

# Working with Urethane

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## Background

Urethane is used alone or in combination with other drugs to produce anesthesia in laboratory animals. One of the key advantages in utilizing urethane is that it provides an extended period of anesthesia with minimal physiological changes. The long lasting and stable anesthesia induced by intravenous administration of urethane produces minimal related cardiovascular and respiratory depression. Another positive characteristic of urethane is that it produces a much deeper degree of analgesia than many other anesthetics. These qualities make urethane an ideal anesthetic for surgical procedures performed on small rodents and rabbits (University of California Irvine, 2003). The use of urethane anesthesia for survival studies, clinical veterinary medicine, and other applications is limited; however, due to adverse post-operative health effects observed in animals and suspected health risks to humans. Urethane has been classified as a mutagen (Lewis, 2004) and as a group 2B carcinogen by the International Agency for Research on Cancer (IARC). It is readily absorbed through the skin, targets multiple organs, suppresses bone marrow, readily crosses the placenta, induces fetal tumor formation (*in utero*), and initiates preneoplastic changes in the skin (Field and Lang 1988). These potentially severe side effects make urethane exposure a significant health threat to laboratory staff, animal handlers and other personnel who may be accidentally exposed. Due to this threat, the [Institutional Biosafety Committee](#) (IBC) has classified urethane as a [reportable hazardous chemical](#) that, when utilized, must be reported on all [Institutional Animal Care and Use Committee](#) IACUC protocols when used *in vivo*.

## Purpose

The purpose of this page is to provide the research community sufficient information regarding specific health threats/exposure routes, implementation of proper work methods, and provision of suitable personal protective equipment for development of research protocols that include measures for effectively reducing risk of occupational exposure to urethane.

## Occupational Exposure Hazards

The primary occupational routes of exposure for urethane include absorption, adsorption, inhalation, ingestion, and accidental injection (Field and Lang 1988). Available scientific literature indicates the following potential consequences related to acute and/or chronic occupational exposure to urethane:

- 1. Cytotoxic Effects:** Studies have shown that urethane at a dosage of 1mg (??)/Kg IP will arrest cell division; thereby exhibiting cytotoxicity to dividing cells (Bastrup-Madien, 1949). Studies have shown that mice are more susceptible to infections following urethane administration (Field and Lang, 1988). This tendency is believed to

attributable to bone marrow suppression (Field and Lang, 1988). Neutropenia, lymphocytopenia, thrombocytopenia, and anemia have developed in cats and humans (Haddow and Sexton, 1946; Paterson et al., 1946); thrombocytopenia, leucopenia, acute-onset anemia, and intestinal hemorrhage have been observed in dogs after exposure to urethane (Cruz and Mousstache, 1948; Moeschlin and Bodner, 1951). Thrombocytopenia purpura of the small/large intestine, skin, heart, lung, renal cortex, omentum, and stomach has also been documented in dogs following urethane exposure (Cruz and Mousstache, 1948). Many of the above-listed health effects have been shown to be reversible; the time period from suppression to recovery is generally proportional to the total dosage of urethane administered. Scientific publications involving the health effects of human exposure to urethane are limited. The available literature; however, does identify hepatic necrosis, sedation, nausea, vomiting, irreversible aplastic anemia, lymph node fibrosis, and fatal pneumonia as adverse consequences exhibited by humans following urethane exposure (Hirschbaeck et al., 1948; Hoover, 1970; Bottner, 1949; Letterer, 1949).

**2. Carcinogenic/Mutagenic Effects:** Urethane is a known animal carcinogen and should be managed as a potential human carcinogen (Class 2B) (IARC; Field and Lang, 1988). Studies with mice have indicated that neonatal mice are more sensitive to the carcinogenic properties of urethane and have developed tumors at a higher rate than older mice. Research indicates the time required for newborn mice to catabolize 50% of urethane decreases steadily during the first 20 days of life, with rate of elimination conversely increasing during the same period (Mirvish, 1968). The slower metabolism of urethane in newborn mice may partially explain their greater sensitivity to urethane carcinogenesis. Studies have shown that pulmonary adenomas are the primary types of tumors formed in mice and rats (Henshaw and Myer, 1944; Kay and Trainin, 1966) in mice and rats (Henshaw and Myer, 1944; Kay and Trainin, 1966; Jaffe, 1947; Tannenbaum et al., 1962) with developments of thymic lymphomas also common in mice following urethane exposure (Doell and Carnes, 1962).

