Tox and Hound – Fellow Friday – Metal Hydrides II – Phosphine (PH3)

November 19, 2021 by **Tox & Hound** Leave a Comment

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Fumigation, Semiconductors, Human Self-Ignition and Methamphetamine

Steven Curry, M.D.[*]
Eugene Ngai, M.S.[#]
Greg Makar, D.O.[*]

[*]University of Arizona College of Medicine
Phoenix Department of Medical Toxicology Banner
University Medical Center Phoenix Phoenix, AZ

[#]ChemicallySpeakingLLC

Introduction

In the previous Fellow Friday on arsine, we introduced metal hydrides, their general physical properties, and how they are used in the semiconductor industry. Our arsine discussion explored the toxicity of hydrides of germanium, antimony, selenium and tellurium. We also noted how garlic odors were associated with various methylated elements surrounding arsenic in the periodic table, and how humans

methylate some metals. The flammability and explosive nature of various hydrides was emphasized using silane as an example.

Element	Formula	Name
Antimony	SbH_3	Stibine
Arsenic	AsH_3	Arsine
Boron	B_2H_6	Diborane
Boron	B_5H_9	Pentaborane
Germanium	GeH_4	Germane
Germanium	Ge_2H_6	Digermane
Phosphorus	PH_3	Phosphine
Selenium	SeH_2	Hydrogen selenide
Silicon	SiH_4	Silane
Tellurium	TeH_2	Hydrogen telluride

Figure 1 – Examples of metal hydride gases.

We now turn our attention to phosphine (PH_3), the hydride of phosphorus. Phosphine can be somewhat confusing to toxicology fellows who hear of phosphine as a semiconductor gas, but also hear about deaths on ships related to phosphine used in grain holds as a fumigant. And they hear of children who have died from phosphine that, in some way, was used to kill rodents near their homes. There are also reports of phosphine being involved in methamphetamine laboratories – why would meth cooks need phosphine? And finally, there are those stories of human self-ignition. After all, every toxicologist should have a differential diagnosis of spontaneous combustion. I again am honored to have Eugene Ngai, an international expert in the production, transportation and use of metal hydrides join me, as well as Dr. Greg Makar, one our medical toxicology fellows, as we attempt to simplify phosphine toxicity.

Phosphine properties

Phosphine is a colorless gas that is slightly heavier than air. Pure phosphine is without an odor, but a garlic odor is commonly noted during phosphine releases from methylated phosphorus contaminants in many instances, especially with the release of phosphine from metal phosphides (described below).

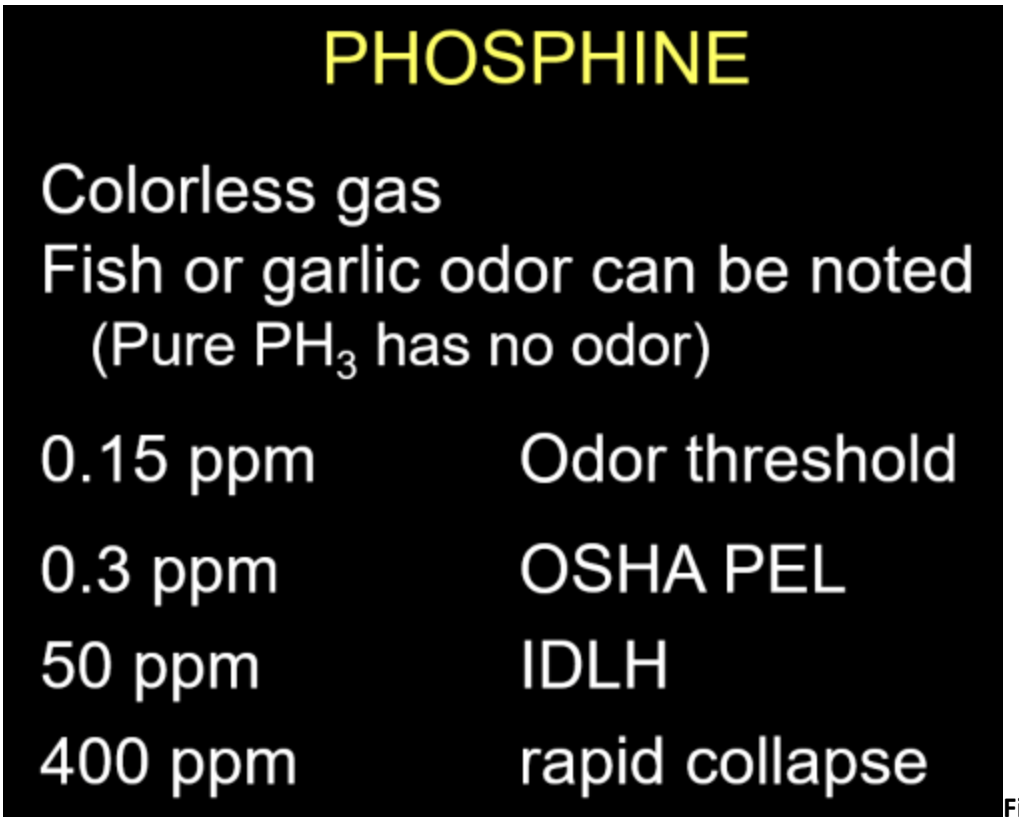

Figure 2 – Some properties of phosphine.

