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A Review of Toxicity and Use and Handling Considerations for Guanidine, Guanidine Hydrochloride, and Urea

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A Review of Toxicity and Use and Handling Considerations for Guanidine Guanidine Hydrochloride Urea

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Executive Summary

A request was received from the Battelle Memorial Institute, Pacific Northwest Laboratories Office of Small Business Programs to perform a review of the toxicity and safe use of guanidine. An extensive information search was conducted to locate toxicity and safety data for this compound. Because so little information was found on guanidine, the search was extended to the most common guanidine compound that is commercially available and chemically similar: guanidine hydrochloride. At the request of John Holbrook, urea was also included in this review, since guanidine decomposes to urea and carbon dioxide.

Based on the published data, guanidine should be considered a toxic compound by oral ingestion. No data is available for inhalation exposures. It is also a significant irritant to the eyes, skin, and lungs; has desiccant effects (is very drying to human tissue) by virtue of being hygroscopic; and in solution the pH may approach corrosivity, depending on the concentration. Guanidine does not appear to be absorbed through the skin.

There are no published studies detailing the effects of guanidine on humans; the only information on human exposure comes from the pharmaceutical industry, where guanidine hydrochloride is used as an orally administered drug. That data indicates that guanidine has significant effects on the gastrointestinal and nervous system as well as the desired therapeutic effect on the neuromuscular systems in persons with a rare disease, the Eaton-Lambert myasthenic syndrome. This effect on the neuromuscular system could be harmful in normal persons. The doses of guanidine hydrochloride used in medical treatment are much higher than would be expected from occupational exposure, and are oral doses as opposed to the inhalation doses expected in industry. However, caution is still warranted due to the potential severity of the effects. Controlling exposures to prevent irritant effects will keep doses low enough to minimize any concerns about these effects.

Because of its irritant properties, exposure to the skin, lungs, and eyes must be prevented. This can best be accomplished by the use of engineering controls such as enclosed systems and local exhaust ventilation to minimize dust generation. Personal protective equipment should be utilized if engineering controls cannot control exposures. Gloves should be worn to prevent skin contact when handling guanidine; no gloves have been tested for resistance to guanidine or guanidine hydrochloride, but nitrile gloves resist corrosives such as sodium hydroxide and should be a reasonable choice if no other chemicals are used in the process.

Based on the published data, urea should be considered relatively non-toxic. It may be slightly irritating to the eyes, skin, and lungs. Controlling exposures for the harmful effects of guanidine should also control for any harmful effects of urea.

Introduction

A request was received from the Battelle Memorial Institute, Pacific Northwest Laboratories Office of Small Business Programs to perform a review of the toxicity and safe use of guanidine. At the request of John Holbrook, urea was also included in this request. Guanidine decomposes to urea and carbon dioxide, and exposures to urea might be expected in facilities handling guanidine.

Methods

An extensive information search was conducted to locate toxicity and safety data for these compounds. The information sources are listed in the References and include national biomedical and toxicology databases, chemistry reference books, and chemical manufacturers. References will be retained in our files.

Because so little information was found on guanidine, the search was extended to guanidine hydrochloride, the hydrochloride salt of guanidine, for which more information is available. Because guanidine hydrochloride is chemically very similar to guanidine, toxicity information for guanidine hydrochloride is likely to be analogous to guanidine; the U.S. Army used guanidine hydrochloride as a surrogate for guanidine in toxicological testing conducted in the 1980s. Results are presented for the two compounds as a group.

Results

A. Description and uses of guanidine and guanidine hydrochloride

Guanidine is a strong organic base that is found in the urine as a normal product of protein metabolism. It is also used as a protein denaturant in biomedical and molecular biology research. It is found naturally in small amounts in a number of foods, including turnips, mushrooms, corn, rice, and mussels. In industry, guanidine and its derivatives are used in manufacture of plastics, resins, photochemicals, fungicides, rubber chemicals, and disinfectants.

