumption needs to be tested with dogs given high doses of ethylene glycol to determine if zero order (saturated) kinetics for alcohol dehydrogenase may be applicable. If this is the case, it may be appropriate to use alcohol dehydrogenase inhibitors at later times.
- Ethanol enhances the diuresis initiated by ethylene glycol.
- Pulmonary edema is more often a complicating factor in ethanol-treated animals.

One treatment approach for dogs includes 20% ethanol in saline intravenously (IV) at 5.5 ml/kg and 5% bicarbonate intraperitoneally (IP) at 8 ml/kg. Both agents are administered initially, then every 4 hours for five treatments and finally every 6 hours for a minimum of four more treatments. Between doses, animals can be re-evaluated, and those regaining consciousness are given more favorable prognosis.

In cats, a recommended dose for ethanol has been 5 ml/kg of a 20% solution and for bicarbonate 6 ml/kg of a 5% solution. Both are given IP every 6 hours for 5 treatments, then every 8 hours for 4 more treatments.

The ethanol therapy is prolonged in all species. This is necessary since, although the production of toxic metabolites is reduced and more unchanged ethylene glycol is excreted in the urine, the overall result is nevertheless a great increase in the half-life of ethylene glycol in the blood.

The experimental use of low-dose ethanol-sodium bicarbonate when given 1 hour after ethylene glycol administration prevented the development of ethylene glycol toxicosis. A solution of 30% ethanol, 1% sodium bicarbonate in 0.9% saline is given by rapid infusion at 1.3 mL/kg; the infusion rate is then reduced to 0.42 ml/kg/hour. The goal is to maintain blood ethanol at 50 mg/dl for 48 hours. The effectiveness of low-dose ethanol therapy when started beyond 1 hour postingestion has not been adequately characterized at this time.

Bicarbonate may be used judiciously in the fluids in an attempt to maintain the urine pH at or above 7.0 - 7.5.

The dosages and routes of administration of sodium bicarbonate recommended above are somewhat controversial. Sodium bicarbonate therapy preferably should be based on serial plasma bicarbonate determinations using the following formula:
Bicarbonate Deficit (in mEq) = 
0.5 x Body Weight (in kg) x [24 - Plasma Bicarbonate (in mEq/L)]

**Note** - In order to prevent overdose, only 80% of the calculated dose (in mEq) is given, and this must be done very slowly in the fluids if given by the intravenous route (i.e., give over 4 - 6 hours).

