ENVIRONMENTAL HEALTH AND SAFETY
University of Nebraska-Lincoln

Safe Operating Procedure

(Revised 11/22)

HEALTH HAZARDS HAZARD ASSESSMENT & RISK MINIMIZATION

Background

The Globally Harmonized System (GHS) of classification and labeling of chemicals recognizes the following classifications of chemicals posing a health hazard.

- ***Acute toxicity*** *refers to those effects following oral or dermal administration of a single dose of a substance or multiple doses given within 24 hours, or an inhalation exposure of 4 hours.*
- ***Skin corrosion/irritation****. Corrosion is the production of irreversible damage to the skin and chemicals assigned to this classification are addressed in the EHS SOP,* ***Corrosive Chemical Hazards & Risk Minimization****. Irritation is the production of reversible damage to the skin. The same general precautions for working with skin corrosives should be followed when working with skin irritants as described in the referenced SOP.*
- ***Serious eye damage/eye irritation*** *is the production of tissue damage or serious physical decay of vision following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application. Effects of contact with eye irritants are fully reversible with 21 days.* Refer to the *EHS SOP,* ***Corrosive Chemical Hazards & Risk Minimization****.*
- ***Respiratory or skin sensitization*** *is described as hypersensitivity of the airways or allergic responses of the skin following inhalation/contact with a chemical substance.*
- ***Germ cell mutagenicity*** *is described as mutations to germ cells of humans that can be transmitted to progeny after contact with a chemical.*
- ***Carcinogenicity*** *is induction of cancer or its increased incidence after contact with a chemical or mixture.*
- ***Reproductive toxicity*** *chemical hazards affect sexual function and fertility and/or development of a fetus from conception through birth.*
- ***Specific target organ toxicity - single exposure/repeated exposure*** *are non-lethal, but reversible or irreversible damage to specific organs after contact with a chemical.*
- ***Aspiration*** *chemical hazards damage the respiratory system after entry into the body directly through the oral or nasal cavity, or indirectly through vomiting.*

Each of the above chemical health hazard classifications have one or more categories and are identified with various pictograms, warning words, and hazard statements as summarized in the tables below.

Acute Toxicity					
Exposure Route		**Pictogram**	**Toxicity Range by Category (LD50)**	**Code**	**Hazard Statement**
Oral (mg/kg body weight)			Category 1: LD50 ≤ 5	H300	Fatal if swallowed
			Category 2: LD50 >5 and ≤ 50	H300	Fatal if swallowed
			Category 3: LD50 >50 and ≤ 300	H301	Toxic if swallowed
			Category 4: LD50 >300 and ≤ 2000	H302	Harmful if swallowed
Dermal (mg/kg body weight)			Category 1: LD50 ≤ 5	H310	Fatal in contact with skin
			Category 2: >50 and ≤ 200	H310	Fatal in contact with skin
			Category 3: >200 and ≤ 1000	H311	Toxic in contact with skin
			Category 4: >1000 and ≤ 2000	H312	Harmful in contact with skin
Inhalation	**Gases (ppmV)**		Category 1: LC50 ≤ 100	H330	Fatal if inhaled
			Category 2: LC50 >100n and ≤ 500	H330	Fatal if inhaled
			Category 3: LC50 >500 and ≤ 2500	H331	Toxic if inhaled
			Category 4: LC50 >2500 and ≤ 20000	H332	Harmful if inhaled
	Vapors (mg/l)		Category 1: LC50 ≤ 0.5	H330	Fatal if inhaled
			Category 2: LC50 >0.5 and ≤ 2.0	H330	Fatal if inhaled
			Category 3: LC50 >2.0 and ≤ 10.0	H331	Toxic if inhaled
			Category 4: LC50 >10.0 and ≤ 20.0	H332	Harmful if inhaled
	Dust/mist (mg/l)		Category 1: LC50 ≤ 0.05	H330	Fatal if inhaled
			Category 2: LC50 >0.05 ≤ 0.5	H330	Fatal if inhaled
			Category 3: LC50 >0.5 and ≤ 1.0	H331	Toxic if inhaled
			Category 4: LC50 >1.0 and ≤ 5.0	H332	Harmful if inhaled