Guanidine hydrochloride, the hydrochloride salt of guanidine, is commercially available. It is a common chemical intermediate in manufacturing, as noted above. It has been used to produce nitroguanidine, a component of rocket propellants.

Guanidine hydrochloride is also available as an orally administered human drug. Its use is for the treatment of muscle weakness and easy fatigue caused by a rare disease known as the myasthenic syndrome of Eaton-Lambert, which is associated with small-cell carcinoma of the lung. The precise action of the drug is not known, but it apparently acts to enhance the release of acetylcholine and to slow the rates of depolarization and repolarization of muscle cell membranes.

Synonyms for guanidine include carbamidine; carbamamidine; iminourea; imidourea; aminoformamidine; and aminomethanamidine.

Synonyms for guanidine hydrochloride include guanidium chloride; guanidium hydrochloride; iminourea hydrochloride; carbamidine hydrochloride; aminoformamidine hydrochloride; and aminomethanamidine hydrochloride.

B. Description and uses of Urea

Urea is made in the liver as an end-product of protein metabolism and excreted in urine. Humans excrete up to 30 grams of urea per day in the urine. Urea occurs normally in skin. It is used in a variety of industrial and consumer applications: in the manufacturing of urea-formaldehyde resins and foams; as a component of animal feeds, where it supplies nitrogen; in hand lotions and topical pharmaceutical preparations, where it promotes rehydration of dry skin and aids in debridement of damaged tissue; and as a protein denaturant in molecular biology research. Urea is accepted as a “Generally Recognized as Safe” food additive and is also used as a fermentation aid in foods and beverages. Urea has limited uses in medicine.

Urea is widely used in industry, and industrial experience in the United States has not suggested problems related to urea exposure.

Synonyms for urea include carbamide; ureaphil; ureapearl; ureophil; carbamimidic acid; carbonyl diamide; carbonyldiamide.

C. Physical Properties

The physical properties of guanidine, guanidine hydrochloride, and urea are described in Table 1.

Table 1
Physical Properties of Guanidine, Guanidine Hydrochloride, and Urea

Property	Guanidine	Guanidine Hydrochloride	Urea
CAS number	113-00-8	50-01-1	57-13-6
Molecular formula	CH_5N_3	CH_6ClN_3	CH_4N_20
Molecular weight	59.071	95.53	60.06
Physical state	Deliquescent crystalline mass	White crystalline powder	Colorless to white crystals or powder
Melting point	~ 50 C	180-185 C	132.7 C
Boiling point	> 160 C (decomposes)	>250 C (decomposes)	No
Specific gravity	Not reported in literature	1.34	1.32
pH	Not reported in literature; expected to be strongly basic (>10) in solution	6.5 (5% solution)	7.2 (10% solution)
Solubility in water	Soluble	200g/100g	Soluble
Solvent solubility	Soluble in alcohol	Soluble in alcohol	Soluble in alcohol
Stability	Hygroscopic	Hygroscopic. Stable under normal conditions.	Hygroscopic. Stable under normal conditions.

D. Toxic Effects of Guanidine, Guanidine Hydrochloride, and Urea

The following definitions are used in this section:

LDLO/LCLO – the lowest published lethal dose or concentration of a substance, determined by testing on animals. The lowest lethal dose may vary by species of animal.

LD50/LC50 – the dose or concentration of a chemical that kills 50% of a sample population of animals. LD50/LC50 values in different types of animals and in different routes of exposure (oral, injected) are not directly comparable. LD50 values are widely used as a measure of the potential toxicity of a chemical. Reports of the effects suffered by animals during the testing and the findings on necropsy are often cited as health effects that may occur in humans, when no human data exists.

Draize Test - a test that measures how irritating a chemical is to the eye or skin. The chemical is applied to the skin or eye of animals, typically rabbits.