Like silane and diborane, phosphine is pyrophoric (autoignites in 1 atm air at 130°F), which leads to fire/explosion hazards when atmospheric concentrations rise high enough, including autoignition when leaking from a cylinder.

Figure 3 – Burning phosphine after autoignition from cylinder valve connection leak in a gas cabinet at a semiconductor facility. This cylinder contained 15% phosphine in argon gas.

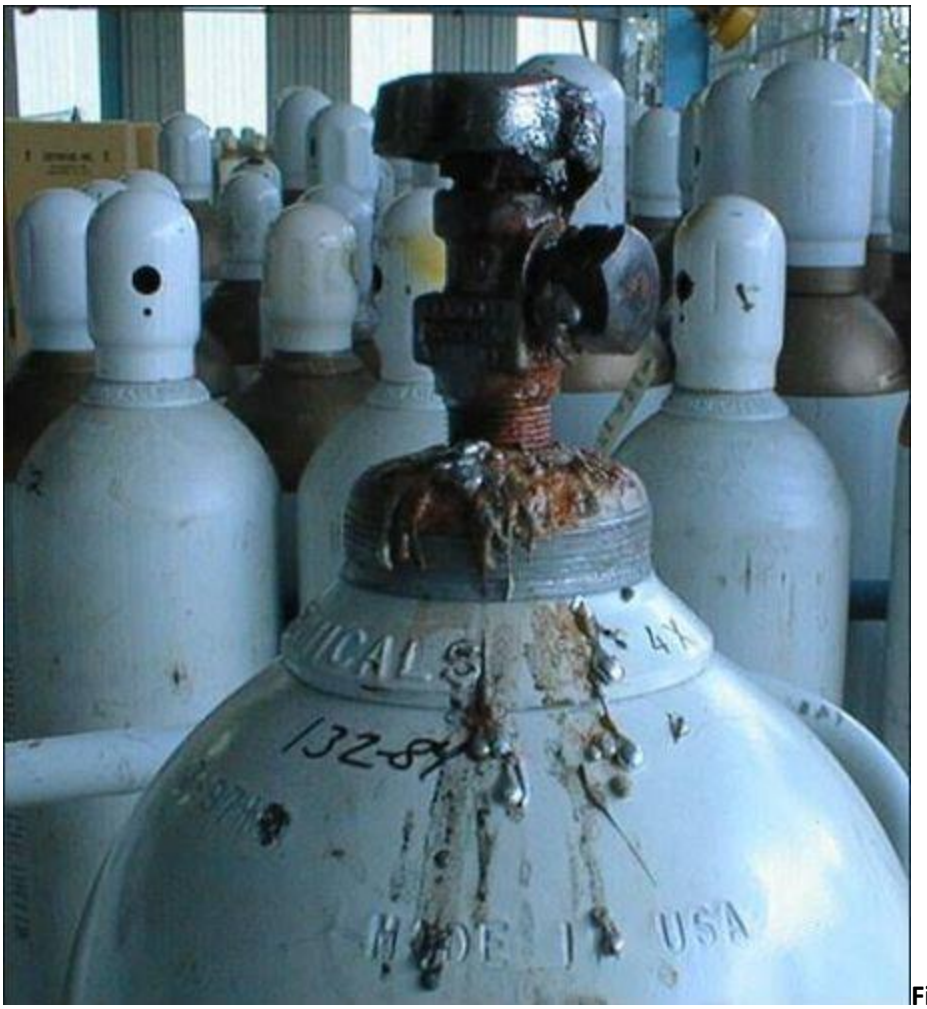

Figure 4 – Results of autoignition and fire when a valve vapor tight seal was loosened when the valve was not completely closed on a cylinder of pure phosphine. Note melted metal from valve handle.

Phosphine sources

Cylinders

Phosphine gas is produced and stored in cylinders for use in fumigation or in the semiconductor industry by the dissociation of polyphosphoric acid. Solvay, the world's largest manufacturer of phosphine, converts pure white phosphorus to polyphosphorous acid. The polyphosphorous acid then, is heated to high temperatures at which it dissociates into phosphine and phosphoric acid.

Figure 5 – Synthesis of phosphine from polyphosphorous acid.