Pictogram	Category	Code	Hazard Statement
Serious eye or skin damage or irritation			
	Skin (Subcat. 1A, 1B, 1C) Eye (Cat 1)	H317	Causes severe skin burns and eye damage
	Skin (Cat. 2) Eye (Subcat. 2A)	H318	Causes skin/eye irritation
Respiratory Sensitization			
	1 (Subcat. 1A, 1B)	H334	May cause allergy or asthma symptoms or breathing difficulty if inhaled
Skin Sensitization			
	1 (Subcat. 1A, 1B)	H317	May cause an allergic skin reaction
Germ Cell Mutagenicity			
	1A	H340	May cause genetic defects
	1B	H340	May cause genetic defects
	2	H341	Suspected of causing genetic defects
Carcinogenicity			
	1A	H350	May cause cancer
	1B	H350	May cause cancer
	2	H351	Suspected of causing cancer
Toxic to Reproduction			
	1A	H360	May damage fertility or the unborn child
	1B	H360	May damage fertility or the unborn child
	2	H361	Suspected of damaging fertility or the unborn child
None	None	H362	May cause harm to breast-fed children
Specific Target Organ Toxicity (Single Exposure)			
	1	H370	Causes damage to organs
	2	H371	May cause damage to organs
	3	None	May cause respiratory irritation May cause drowsiness or dizziness
Specific Target Organ Toxicity (Repeated Exposure)			
	1	H372	Causes damage to organs through prolonged or repeated exposures

	2	H373	May cause damage to organs through prolonged or repeated exposures
Aspiration Hazard			
	1	H304	May be fatal if swallowed and enters airways

Routes of Exposure

A chemical substance or mixture will harm health only if there is exposure to it. There are four possible routes of exposure:

- Inhalation
- Ingestion
- Absorption
- Injection

Of these, inhalation tends to pose the greatest risk. Relative to skin (absorption) and the digestive system (ingestion), the respiratory system has the largest exposed surface area at 70 to 100 square meters, most of which consists of the lungs. In comparison, the digestive system has an exposed surface area of 10 square meters; the skin 2 square meters. Also, the respiratory system is designed to absorb oxygen and release carbon dioxide. This exchange occurs in the alveoli (primary gas exchange unit of the lungs), which are fragile and moist. This is a perfect environment in which chemicals can dissolve and either be absorbed by the body or directly damage the lungs.

Like the respiratory system, the digestive tract is also designed to absorb certain chemicals (e.g., food, water) while excreting wastes. Inadvertent ingestion occurs in one of two ways. Either the chemical is caught in or dissolves in nasal or throat mucus and is swallowed, or chemicals contaminate the hands, cups or eating utensils, food, etc. and are swallowed while drinking and eating. Like the respiratory system, the digestive system is moist which can aid absorption. In addition, digestion in the stomach involves acids, which can draw metals and other chemicals into solution where they can be absorbed by the body.

The skin, by design, is a protective barrier to many chemicals. Generally speaking, solids, gases, chemical salts in solution and other polar (i.e., water miscible) chemicals find it difficult to pass the protein layer of the epidermis (surface layer of skin) and the fatty tissues of the dermis (underlayer of skin). In contrast, some chemicals readily pass both the epidermis and the dermis and can be transported throughout the body by the circulatory system. Some chemicals, like dimethyl sulfoxide, while not very toxic in and of themselves are capable of significantly aiding other chemicals that are toxic across the barrier posed by skin.

Injection as a route of exposure involves penetration of the skin. Most often this is through a puncture or cut with a contaminated object, but it can also occur with high-pressure contact (e.g., spraying of fluid from a ruptured high-pressure hydraulic line). As with absorption, exposure by injection can lead to

local or systemic effects.

Physical State

With regard to the routes of exposure, the state of the chemical is also important. Chemical gases and vapors generally pose the most risk by inhalation. Levels of gases and vapors that pose a threat by absorption are generally already lethal by inhalation.

Liquids generally pose the greatest risk by absorption though they can pose a threat by ingestion. With chemical solids, the form of the solid is important. Granules, chips, and other relatively large particles do not readily become airborne and so are not likely to be inhaled, nor do they readily stick to other surfaces such as the hands to be ingested. However, dusts can become airborne and easily inhaled and/or ingested. Due to static and other attractive forces, they are more likely to stay on surfaces such as the hands.

Elimination After Exposure

Related to exposure are the body's mechanisms to deal with it. This is done through transformation (i.e., changes the body makes to a chemical) and elimination. Transformation is not necessarily needed for elimination. For most chemicals that are transformed, the purpose is to make those chemicals less toxic and more polar (i.e., more able to dissolve in water) in order for the body to eliminate them. Chemicals that are already polar are eliminated from the body fairly rapidly. While transformation usually makes the chemical less toxic, it can also make it more toxic. For example, methanol is moderately toxic to the body but its transformation by the body into formaldehyde is what makes it dangerous.