Buehler Test – a test the measures whether a chemical produces sensitization (allergic) skin responses on repeated skin exposure to the chemical.

Toxicity data was obtained from the Registry of Toxic Effects of Chemical Substances (RTECS), TOXLINE/TOXNET, and the National Library of Medicine's Specialized Information Services.

Toxicity data is shown for each substance in separate tables. LD50 data is shown first in each table.

Table 2
Guanidine – Toxicity Data

Test Type	Species	Route	Reported Dose	Year of Study
LD50	Mouse	IP injection	350 mg/kg	1966
LDLO	Frog	SC injection	3000 mg/kg	1935
LDLO	Mouse	SC injection	266 mg/kg	1935
LDLO	Rabbit	Oral	500 mg/kg	1989
LDLO	Rat	SC injection	150 mg/kg	1935

IP – Intraperitoneal (in the abdomen)
SC – Subcutaneous (under the skin)

Table 3
Guanidine Hydrochloride – Toxicity Data

Test Type	Species	Route	Reported Dose/Effect	Year of Study
LD50	Mouse	Oral	571 mg/kg; muscle contraction, shortness of breath, irritability, altered sleep patterns	1993
LD50	Mouse	IP injection	500 mg/kg	unknown
LD50	Rat	Oral	475 mg/kg ; excitement, diarrhea, altered sleep	1986
LDLO	Rat	SC injection	404 mg/kg	1926
LDLO	Unspecified	Oral	300 mg/kg; muscle contraction, shortness of breath, convulsions	1931
LDLO	Guinea pig	SC injection	100 mg/kg	1935
LDLO	Guinea pig	IV injection	500 mg/kg	1928
LDLO	Guinea pig	IA injection	500 mg/kg	1928
LDLO	Dog	SC injection	200 mg/kg	1935
LD	Rabbit	Dermal	>2000 mg/kg; no deaths; severe skin irritation	1993
Draize	Rabbit	Ocular	Moderate eye irritation	1987
Buehler	Guinea Pig	Dermal	No skin sensitization	1984
Draize	Guinea Pig	Dermal	Severe skin irritation	1986

IP – intraperitoneal (in the abdomen)
SC – subcutaneous (under the skin)
IV – intravenous (in the vein)
IA – intraarterial (in the artery)

Table 4
Urea – Toxicity Data

Test Type	Species	Route	Reported Dose/Effect	Year of Study
LD50	Rat	SC	8200 mg/kg; altered sleep, changes in motor activity	1977
LD50	Rat	Oral	8471 mg/kg	1986
LD50	Rat	IV injection	5300 mg/kg; altered sleep, changes in motor activity	1977
LD50	Rat	Intratracheal	567 mg/kg; convulsions, shortness of breath, methemoglobinia, carboxyhemobinia	1986
LD50	Rat	IP injection	>5000 mg/kg	1967
LD50	Mouse	SC injection	9200 mg/kg; altered sleep, changes in motor activity	1977
LD50	Mouse	Oral	11,000 mg/kg	1977
LD50	Mouse	IV injection	4600 mg/kg; altered sleep, changes in motor activity	1977
LDLO	Dog	IV injection	3000 mg/kg	1935
LDLO	Dog	SC injection	3000 mg/kg	1935
LDLO	Goat/sheep	Oral	511 mg/kg; tetany, shortness of breath, changes in salivary glands	1948
LDLO	Frog	SC injection	600 mg/kg	1935
LDLO	Mouse	IP injection	6608 mg/kg; convulsions, coma	1936
LDLO	Pigeon	SC injection	14,800 mg/kg	1931
LDLO	Rabbit	IV injection	4800 mg/kg	1935
LDLO	Rabbit	Oral	10,000 mg/kg; degenerative brain changes, hemorrhage, changes in trachea/bronchi	1953
LDLO	Rabbit	SC injection	3000 mg/kg	1935
Draize	Human	Dermal	Mild irritation	Unknown