Pure phosphine in cylinders is commonly used for metal organic chemical vapor deposition (MOCVD) processes as discussed in the arsine post. It frequently, but not always, is mixed with other gases for use as a dopant or to grow an electrical insulating layer on semiconductor chips.

Figure 6 – Cylinders of pure phosphine for MOCVD.

Phosphine from cylinders is also used around the world for fumigation of grains and commodities. In commodity fumigation, phosphine released from cylinders is meant to remain at a relatively low, but adequate, constant concentrations for at least 2-3 days in order to kill pests. In this setting, phosphine is diluted in CO_2 or nitrogen, in part, to lessen flammability.

Figure 7 – Phosphine in nitrogen for grain fumigation. Photo used with permission of Messer (messer-us.com).

Metal phosphides

A second major source of phosphine is the liberation of phosphine from aluminum, magnesium or zinc phosphide. These metal phosphides are solids, and when they react with water, including ambient humidity, phosphine is released. Of course, acids produce even more rapid phosphine formation. These reactions are similar to arsine generation from metal arsenides discussed in the previous post.

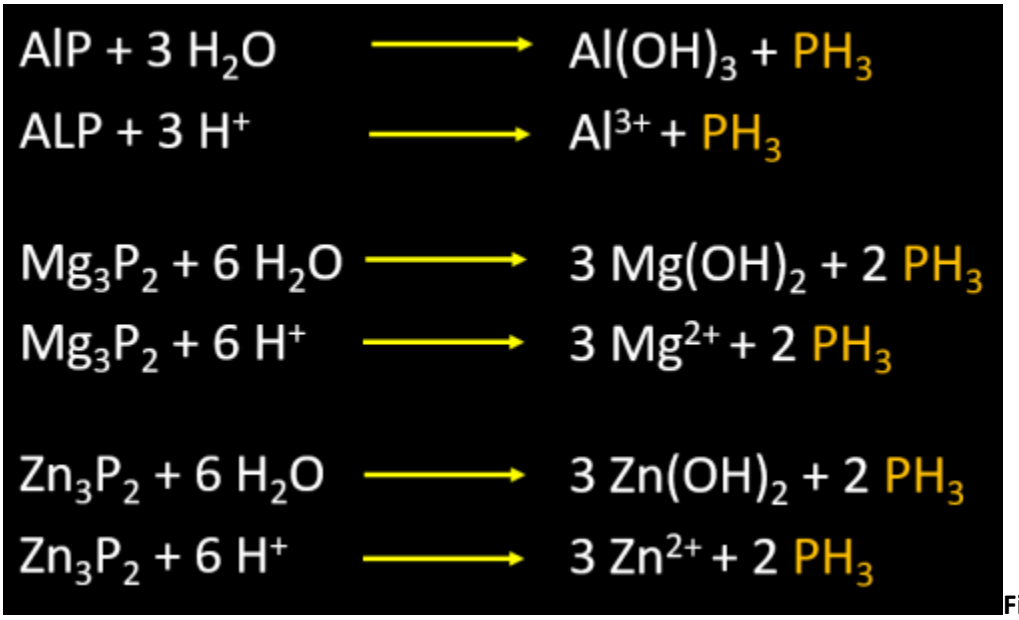

Figure 8 – Generation of phosphine from metal phosphides reacting with water and/or acid.

Metal phosphides, especially AlP and Mg_3P_2 , are used for commodity fumigations (grain, lumbar, etc.), such as during transportation by ship, but also when products require significant storage time, such as in silos. The solid phosphides (e.g., tablets, sachets of granules, dust, etc.) are dispensed into sealed atmospheres (e.g., ship holds, grain elevators) or under plastic tarps. Over time, phosphine is released as the phosphide reacts with ambient humidity. The phosphide products commonly contain other ingredients to slow liberation of phosphine and to lessen spontaneous flammability.

Figure 9 – Aluminum phosphide tablets for fumigation.By اثر شخصی توسط بارگذار – همان, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=78255494

Figure 10 – Checking to be sure phosphine is not leaking from sealed ship hold containing magnesium phosphide. Photo used with permission of Fumiteam.ee.


Figure 11 – Dispensing granular magnesium phosphide onto grain. Photo used with permission of Fumiteam.ee.

When used as a rodenticide, the metal phosphide is placed in burrows and typically covered with dirt. Care must be taken to use these products well away from occupied structures to prevent egress of phosphine into the buildings. Tragic deaths have also resulted from spraying metal phosphide rodenticides with water in an effort to wash them away, with liberation of large amounts of phosphine gas.[1] Zinc phosphide, which does not release phosphine as readily from ambient humidity, is also used as a bait for rodents – ingestion is quickly followed by phosphine formation.