Elimination can occur by:

- Exhalation. This is limited to volatile chemicals and transformation products that are transferred from the circulatory system to the respiratory system and expelled from the body during exhalation. An example is the consumption of alcohol. The test administered by law enforcement measures the alcohol in exhaled breath to determine sobriety.
- The excretory system as urine. This is a primary excretion mechanism since the kidneys filter chemicals from the blood. Depending on the chemical, the kidneys can react by 'flushing' greater volumes of water from the body in order to eliminate chemicals recognized as toxic. This is why both caffeine and alcohol are described as diuretic (i.e., increasing the rate of urination).
- The digestive system in feces. This appears to be most closely related to transformation products, though it can include chemicals that are not absorbed but are dangerous to the lining of the digestive system.
- Through the skin. Elimination of chemicals though the skin plays a limited role and is confined generally to volatile chemicals and transformation products as well as some salts.

Acute Toxicity, Inhalation, Oral & Dermal

For chemicals that are acutely toxic, the rates of exposure and elimination determine whether an acutely toxic exposure occurs. For example, carbon monoxide is a Category 3 acute toxin by inhalation. Brief exposure to it at concentrations of 500 ppm (similar to being in the smoke of a camp fire) will cause no symptoms. However, once exposed, it may take as long as 5 hours for carbon monoxide to be completely eliminated from the body. Thus, repeated exposures within that 5 hour window will increase the amount of carbon monoxide in the body and eventually result in headaches and dizziness. Severe exposures (>10,000 ppm) can cause death in seconds.

Each chemical has its own rate of transformation/elimination by the body. Exposures that remain below the transformation/elimination rate will not give rise to acutely toxic exposures.

As noted, polar chemicals and chemicals the body can make more polar are more readily eliminated by the body. Some, mostly man-made, chemicals are very nonpolar and resistant to transformation. Some of these chemicals are fat soluble and, in effect, can undergo absorption into fatty tissue where they can remain for years. Polychlorinated biphenyls (PCBs) are an example.

The most common way acute toxicity is measured is Lethal Concentration (LC) and Lethal Dose (LD). In other words, concentrations and doses that will cause death in test animals. Concentrations, measured in parts per million (ppm), mg/l and mg/m^3, are used for gases, vapors, and dusts and are administered by placing test animals in chambers with the chemical for a specified length of time; typically four hours. Doses, measured in milligrams of chemical per kilogram of the test animal body weight, are used for solids and liquids and, most commonly, are administered orally or applied to the skin. An exposure that results in lethality for 50% of the test animals is called the Lethal Concentration or Dose - Fifty or LC_{50} and LD_{50}. Data on toxicity is generated based on the expected routes of exposure.

A serious limitation to acute toxicity is that it only addresses relatively brief, one time exposures and only toxicity. LC_{50} and LD_{50} do not address long term (chronic) exposures/effects or other health hazards such as carcinogenicity, mutagenicity, sensitization, etc.

Respiratory or Skin Sensitization

As described in the definition, sensitizers act similarly to allergens. Like allergens, not all people will react to a sensitizer the same way. Some people will not readily develop sensitivity while others may develop severe allergic reactions. Also, like allergens, people who are sensitized to a chemical will react to exposures not normally considered acute. This is called hypersensitivity. Respiratory sensitivity is generally characterized by asthma-like symptoms (e.g., difficulty breathing, running nose, watering eyes). Skin sensitization is usually characterized by rashes and swelling. The first encounter with a sensitizer does not evoke an allergic reaction. However, each subsequent exposure leads to more severe bodily reactions.

Germ Cell Mutagenicity

Germ cells are male (sperm) and female (egg) cells that are necessary for reproduction. Within each is genetic code in the form of deoxyribonucleic acid (DNA). The code directs the development of the fetus. Mutagens act by entering germ cells and changing this code. This is called a mutation. Offspring produced by the altered code will carry this mutation and pass it along to their offspring. In other words, the mutation is inheritable.

Carcinogenicity

Cancer is a disease where cells reproduce in an uncontrolled manner. In doing so, the cancerous cells destroy the organ where they are located or invade other parts of the body and grow there. This is called metastasizing. The direct cause of cancer is genetic code in a cell(s) that is damaged in such a way that the body is unable to shut off the cell reproducing itself.

Reproductive Toxicity

Reproductive toxins are chemicals that have adverse effects on sexual function and fertility and/or development of offspring. With regard to offspring, what makes these chemicals different from mutagens is that the effects are not inheritable. A word related to this class of chemicals and sometimes encountered in Safety Data Sheets (SDS) is 'teratogen.' Teratogens are chemicals known to cause adverse effects on a developing fetus.