IP – intraperitoneal (in the abdomen)
SC – subcutaneous (under the skin)
IV – intravenous (in the vein)

Summary and Interpretation of Findings

A. Guanidine and guanidine hydrochloride

Based on the available toxicity data, guanidine and guanidine hydrochloride both fall into the category of toxic compounds, based on oral (ingestion) data. There is almost no data on guanidine, and minimal data for guanidine hydrochloride, but the test results for each compound are relatively consistent, and when the results for guanidine and guanidine hydrochloride are compared, they are also similar. For this reason, it is reasonable to consider that the toxicity of guanidine hydrochloride is similar to that of guanidine. There is no data based on inhalation exposure, which is the most common route of exposure in industry.

The existing toxicity data is based on animal studies, and there could be slightly different effects or dose relationships in humans.

In the laboratory or industrial setting we are primarily concerned about exposures from inhalation and skin contact, rather than ingestion, and it is important to anticipate what health effects might occur on exposure. There is limited health effects data available for guanidine hydrochloride; however, these effects likely extend to guanidine as well. Of course, guanidine should not be swallowed and inadvertent hand-to-mouth transfer should be avoided.

Guanidine hydrochloride is very irritating to the skin and eyes. Since guanidine hydrochloride is irritating to the skin and eyes, it is also likely to be irritating to the lungs if inhaled. In addition, its hygroscopic properties mean that it may cause desiccation, or severe drying, of the tissues of eye, skin, and lung on direct contact. Guanidine in aqueous solutions is likely to be highly alkaline, which means that the solutions could be corrosive, causing burning and scarring of tissue exposed to the liquid. Corrosives cause more severe injury than materials that are irritating, although one should not underestimate irritant effects, which can be quite serious and disabling.

There is limited evidence that guanidine is not absorbed to any significant degree through the skin in animals. However, the severe irritant effects of guanidine on the skin and eyes mean that exposures via the airborne and skin exposure routes must be minimized. This can best be achieved by limiting the transfer and delivery of guanidine to enclosed systems, or operations carried out under local exhaust ventilation. Personal protective equipment such as protective eyewear, respirators, and gloves may be necessary depending on the level of engineering control that can be achieved. More information on the planned work process would be needed to prescribe the exact respirator and gloves; for instance, are any carrier agents or other chemicals used in the process, will the material be handled dry, will aerosols be generated, etc.

Shortness of breath, gastrointestinal effects such as diarrhea, and increased muscle contractility were reported in test animals and might occur in humans as well. Shortness of breath might occur upon inhalation exposure due to irritant effects. Gastrointestinal effects would most likely be seen with ingestion.

It is unclear whether inhalation could produce a high enough dose for increased muscle contractility; this effect would most likely occur with ingestion. This is an effect which is desired when guanidine hydrochloride is used as a pharmaceutical agent, but could be dangerous to a normal person because of potential effects on the cardiac muscle. When used as medical treatment, the therapeutic dose of guanidine hydrochloride is from 10-15 mg/kg (5 to 7 mg/lb) of body weight per day, not to exceed a daily dose of 30 mg/kg. For a 150 pound this would be a daily dose ranging from 750 to 1050 mg. Drug literature indicates that individual tolerance is highly variable for this drug and side effects on the neurological, gastrointestinal, skin, renal, hepatic, and cardiac systems are common, with the gastrointestinal and neurological effects of nausea/ diarrhea and nervousness/mood changes/irritability being the most frequently observed. Fatal cases of bone-marrow suppression have been reported in patients who took high doses of the drug. It would be highly unlikely that an exposure to even the lower range of the therapeutic dose of guanidine would occur in industrial use, but these effects provide additional evidence that exposure should be minimized.

Limited evidence does not indicate that guanidine or guanidine hydrochloride have any mutagenic (damage to DNA) effects.