Illicit methamphetamine production

Several methods are used for the illicit production of methamphetamine from ephedrine/pseudoephedrine. Methamphetamine synthesis requires reduction of the alcohol group on ephedrine. One means of reduction is the phosphorus-iodine method. In the final steps of synthesis, ephedrine, red phosphorus and iodine are placed in a round-bottom flask. Water is typically added, although the reaction will proceed without it.

Figure 12 – **Left**: iodine and phosphorus in round-bottom flask. **Right**: addition of ephedrine to iodine and phosphorus – ready for addition of water in this small-scale demonstration.

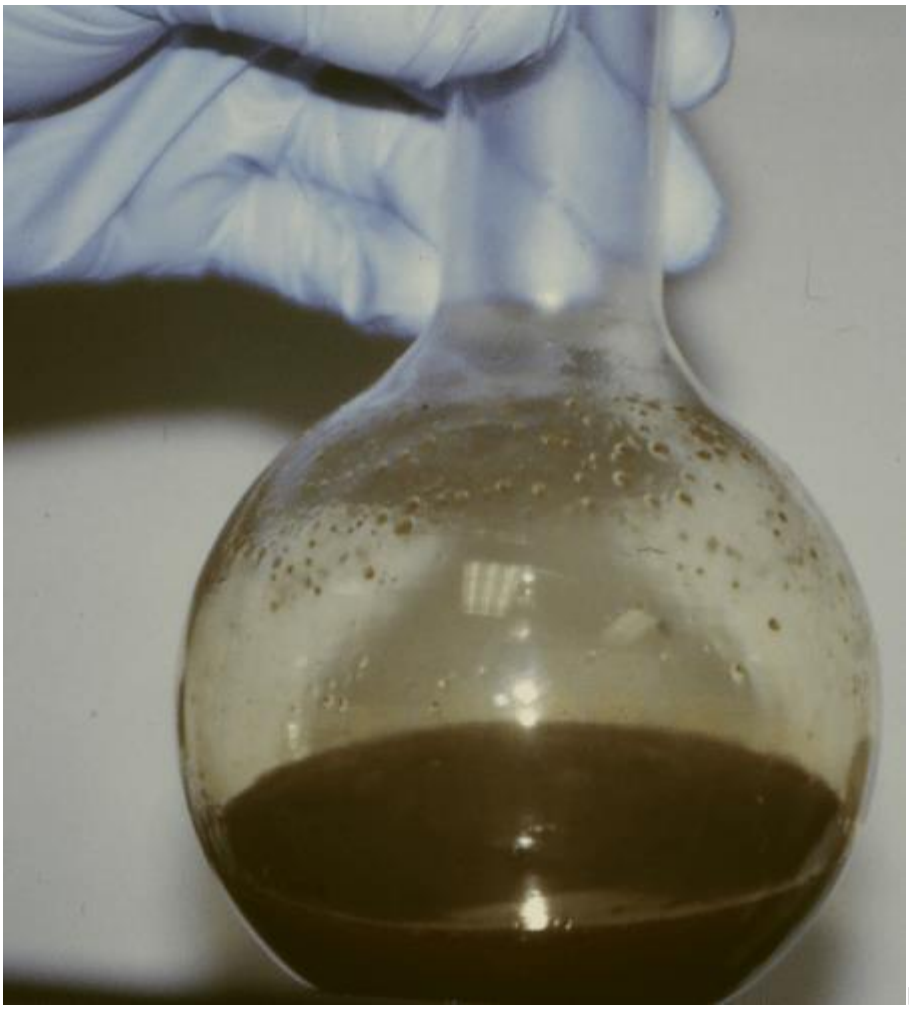

Figure 13 – Iodine, phosphorus, ephedrine and water. Ready for heat and refluxing. Note particles of red phosphorus on walls of flask.

In the round-bottom flask, red phosphorus mixes with iodine to form hydroiodic acid (HI) and phosphorous acid, as below.

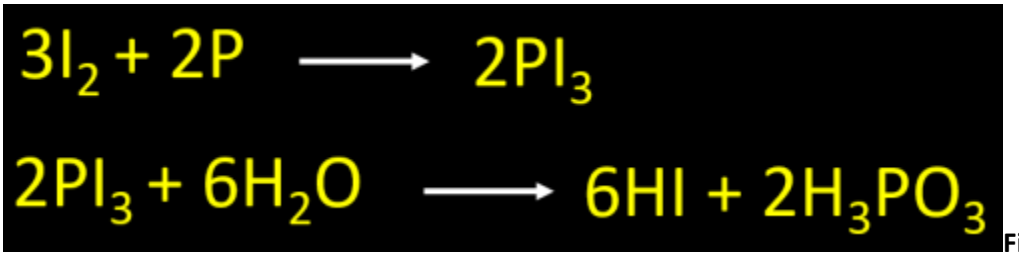

Figure 14 – Formation of hydroiodic acid (HI) from iodine and phosphorus.