Specific Targe Organ Toxicity Single/Repeated Exposure

Chemicals with specific organ toxicity have adverse effects on the body at relatively low doses, which makes them similar to chemicals classified as acutely toxic under the GHS system. However, when a chemical is listed under the specific target organ toxicity classification, the specific organs affected and the route of exposure is identified. For example, asbestos dust is classified as a chemical with specific target organ toxicity. When inhaled, asbestos particles can permanently lodge in the lungs and cause cancer or other pulmonary diseases. Hydrofluoric acid is another example; when absorbed through the skin it can cause bones to decalcify.

Aspiration Hazard

Aspiration hazards pertain to liquids and solids that are inhaled into the respiratory system directly or that are vomited and then inhaled. Induced vomiting is not recommended as a first aid measure for chemicals that are an aspiration hazard. Damage caused by aspiration into the respiratory system while vomiting is expected to be more severe than the damage caused by initial ingestion, or other safer treatment options might be available such as stomach pumping, ingestion of activated charcoal to absorb the substance, or use of other substances to block the first substances.

Occupational Exposure Limits

Several national organizations establish numerical occupational exposure limits for various chemicals.

- The American Counsel of Governmental Industrial Hygienists (ACGIH) publishes inhalation exposure limits as Threshold Limit Values (TLVs).
- The National Institute of Occupational Safety and Health (NIOSH) publishes inhalation exposure limits as Recommended Exposure Limits (RELs).
- The Occupational Safety and Health Administration (OSHA) publishes inhalation exposure limits as Permissible Exposure Limits (PELs).

All three types of limits, TLVs, RELs, and PELs, can be expressed in one of three ways. These are:

- An 8-hour Time-Weighted Average (TWA), which is an expression of the level of exposure when averaged over a typical 8-hour workday. The level of exposure can vary greatly during any given period of the day.
- A Short-Term Exposure Limit (STEL), which is an expression of the maximum amount of exposure that can occur during a short period of time (e.g., 15 minutes) regardless of the exposure when calculated as an 8-hour TWA.
- A Ceiling Limit (C), which is the maximum amount of exposure that can occur for any period of time regardless of how short the duration.

In addition to this, NIOSH has also created an IDLH (Immediately Dangerous to Life and Health), which represents the concentration of a substance that may be fatal even during extremely brief exposure.

These values may be different depending on the agency and some agencies do not have values for a particular substance or exposure while other agencies do. What is important is these limits consider all aspects of the hazards posed by a substance. Chemicals that have acute toxicity and carcinogenic effects will have lower exposure limits than chemicals that have only acutely toxicity effects.

Limitations of the GHS and Other Hazard Data

Most of the data used to determine the GHS classes and categories as well as exposure limits were based on animal studies. Rabbits, mice, rats, and guinea pigs are the most common animals used. However, animals are not people. They can be more or less sensitive to an exposure than is exhibited by people. Where human data is available, often due to accidents, it lacks the rigorousness of sound science.

Another limitation of occupational exposure limits is that data is often based on a population characterized as young, healthy men. Children, the aged, the sick, and in some cases women are more susceptible to hazardous substances. Thus, while the classes and categories and exposure limits are useful, exposures to health hazards should be kept to a minimum for all chemicals with extra care for those with known hazards.

Substances and Mixtures without Health Hazard Data

Manufacturers/distributors are required to provide Safety Data Sheets (SDSs) for all hazardous substances that they market, but they are not required to generate new data when data is lacking. Many of the substances and mixtures on the market today have not been fully characterized, particularly with respect to their health hazards. In these cases, evaluate the substance based on its parent compound, or to chemically related compounds, or by the purpose for which the compound was made.

In addition, SDS information does not account for particular end uses. Hazards can change dramatically with changes to state, mixtures, concentrations, etc. For example, cleaning baths prepared by mixing ethanol and potassium hydroxide are, by design, much more aggressive to human tissue than either chemical on its own. Thus, not only must the warnings provided in the SDS and GHS labeling be considered, but also any other changes to the substance during use.