There have been no studies to determine whether guanidine and guanidine hydrochloride cause cancer. These two compounds are not listed or classified in any carcinogen categories as by the International Agency for Research on Cancer (IARC), the National Toxicology Program, or the American College of Governmental Industrial Hygienists.

There are no published studies on reproductive effects of guanidine or guanidine hydrochloride.

There are no occupational exposure limits for guanidine or guanidine compounds from the Occupational Safety and Health Administration, the American Conference of Governmental Industrial Hygienists, or the American Industrial Hygiene Association. An appropriate exposure limit to apply, by analogy, to control the respiratory and skin irritant properties of guanidine hydrochloride, would be an exposure limit similar to that of sodium hydroxide, another strong base. That exposure limit is 2 milligrams per cubic meter of air, as a ceiling concentration, averaged over a 15-minute period.

There are no public exposure limits for guanidine or guanidine compounds listed by the Environmental Protection Agency.

B. Urea

Urea falls into the category of non-toxic, based on the oral data. No studies of toxicity from inhalation exposure were found in the literature.

Urea is noted to cause slight irritation of the skin, lungs, and eyes; however, urea's irritant effects appear to be significantly less than that of guanidine.

Limited evidence indicates that urea may have some mutagenic (damage to DNA) effects. The significance of these findings and how they apply to occupational exposures is unclear.

There have been several studies to determine whether urea causes cancer. Urea is not listed or classified in any carcinogen categories by the International Agency for Research on Cancer (IARC), the National Toxicology Program, or the American College of Governmental Industrial Hygienists.

No studies have identified adverse reproductive effects from inhaled, ingested, or skin/eye exposures to urea in animals or humans.

There are no occupational exposure limits for urea compounds from the Occupational Safety and Health Administration, the American Conference of Governmental Industrial Hygienists. The American Industrial Hygiene Association has published a Workplace Environmental Exposure Level for urea of 10 milligrams urea per cubic meter of air, averaged over an 8-hour workday, which is based on irritant effects.

There are no public exposure limits for urea listed by the Environmental Protection Agency.

Conclusions and Recommendations

Based on the published data, guanidine should be considered a toxic compound by oral ingestion. No data is available for inhalation exposures. It is also a significant irritant to the eyes, skin, and lungs; has desiccant effects by virtue of being hygroscopic; and in solution the pH may approach corrosivity, depending on the concentration. Guanidine does not appear to be absorbed through the skin.

There are no published studies detailing the effects of guanidine on humans; the only information on human exposure comes from the pharmaceutical industry, where guanidine hydrochloride is used as an orally administered drug. That data indicates that guanidine has significant effects on the gastrointestinal and nervous system as well as the desired therapeutic effect on the neuromuscular systems in persons with a rare disease, the Eaton-Lambert myasthenic

syndrome. This effect on the neuromuscular system could be harmful in normal persons. The doses of guanidine hydrochloride used in medical treatment are much higher than would be expected from occupational exposure, and are oral doses as opposed to the inhalation doses expected in industry. However, caution is still warranted due to the potential severity of these effects. Controlling exposures to prevent irritant effects will keep doses low enough to minimize any concerns about these effects.

Because of its irritant properties, exposure to the skin, lungs, and eyes must be prevented. This can best be accomplished by the use of engineering controls such as enclosed systems and local exhaust ventilation to minimize dust generation. Personal protective equipment should be utilized if engineering controls cannot control exposures. Gloves should be worn to prevent skin contact when handling guanidine; no gloves have been tested for resistance to guanidine or guanidine hydrochloride, but nitrile gloves resist corrosives such as sodium hydroxide and should be a reasonable choice if no other chemicals are used in the process. If other chemicals are also used, a manufacturer's glove chart should be consulted, or you may contact the author for assistance.

Based on the published data, urea should be considered relatively non-toxic. It may be slightly irritating to the eyes, skin, and lungs. Controlling exposures for the harmful effects of guanidine should also control for any harmful effects of urea.

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