Hydroiodic acid, then, reduces the alcohol group in ephedrine to form methamphetamine.

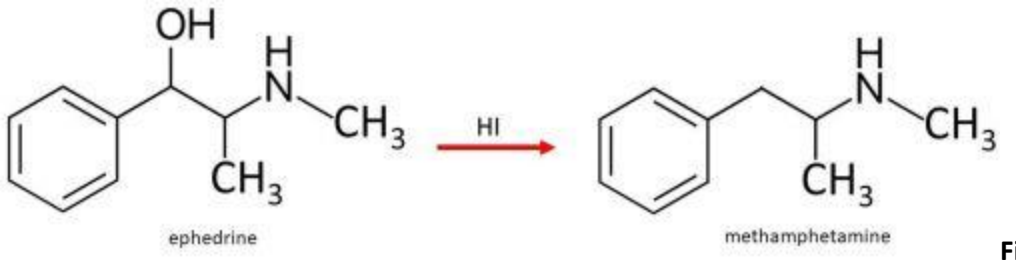

Figure 15 – Reduction of ephedrine by hydroiodic acid to form methamphetamine.

You may ask, wouldn't it be a lot simpler to just acquire hydroiodic acid? The US Drug Enforcement Administration has tightly regulated hydroiodic acid since 1993, making it difficult to obtain.

As long as the temperature in the flask does not become too elevated, ephedrine will undergo reduction to methamphetamine without much phosphine formation. But two bad things can happen during refluxing of heated iodine, phosphorus and ephedrine. First, recall those red phosphorus particles on the side of the glass as the contents are mixed in figure 13. If they are allowed to dry and overheat, the red phosphorus will convert to white (yellow) phosphorus, which will spontaneously ignite in air. Historically, this has been the second most common cause of illicit drug lab fires in Arizona.

Second, phosphorus acid that was produced as a byproduct in the synthesis of HI (**Figure 14**), when overheated, will be converted to phosphine, just as occurs in commercial phosphine production.[2–4]

Figure 16 – Formation of phosphine from phosphorous acid.

Cellular actions of phosphine

The cellular mechanism by which phosphine causes toxicity is not completely understood.[5] One action is that phosphine inhibits complex IV (cytochrome oxidase) of the electron transport chain in the mitochondrial inner membrane, thus decreasing electron transport, oxygen consumption and oxidative phosphorylation. As we have discussed in previous posts on cyanomythology, microvesicular steatosis, and the origins of protons in lactic acidosis, electrons from the iron of cytochrome c on the external surface of the mitochondrial inner membrane are first shuttled to a copper atom in complex IV. As shown in **Figure 17**, electrons then move onto a second copper atom before shuttling to an iron in the heme moiety of cytochrome a. From cytochrome a, electrons move to the binuclear center of cytochrome a_3, made up of an iron and another copper atom, and then, finally, combine with oxygen to form water. Most complex IV inhibitors medical toxicology fellows study work by binding, in their undissociated form, to the binuclear center of cytochrome a_3. Spectral absorption studies suggest that phosphine acts to keep the iron in cytochrome a reduced, impairing electron transport within complex IV, though some lesser activity at the binuclear center cannot be complete excluded.[6]