- Plasma bicarbonate should be checked every 4 - 6 hours. When actual plasma bicarbonate measurements cannot be performed and the clinical history and signs are highly supportive of acidosis due to ethylene glycol toxicosis, a plasma bicarbonate value of 8.5 mEq/L value may be assumed for significantly affected animals, and using the 80% safety factor one can calculate an estimated dose of sodium bicarbonate of 6.2 mEq/kg bw, which is equivalent to 10.4 ml/kg bw of a 5% solution of sodium bicarbonate, every 4 - 6 hours given slowly IV in fluids.
- **Correction of the acidosis** does not decrease the depth of coma, but it greatly increases the chances for survival.
- **Fluids are essential** to correct dehydration, increase tissue perfusion, alleviate acidosis, promote excretion of ethylene glycol and its toxic metabolites and avoid concentration of these nephrotoxic compounds in the kidneys. Fluid volumes depend upon the deficit, maintenance needs and continuing losses of the patient.
- Monitoring urine output, body weight, and central venous pressure is helpful in assessment of renal function and avoiding overhydration, which may cause or aggravate pulmonary edema, especially in anuric animals.
- The renal clearance of ethylene glycol varies inversely with tubular water reabsorption; therefore, after hydration is reestablished and, provided there is no evidence of pulmonary edema in the patient, osmotic diuretics such as 50% dextrose or mannitol may be used to promote excretion and reduce intrarenal edema.
- When oliguria or anuria are not correctable or when life-threatening toxicosis exists, peritoneal dialysis may be used. Dialysis is intended to remove ethylene glycol and its toxic metabolites and to alleviate uremia and acidosis.
- Peritoneal dialysis can be performed with a column-disk peritoneal catheter placed into the ventral abdominal cavity. Peritoneal dialysis involves instilling 1.5% dextrose (37 ºC) with 125 mg of cephradine/l and 500 U heparin/l added to alternate exchanges. Dialysate is instilled at a rate of 5 - 20 ml/kg by gravity. Dialysate is allowed to remain in the peritoneal cavity for 1 - 2 hours. Dialysate is then drained from the peritoneal cavity. Peritoneal dialysis can be associated with mild peritoneal irritation and hypothermia if inadequately warmed dialysate fluids are used.
- Hemodialysis is very effectively used to remove ethylene glycol in humans and may be used with concomitant ethanol therapy. A high bicarbonate dialysate is much safer than standard acetate dialysates, which may further deplete the patient's serum bicarbonate.
- Pyridoxine and thiamine are suggested since they are cofactors in the metabolism of glyoxylic acid in pathways that do not lead to oxalic acid.
- Calcium may be given judiciously if hypocalcemia occurs (especially if the animal has low ionized calcium).
- Pyrazoles, butanediol and propylene glycol are alcohol dehydrogenase blockers that have been used to treat dogs, monkeys, and rodents in experimental ethylene glycol poisoning. Treatment with 4-methylpyrazole has been recently advocated for ethylene glycol toxicosis in dogs. The recommended dose for the dog is an initial IV dose of 20 mg/kg using a 5% solution, then 15 mg/kg IV at 12 and 24 hours and 5 mg/kg IV at 36 hours after the first dose. The use of 4-methylpyrazole is not associated with the severe CNS depression as occurs in high dose ethanol therapy. To use 4-methylpyrazole, it is important to work with a compounding pharmacist and to have this individual prepare a sterile dosing solution. Aldrich Chemical of Milwaukee, WI, and Sigma Chemical Company of St. Louis, MO, sell the 4-methylpyrazole. It apparently is no longer necessary to receive FDA approval for this use of 4-methylpyrazole. The solution is made up by combining 5 grams of 4-methylpyrazole with 45 ml of polyethylene glycol 400. Then, with continuous stirring, 50 ml of bacteriostatic water is slowly added. The solution is then filtered with a 0.22 micron filter. The refrigerated solution is stable for at least one year. At the current time no safe and effective dosages of 4-methylpyrazole have been identified for domestic cats. Ethanol remains the alcohol dehydrogenase inhibitor or choice for cats. It presently appears that 4-methylpyrazole has some advantages over ethanol in the dog while the reverse is clearly true in the cat.
- The use of vasopressor agents (e.g., dopamine 2 - 3 µg/kg/minute IV) and diuretics (e.g., furosemide 2.2 mg/kg, q8h, IV) may be required to correct unresponsive anuria and/or pulmonary edema.
Propylene Glycol Antifreeze

- Less toxic than ethylene glycol but still somewhat toxic.
  - Oral LD₅₀ dog - 19 - 22 ml/kg.
  - Rapidly absorbed with peak blood levels at 1 hour after ingestion.
- Metabolized by alcohol dehydrogenase to lactaldehyde which is converted to lactic acid but most leaves the body as parent compound or as a glucuronide conjugate (with the possible exception of cats).
- Treatment.
  - Limit absorption.
  - Fluids.
  - Bicarbonate as needed for acidosis (slow in the fluids).
  - Assist respiration if needed.