Mitigating the Risks of Health Hazards

A written, comprehensive project-specific risk assessment with additional oversight is required for any experiment involving chemicals classed as "Acute Toxicity - Category 1." See the companion EHS SOP, ***Chemical Hazard Assessment and Risk Minimization***. A specific risk assessment with additional oversight may also be required for chemicals posing other health hazards depending on the specific experiment or protocol, as described in the companion EHS SOP referenced above. General risk mitigation measures for chemicals posing a health hazard are as follows:

- Conduct a thorough literature search, including review of Safety Data Sheets for those chemicals to be handled to establish a thorough understanding of the routes of exposure, exposure limits, signs and symptoms of exposure, specific health hazards, and recommended control measures. As appropriate also review the following EHS resources:
    - EHS SOPs, ***Acrylamide*** and ***Gases Under Pressure Hazards & Risk Minimization***.
    - EHS Laboratory Safety Colloquium archive presentations titled ***Safe Handling: Highly Toxic Chemicals, Reproductive Toxins (Mutagens & Teratogens) and Biologically-derived Toxins*** and ***Flammable-Corrosive-Toxic Gas Safety***.
- Follow general safe chemical handling practices as described in the EHS SOP, ***General Guidance for Chemical Ordering, Receipt, Distribution, Use and Storage***.
- Use less toxic/hazardous substitutes where possible.
- Wear the appropriate Personal Protective Equipment. See EHS SOP, ***Personal Protective Equipment for Chemical Exposures***. At a minimum, this will consist of standard laboratory/work attire (closed-toed shoes and long pants), laboratory coats (or other outer protective garment), gloves (constructed of a material resistant to the chemical(s) of concern), and eye protection.
- Plan for and implement measures designed to eliminate to the extent practicable susceptible routes of exposure:
    - Inhalation
        - Use chemical fume hoods when at all possible. For extremely toxic materials, a glove box may be necessary. As described above, inhalation is generally the

most serious route of exposure. Conducting operations in a fume hood or glove box will result in the capture of gases, vapors, and dusts and prevent them from reaching the breathing zone. Proper and effective use of fume hoods and glove boxes is discussed in the EHS SOP, ***Laboratory Hood/Cabinet Identification and Use***. See also the Laboratory Safety Colloquium archive presentation titled ***Exposure Control – Ventilated Hoods, Cabinets, & More.*** Consult EHS if local exhaust ventilation is not possible to evaluate the need for a respirator and enrollment in the UNL Respiratory Protection Program.

        - Keep containers closed when not in use to limit vapor generation.
        - Transfer volatile liquids in a manner that limits splashing and mixing with the air.
        - Transfer solids, especially powders using spatulas and spoons instead of pouring them directly from a container. This will reduce the generation of dusts. Use wet/damp cleaning methods for solids/dusts- do not dry sweep.
    - Absorption
        - Remove PPE before leaving the work area. Learn how to remove the gloves without touching the outside of them with bare fingers, using the rolling technique.
        - Practice good personal hygiene. Wash hands (or exposed skin) after known or suspected chemical contact, after removing PPE, and before leaving the work area.

    - Ingestion
        - Practice strict contamination control. Keep the workspace clean. This includes the floor. Chemicals on the floor can be tracked to office and eating spaces where they can contaminate the hands or other surfaces.
        - Do not eat, drink, chew gum, apply cosmetics, or store such materials in chemical use areas.
    - Injection
        - To the extent feasible, eliminate the use of sharp objects and breakable glass apparatus.
        - If it is necessary to use a sharp object, use remote handling devices such as forceps.
        - When there is risk of cuts or sticks, use cut/puncture-resistant gloves.
        - Properly containerize used sharps (labeled, hard-sided container that is puncture/cut resistant, and which can be securely closed when full)
- Observe all specific safety procedures established for the laboratory/procedure.
- Use chemicals on the smallest scale and concentration feasible.
- Use heightened security measures for particularly toxic materials to reduce potential for theft or illicit use.
- If using vacuum pumps with toxic/hazardous materials, ensure that exhaust is vented outside of the work space.
- If pregnant or planning to conceive, consult your supervisor and physician prior to working with known teratogens or mutagens.

- Restrict use of reproductive toxins and highly toxic chemicals to designated work areas and ensure that all persons who frequent the area or work with such chemicals are aware of the location and hazards. Special precautions should be observed when administering reproductive toxins or acutely toxic materials to animals, and should be detailed in the research protocol. Establish and adhere to effective decontamination/cleaning protocols. Clean designated work locations upon known contamination and at the end of each workday. It may be advisable to work in containment trays or cover workbenches with absorbent paper to facilitate cleaning. Clean equipment in accordance with manufacturer's recommendations.
- Seek medical consultation for exposures that likely approach or exceed any established occupational limits or result in signs or symptoms of exposure. See EHS SOP, ***On-the-Job Injuries***.
- To the extent feasible, minimize the amount of material handled and stored. Consult EHS for an industrial hygiene/exposure assessment if handling toxicologically significant quantities at any given time. In some cases, medical surveillance may be recommended.
- Containerize waste solutions/solids, spill residues and related clean-up materials, and grossly contaminated disposable items for pickup by EHS.