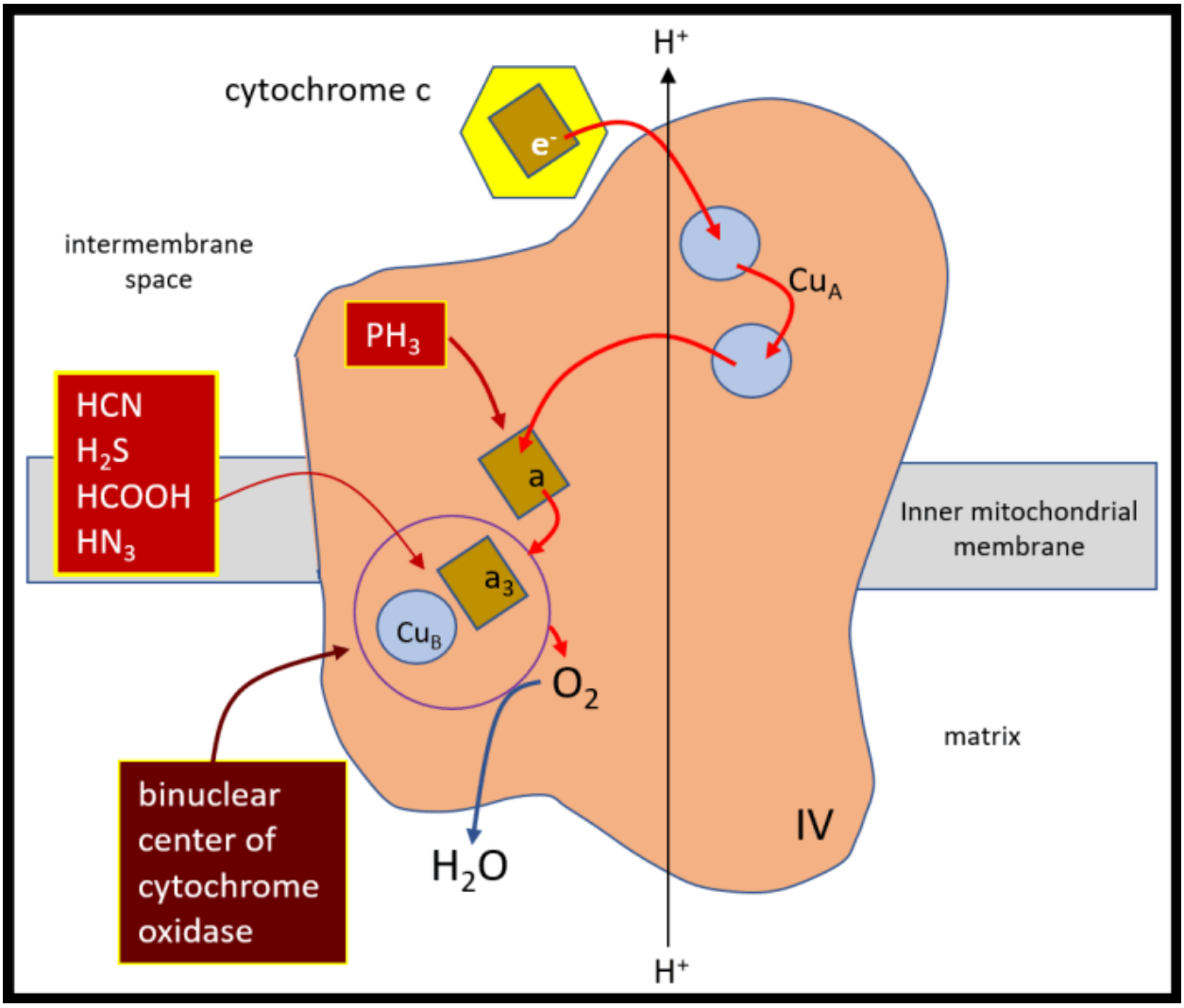

Figure 17. Complex IV (cytochrome oxidase). HCN, H_2S, HCOOH, and HN_3 inhibit by binding to the binuclear center of cytochrome a_3. In vitro data suggest phosphine keeps iron reduced in the heme of cytochrome a.

However, inhibition of complex IV seems unlikely to explain much or most of phosphine's toxicity.[7] Phosphine inhibits complex IV much more in *in vitro* than *in vivo*. It is also difficult to extrapolate from mechanisms of toxicity in insects which encounter low phosphine concentrations over hours to weeks compared to acute phosphine poisoning in mammals. Humans with phosphine poisoning do demonstrate decreased complex IV activity, but such inhibition is similar in those who die or live, and is somewhat similar to patients in shock from other causes.[8] Cholinesterase inhibition is found in vitro, but there is no convincing evidence of a cholinergic crisis or meaningful depression of cholinesterase activity in poisoned humans. Thus, other mechanisms for phosphine toxicity have been sought, with examples shown in **Figure 18**. But oxidant stress has gained lots of attention and will be addressed next.