Methanol
(Methyl Alcohol, Wood Alcohol)

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Cause Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostly pet animals</td>
<td>Minutes to hours</td>
<td>Few hours to 2 days; potentially lethal</td>
<td></td>
</tr>
</tbody>
</table>

Sources
Methanol is encountered most commonly in windshield washer antifreeze/cleaner solutions for automobiles. In years past, it was used as antifreeze for automobile radiators and is still used in air brakes and as an antifreeze for gasoline and diesel fuel. It is sometimes used as a fuel for some picnic stoves, in soldering torches, and in denaturing ethanol, although not all denatured ethanol contains methanol.

Structure
CH₃-OH.

Toxicity
- Toxicosis may result from oral, inhalation, or percutaneous exposure.
- Minimal lethal dose:
  - Rat 9.5 g/kg
  - Rabbit 7.0 g/kg
  - Dog 8.0 g/kg
  - Rhesus monkey 3 g/kg
- Approximate lethal dose in man: 1 g/kg.
- The toxicity of methanol, at least in humans, is, however, quite variable. Deaths have been reported following ingestion of 15 ml of 40% methanol, yet survival has been documented after ingestion of 500 ml of the same concentration. The usual fatal dose of absolute methanol in humans is 100 - 250 ml.

Absorption, Distribution, Metabolism and Excretion (ADME)
- Rapidly absorbed from the stomach.
- The half-life of methanol elimination in the dog has been reported to be 43 hours.
- Oxidation by hepatic metabolism to formaldehyde and formic acid.
- Initial reaction is often catalyzed by liver alcohol dehydrogenase. In some species, oxidation of methanol and formate is by the catalase-peroxide enzyme system.
- Formic acid and formaldehyde excreted in the urine.
- Formic acid inhibits cytochrome C oxidase, succinate-cytochrome C reductase, and catalase enzyme activity.

Signs
- Methanol causes three primary effects: 1) CNS, 2) metabolic acidosis, and 3) in man, rhesus monkeys, and possibly some non-primate animals, ocular signs occur. Ocular problems do not seem to be a problem in dogs.
- Signs may appear from 40 minutes (CNS signs) to 72 hours (ocular effects) after exposure (at least in man).
- CNS.
  - Depression, malaise, ataxia, weakness, and coma. Convulsions are sometimes reported. Ataxia, depression, and hyperexcitability were observed in experimentally poisoned dogs; signs developed from 15 minutes to 5 hours post-exposure.
Metabolic Acidosis:
- An anion-gap, metabolic acidosis is a classical finding in human methanol toxicosis. If plasma osmolarity is measured using a freezing point determination, methanol, like ethanol and ethylene glycol, will cause an osmolal gap.
- Methanol is associated with abdominal pain and like other conditions in which a metabolic acidosis occurs, vomiting commonly occurs, although the absence of vomiting or abdominal pain does not rule out methanol toxicosis.
- Metabolic acidosis was reproduced in only 10 - 15% of experimentally exposed dogs. Metabolic acidosis can be reproduced in experimentally poisoned rhesus monkeys.
- Formic acid is thought to contribute to the development of a metabolic acidosis.
- If metabolic acidosis occurs, tachypnea should be expected as the animal attempts respiratory compensation.

Ocular:
- Ocular lesions in experimentally poisoned rhesus monkeys include optic disc edema, identical to that caused by increased intracranial pressure. Retinal vessels appear engorged.
- Formate is considered to be the most important toxic metabolite. Administration of formate or formic acid will reproduce clinical signs and ocular manifestations in rhesus monkeys.
- Formaldehyde is rarely detected in vitreous and aqueous humors. By contrast, administration of formaldehyde will not reproduce clinical signs of blindness, however changes in electroretinograms (ERG) occur.
- As little as 4 ml of absolute methanol has caused blindness in humans.

Humans:
- Funduscopic examination may be normal, or there may be papillary or retinal edema, and/or hyperemia of the optic disc. Later retinal atrophy may occur.
- Early blurred vision often occurs and frequently the syndrome terminates in blindness.