**3. Transplacental Effects:** Research studies involving mice have indicated serious and startling results following transplacental exposure of fetuses. The primary reported adverse post-exposure effect is the formation of pulmonary adenomas in fetuses (Klien, 1954). Research studies have indicated that exposure of pregnant mice to urethane during late gestation results in increased incidence of hepatomas, ovarian tumors, and harderian gland cystadenomas (Vesselinovitch et al., 1971).

### **Safe Work Practices**

The list of potential urethane-related health hazards identified above makes it imperative that PIs conduct thorough risk assessments and prepare protocols which include standard operating procedures (SOPs) identifying appropriate administrative controls, personal protective equipment (PPE), work methods, engineering controls, and waste disposal procedures for eliminating or sufficiently reducing exposure potential to all staff involved in the affected research.

## **1. Administrative Controls**

- a. Management considerations for urethane and other potentially hazardous chemicals must be included in the laboratory [Chemical Hygiene Plan](#).
- b. Protocols involving urethane use *in vivo* must include completion of [reportable hazardous chemical](#) form and approval through the [Institutional Animal Care and Use Committee](#).
- c. Principal investigators will develop and implement SOPs by which laboratory staff will prepare/administer urethane with minimal potential for occupational exposure.
- d. All tasks having potential for occupational urethane exposure (mixing of doses, dose preparation, administering of injections, etc.) will be conducted by competent staff who have received appropriate training (OSHA: “Worker Right-to-Know”) regarding specific urethane-related health and safety risks, SOPs, and procedures to be followed in event of an exposure incident.
- e. All staff engaging in processes identified above are also required to complete applicable modules of the [VCU Laboratory Safety Training Modules](#).
- f. Pregnant females should not handle urethane due its fetotoxic potential.

## **2. Engineering Controls**

- a. In cases where the recommended level of PPE does not provide sufficient protection (e.g., splash potential or aerosolization potential) tasks should be conducted within a chemical fume hood utilizing sash for added protection.
- b. Syringes used for urethane injection should be safety engineered (self-sheathing syringes, luer-lock syringes, etc.).

**3. Personal Protective Equipment:** Staff involved with any tasks where potential for urethane exposure exists must don the following PPE:

- a. Examination gloves.
- b. Safety glasses or safety goggles (ANSI Z-87 approved).
- c. Lab coat.
- d. Appropriate laboratory attire.
- e. If aerosol exposure threat exists, suitable respiratory protection must be provided. Prior to instituting respiratory protection to personnel, the laboratory must participate in the university [Respiratory Protection Program](#).

#### **4. Work Methods**

a. Whenever feasible, procedures with the potential for producing urethane aerosols (such as the mixing of solutions from the powder form) should be conducted with a certified fume hood.

b. Needles used for urethane injection will be disposed of in approved containers and should never be bent, sheared, or recapped. If recapping is absolutely necessary, a "[Needle Recapping Waiver](#)" must be submitted for IBC review/approval prior to proceeding.

c. Areas where urethane is prepared and/or administered should be cleaned immediately following each task completion utilizing a detergent/water solution.

#### **5. Waste Disposal**

a. Surplus urethane must be disposed of as a hazardous chemical through the OEHS [Chemical Waste Management Program](#).

b. Very little scientific information has been published regarding the metabolism and resulting metabolic products of urethane. According to one study, urethane is metabolized to ammonia, carbon dioxide, and ethyl alcohol (Bryan et al., 1957). Most of the carbon associated with urethane is eliminated through exhalation as carbon dioxide (90%) with another 5-10% eliminated in urine as ammonia and other carbon compounds (Bryan et al., 1957). Additional research indicates that during the metabolic process, urethane breaks down to urea and water within hours of dosing, leading to urine, feces, and bedding waste which does not have hazardous characteristics (MIT, 2005). Based upon the limited available information, it is acceptable to dispose of bedding materials generated following administration of urethane anesthesia under normal procedures and circumstances as non-hazardous waste, provided that other chemical or biological hazards are not suspected or known to be present within the bedding. Carcasses anesthetized or otherwise suspected to be contaminated with urethane must be disposed of through DAR as regulated medical waste (RMW).

c. All contaminated sharps waste materials must be placed in proper sharps container and disposed of as RMW.

**6. Spills:** Small spills of urethane should be cleaned with absorbent paper and soap and water. Don appropriate PPE during clean-up, dispose of all waste generated through OEHS. For larger spills of urethane contact the OEHS emergency line (828-9834) for assistance.

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