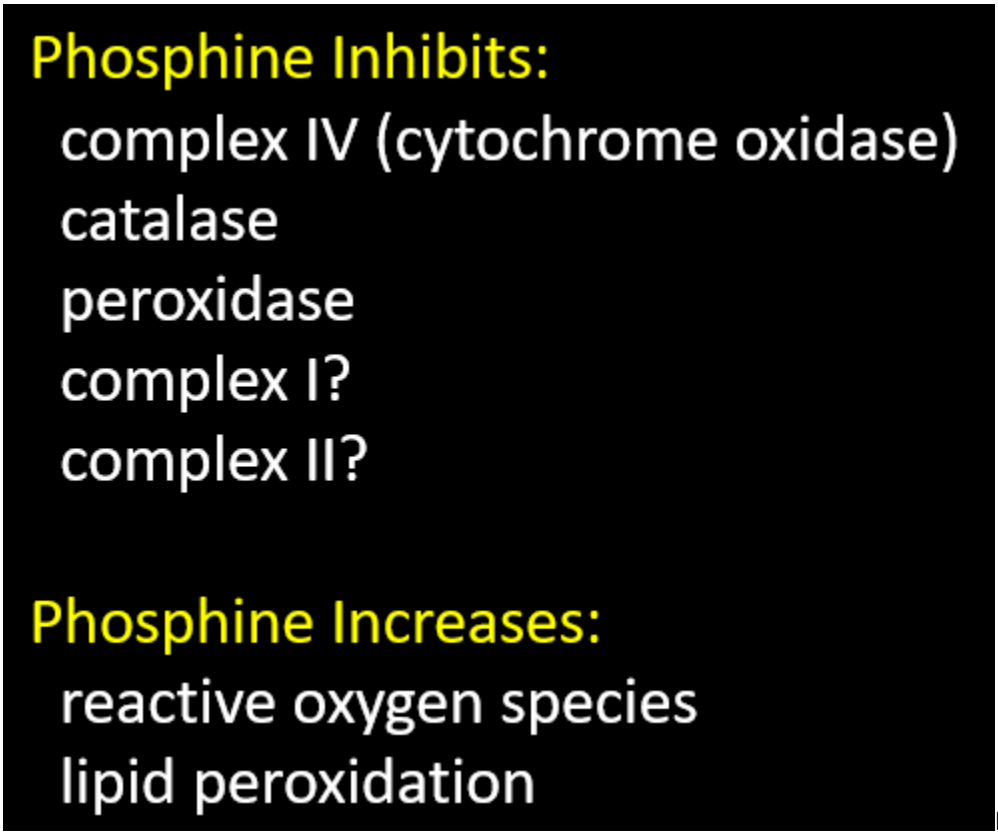

Figure 18 – Examples of actions of phosphine.

We noted in the post on microvesicular steatosis that when electron transport is inhibited, NADH will transfer electrons onto oxygen to form superoxide (O_2^-) rather than onto complex I. And electrons can also move from other members of the transport chain (e.g., ubiquinone, complex III) onto oxygen to form superoxide, as well. Superoxide (O_2^-) is a substrate for mitochondrial superoxide dismutase, which coverts O_2^- to H_2O_2, another reactive oxygen species. Phosphine increases concentrations of reactive oxygen species, and high and sustained concentrations of H_2O_2 and other species produce various damaging effects, including peroxidation of lipids in the mitochondrial inner membrane, causing further mitochondrial insult and cell death. The oxidant stress may be accentuated by phosphine's inhibition of catalase and peroxidase.[5] But there is probably more to phosphine toxicity than our limited understanding of its action on electron transport and oxidant stress.

Phosphine poisoning

Phosphine toxicity results from inhalation of phosphine gas or ingestion of metal phosphide.[9] Death has resulted from inhalation of phosphine liberated from metal phosphides in buildings, on ships, and elsewhere. Of particular concern in shipping is leakage of phosphine from "sealed" grain holds into other areas of the ship from defects in seals or in the walls of holds, themselves.[10,11] Stow-away passengers hiding in holds have been found dead from phosphine toxicity when holds were opened for unloading, usually about a day prior to reaching port. While inhalation of phosphine released from cylinders in fumigation operations or from metal phosphides reacting with water can produce lethal poisoning, neither Eugene nor I am aware of any fatality from inhalation of phosphine gas in the semiconductor industry over the last 50 years.

In general, phosphine produces a relatively rapid onset of symptoms with metabolic acidosis and death, mainly from cardiac failure. Pulmonary edema is commonly present in those who die, though it is not always clear how much is cardiogenic versus ARDS.

Ingestion of phosphide products quickly produces vomiting, epigastric and chest pain, hypotension, shock, cardiac arrhythmias and corrosive injury to the esophagus and stomach, sometimes with hematemesis.[7,9] A garlic odor may be noted.[12] Foaming about the mouth and throat can be seen. Impaired ventricular contractility is noted on echocardiography during times of shock. *Self-combustion* is possible from liberated phosphine. In one instance, moving the body of a deceased phosphine victim was accompanied by an explosive sound with flames exiting the mouth.[13] Facial burns from vomiting of hot/smoking stomach contents (including activated charcoal) has occurred.[14] Flames may appear at the ends of NG tubes.[12,15]

Liver injury is usually not severe in most patients who survive, but can be found at autopsy. Occasional oxidant hemolytic anemia is noted (especially in patients with G6PD deficiency), and methemoglobinemia is possible.[7,16–18] Hypoglycemia has been reported. Other nonspecific findings include rhabdomyolysis, adrenal hemorrhage, and kidney failure from tubular necrosis.[19] Tripathi and Pandy described brain congestion, edema, petechial hemorrhages and cerebral and cerebellar necrosis in 239 cases of phosphine poisoning.[20] Liang and colleagues described similar brain changes in 8 children who died from phosphine inhalation as the gas spread from fumigated grain into buildings where they resided.[17]

In countries where ingestion of phosphides are common, diagnostic screening for phosphine involves placing gastric contents or exhaled air in contact with silver nitrate paper, which will turn dark from formation of metallic silver (**Figure 19**).[21,22] However, sulfur compounds such as H_2S will also produce a positive test.[23] Additional screening of gastric contents with ammonium molybdate can confirm presence of phosphine.[23]

Figure 19 – Darkening of silver nitrate paper in presence of phosphine gas generated from zinc phosphide.