Respiratory:
- Respiratory arrest occasionally occurs in experimentally poisoned dogs and monkeys.
- Death may result from sudden respiratory failure in the terminal stages of poisoning. In humans, opisthotonus is followed by a deep gasp and locking of the chest in the full inspiratory position, while the heart temporarily continues beating.

Diagnosis
- History of ingestion.
- Anion-gap, metabolic acidosis; possible osmolal gap.
- Plasma bicarbonate may sometimes be severely decreased.
- Urine pH also low.
- Pancreatic necrosis has been reported, and pancreatic enzymes may be elevated.
- Blood methanol concentrations may be determined at certain human hospitals or other toxicology laboratories.
- Detection of formaldehyde in urine, blood, and other tissues.

Treatment
- Check and maintain respiration.
- Methanol is rapidly absorbed from the stomach. Therefore, emesis should be instituted only if presented very shortly after ingestion (less than 1 hour?) and only if the animal is alert and has intact postural and gag reflexes.
- Activated charcoal (1 g/kg) would have limited value due to low affinity for methanol.
- Saline cathartic (sodium or magnesium sulfate: 250 mg/kg as a 10 - 20% solution in water; may be mixed with activated charcoal).
- At the present time, treatments for poisoned animals generally include therapy to reduce metabolic acidosis and, in the case of primates, to slow the production of formate and formaldehyde. The effectiveness or necessity of these therapies in nonprimate animals is not proven. The need is likely to vary among animals with some experiencing significant benefit.
- Administer fluids with sodium bicarbonate (as needed) at up to 1 - 2 mEq/kg every 1 - 2 hours (slowly in the fluids); blood gases may be used to determine bicarbonate deficit to adjust therapy (see Ethylene glycol section).
- For primates, ethanol is recommended as an inhibitor of alcohol dehydrogenase as per ethylene glycol intoxication. Methanol has roughly 20 times less affinity for alcohol dehydrogenase than ethanol and is metabolized at 1/5 the rate of ethanol. Therefore, ethanol must be administered periodically. Although not adequately studied at this time, it seems likely that 4-methylpyrazole could be used instead of ethanol (see section on Treatment under Ethylene Glycol).
- Monitor glucose and potassium; hypokalemia in the presence of acidosis is a bad prognostic sign.
- Leucovorin (folinic acid) and folic acid decrease the persistence of formic acid and promote its conversion to carbon dioxide and water.
Aspirin and Salicylates

**Sources**

- Aspirin (acetyl-salicylic acid; alternative name is 2-acetyloxy-benzoic acid) is a phenol derivative and is often available in 5 or 7.5 grain (325 - 500 mg) tablets.
- Salicylates in common use also include sodium salicylate and salicylic acid.
- Products containing aspirin also include: Alka-Seltzer, Aspergum, Bufferin, APC, Anacin, etc.
- Salicylates are commonly combined with other drugs including caffeine, codeine, and acetaminophen.
- Pepto Bismol liquid contains bismuth subsalicylate at a concentration of 262 mg/15 ml which equals 130 mg of salicylate/ml.
- Salicylates are also contained in topical preparations (e.g., methyl salicylate [oil of wintergreen]) are used as keratolytic agents.

**Toxicity**

- An aspirin dosage of 25 mg/kg once daily will produce a serum salicylate concentration in the cat which is equivalent to that providing a therapeutic effect in man.
- Cats given one 5-grain tablet of aspirin per day (80 - 120 mg/kg/day) developed clinical signs of poisoning within 12 days.
- Administration of aspirin to dogs at a rate of 25 - 35 mg/kg every 8 hours provided an "optimal" serum salicylate concentration.
- Dogs given 100 - 300 mg/kg/day developed gastric ulceration and hematemesis within 1 - 4 weeks. At a lower dose of 50 mg/kg/12 hours, vomiting was seen approximately 2 hours after each dose.

**Mechanisms of Action**

- Aspirin blocks the activity of cyclooxygenase, an important enzyme in the pathway leading to prostaglandin synthesis. The net result is a decrease in concentration of prostaglandins.
- Similarly, by inhibition of platelet cyclooxygenase, there is an increase in bleeding time due to the decreased aggregation of platelets.
- At high doses, aspirin and other salicylates may uncouple oxidative phosphorylation and may cause hyperglycemia and glycosuria. Occasionally hypoglycemia is seen.
- An early effect may include stimulation of the respiratory center, which may result in respiratory alkalosis and secondary bicarbonate excretion in the urine. This stage will probably never result in presentation to the veterinarian, although persons aware of the significance of overexposure may bring animals in during this phase.
- A metabolic acidosis results from several aspects of the toxicosis:
  - Salicylates are weak acids; however, due to their high degree of protein binding and low plasma concentrations, it is unlikely that this is the cause of the acidosis.
  - An anion gap is produced in part by the presence of salicylic acid and other salicylate metabolites. Lactic acidemia develops secondarily from inhibition of normal glycolysis and contributes to the development of metabolic acidosis.
  - The early respiratory alkalosis may stimulate renal excretion of bicarbonate.
  - Metabolic derangement and resultant production of acetoacetic acid and other ketone acids have been reported.
  - Decreased renal excretion of sulfate, phosphate, and other acidic moieties may occur.

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### Table: Toxicants that Cause Acidosis

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<td>Cats, dogs</td>
<td>Minutes to chronic</td>
<td>Days; potentially lethal</td>
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Absorption, Distribution, Metabolism and Excretion (ADME)

- The acid pH of the stomach protonates the acetylsalicylic acid, and as a result, the uncharged form is readily absorbed directly through the gastric mucosa. Significant absorption, however, also occurs in the small intestine.
- Enteric-coated aspirin formulations may delay and prolong absorption. In dogs dissolution and absorption of aspirin from enteric coated products was extremely variable.
- Plasma esterases rapidly hydrolyze aspirin to free salicylic acid.
- Aspirin is eliminated principally as free salicylic acid and as a conjugate of either glycine or glucuronic acid. Because of the limited capacity of cats to conjugate some xenobiotics including aspirin via the glucuronidation pathway (limited glucuronyl transferase), cats and neonates of many species are predisposed to toxicoses.
- Salicylates are extensively bound to plasma albumin.
- Serum half-lives in the cat were dose dependent:
  - 5 mg/kg BID - 21.8 hours.
  - 12 mg/kg/day - 26.8 hours.
  - 25 mg/kg/day - 44.6 hours.
- Half-lives for elimination include cat - 37.6 hr, dog - 8.6 hr, swine - 5.9 hr, horse - 1.0 hr, goats - 0.8 hr, and cattle 0.5 hr.

Signs

- Respiratory stimulation, tachypnea, and hyperventilation.
- Acidosis may require 12 - 24 hours to develop based on human literature.
- Fever with extremely high doses.
- Gastric irritation is the most common adverse side effect of aspirin.
- Gastric ulcers, with hematemesis in dogs or cats.
- Vomiting. In humans, vomiting commonly occurs 3 - 8 hours postingestion. May be blood tinged in 10 - 20% of toxicosis cases. Dogs may vomit within 2 hours of exposure.
- Anorexia.
- Dehydration, occasionally anuria develops.
- Depression. Animals may develop semi-comatose states. Muscular weakness.
- Toxic hepatitis (sometimes).
- Anemia, with Heinz bodies and reduced RBC production in cats.
- Pulmonary edema may occur.
- Ototoxicity reported in man due to increased labyrinth pressure.
- Convulsions and cerebral edema occasionally occur in animals. Seizures may be related to the effects of hyperventilation and/or reduced cerebral glucose concentrations.
- Death.

Clinical Pathology

- Hyperglycemia or hypoglycemia can occur.
- Hypokalemia and hypernatremia can occur.
- Large doses in humans have been associated with interference with the production of vitamin K dependent clotting factors, with secondary hypoprothrombinemia and hemorrhage.
- In the cat, Heinz body production and possibly hemolysis and bone marrow suppression may result in anemia.