Commonly performed procedures following ingestion of phosphides include gastric lavage with potassium permanganate and administration of activated charcoal, but their effectiveness is unproved.[7] ECMO has been used as a supportive measure with survival. There are no roles for cyanide antidotes at present.[24]

Some standard occupational medicine sources list phosphine inhalation as a cause of delayed-onset pulmonary edema. This may be somewhat true in patients who are already symptomatic from phosphine/phosphide poisoning, but I can't locate convincing reports of asymptomatic patients who developed ARDS, alone, minutes to hours after an acute phosphine exposure (unlike phosgene). I've

evaluated quite a few semiconductor workers over the years who have accidentally inhaled phosphine and have never seen any become ill as long as they were never symptomatic (usually just smelled the garlic odor).

Finishing up

We've seen that many metal hydride gases are quite toxic and/or combustible. What do emergency response crews do when confronted with a leaking cylinder of a metal hydride gas? Frequently the solution is to place the cylinder into a specially constructed emergency response containment vessel (ERCV), as shown below.

Figure 20 – A portable emergency response containment vessel (ERCV).

These ERCVs are commonly found at facilities that manufacture, store or use cylinders of metal hydrides as well as other toxic gases, such as boron trichloride, hydrogen, chlorine, and ammonia. A full-sized cylinder of a metal hydride is placed in the ERCV and then the vessel door is sealed closed. The leaking cylinder is then safely transported to a site that is setup for safe disposal of the gas.

Figure 21 – Cylinder placed in an ERCV before the vessel door is sealed closed.


Figure 22 – ERCV valve and pressure gauge to monitor pressure in the ERCV. Nitrogen purge cylinder is shown connected to ERCV for use to purge and leak check ERCV.

After the door is closed the nitrogen from the small cylinder on top is flowed into the ERCV through the rear valve and out the front valve. The ERCV must be purged of air since phosphine is pyrophoric and the leak could create an explosive mixture inside. As a final step, the nitrogen pressure is allowed to build up so that the ERCV can be leak-checked prior to transport.

We've moved through metal hydrides now with the exception of the hydrides of boron.

Element	Formula	Name
Antimony	SbH_3	Stibine
Arsenic	AsH_3	Arsine
Boron	B_2H_6	Diborane
Boron	B_5H_9	Pentaborane
Germanium	GeH_4	Germane
Germanium	Ge_2H_6	Digermane
Phosphorus	PH_3	Phosphine
Selenium	SeH_2	Hydrogen selenide
Silicon	SiH_4	Silane
Tellurium	TeH_2	Hydrogen telluride

Figure 23 – Metal hydrides.

So, next time we will finish up this series with boron hydrides, including, the green dragon. Fellows, please leave brief feedback and comments so we can be sure we are providing information that is of value to those of you in training. Thanks.

Postscript

Medical toxicology fellows, here are some items for consideration and discussion.

- Reduction of the alcohol group in ephedrine results in formation of methamphetamine. What substance results from oxidation of that same alcohol group?

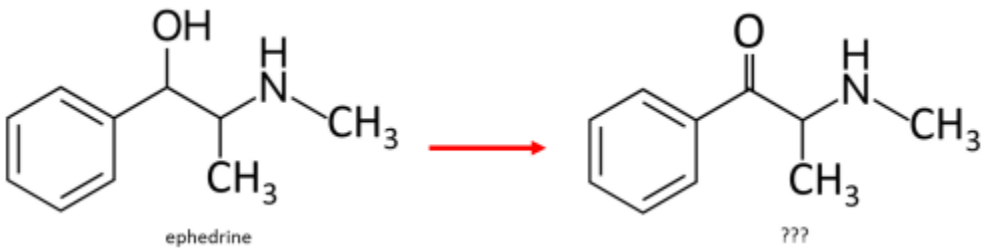

Figure 24 – Oxidation of ephedrine.

- It's always best to have a differential diagnosis of human self-ignition apart from spontaneous human combustion. We've seen that ingestion of metal phosphides can result in self-ignition of phosphine as the gas mixes with oxygen in air and exhaled breath while exiting the mouth and nose. The ingestion of what other substance can produce smoking and flaming stools?
- Darkening of silver nitrate paper can occur when it comes in contact with phosphine in exhaled breath or gastric contents. What substance on the breath of a comatose victim will darken lead acetate paper?

Figure 25 – Lead acetate paper.

- Don't confuse phosphine and phosgene. We discussed how phosphine really doesn't produce delayed-onset pulmonary edema in the absence of being symptomatic with moderate to severe toxicity. But inhalation of phosgene gas certainly can. What is the chemical formula for phosgene and what odor does it possess?

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