Diagnosis

- Blood or serum salicylate concentrations are used routinely in human medicine, but concentrations associated with toxic effects have not been defined in veterinary medicine. Extrapolation from man could nevertheless be attempted.
- Toxic concentrations in human blood are reported to be 50 - 100 mg/dl, while concentrations of less than 50 mg/dl rarely produce serious toxicosis. In cats, 60 mg/dl has been associated with deaths.
- History of excessive exposure and appropriate acid-base alterations and clinical effects are important in establishing a diagnosis.

Treatment

- For very recent exposure and provided no contraindications exist, an emetic may be used.
- Activated charcoal and a saline cathartic may be used.
- Gastric lavage may be required. Effectiveness of activated charcoal and/or lavage may be prolonged (6 - 12 hours postingestion) if enteric-coated formulations have been ingested. Occasionally aspirin tablets may form insoluble concretions causing slowed but very
Metabolic acidosis is treated by very slow infusion of sodium bicarbonate (1 - 3 mEq/kg) in fluids IV. This may also enhance the removal of acetylsalicylic acid and other acidic metabolites in the urine to shorten the duration of the whole syndrome. Bicarbonate and fluid therapy must be monitored closely and be adjusted if pulmonary edema develops. Development of diuresis may be delayed 1 - 4 hours (or more) and circulatory overload can develop. Diuresis may be promoted with the loop diuretic furosemide. The use of mannitol is generally not recommended.

- Intravenous glucose may be needed if the animal is hypoglycemic.
- If indicated, correction of electrolyte imbalance may be of value.
- Whole blood transfusions may be used if significant hemorrhage or anemia has occurred.
- Hyperthermia or hypothermia is controlled by external manipulation, not by drugs.
- In severe overdose, salicylates and metabolites may be removable by osmotic (alkaline) peritoneal dialysis as well as by hemodialysis.
- Exchange transfusions are sometimes used in pediatric human patients and could be employed in small animals as well.
- Misoprostol, a prostaglandin E1 derivative, may help prevent aspirin-induced gastric ulcers.
- Sucralfate (synthetic disaccharide; Carafate ®) probably should be given if gastric erosions have occurred.

### Other Agents that Cause Acidosis

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>d,l-Methionine</td>
<td>(See Toxicants with Mixed Effects on the Central Nervous System)</td>
<td></td>
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<tr>
<td>Phenolics</td>
<td>(See Hepatotoxic Drugs and Chemicals)</td>
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<tr>
<td>Any shock-inducing syndrome</td>
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<tr>
<td>(metabolic acidosis)</td>
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<td></td>
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<tr>
<td>Any syndrome with prolonged exertion or seizures</td>
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<tr>
<td>(metabolic acidosis)</td>
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<td></td>
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<tr>
<td>Any Syndrome with severe pulmonary failure or respiratory paralysis</td>
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<tr>
<td>(respiratory acidosis)</td>
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<tr>
<td>Other agents that cause acidosis</td>
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</tbody>
</table>

- Any toxicoses which cause profound circulatory shock may cause a secondary metabolic acidosis.
- Toxicoses that cause prolonged seizures may cause acidosis due to the extreme exertion and exhaustion involved.
- Uncouplers of oxidative phosphorylation may cause significant acidosis.
- Phenolics may cause respiratory alkalosis caused by stimulation of the respiratory center which may later be followed by a metabolic acidosis. Phenolics will be discussed under toxicants that affect the liver. In general the phenolics exert effects on the gastrointestinal tract, the liver, the kidneys and sometimes the nervous system (infrequently seizures have been associated with phenol toxicoses).
References

Ethylene Glycol

Methanol (Methyl Alcohol, Wood Alcohol)

Aspirin and Salicylates

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