Existing Chemicals Information Sheet

UREA

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Chemical Abstract Service (CAS) Number: 57-13-6

General

Urea is a colourless to white crystalline powder with many industrial uses and is present in domestic products.

Background

In 2002 the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) published a list of High Volume Industrial Chemicals (HVIC) that are manufactured in and/or imported into Australia in volumes of 1000 tonnes/year or greater based on information supplied by industry. To address the increasing public demand for concise and easily accessible information on chemicals, NICNAS has undertaken a program to provide information, in the most suitable format, on those chemicals on the HVIC list deemed appropriate (e.g. excluding mixtures) for which a full independent hazard assessment has not been conducted by NICNAS. Urea is identified as one such chemical on the HVIC list.

A literature search by NICNAS indicated urea had been reviewed in international review programs. Thus, an information sheet was considered the most suitable format to report data on the human health effects of urea. The data presented here are from secondary sources and though creditable publications, original publications have not been obtained and it has therefore not been possible to determine the robustness of the reported studies.

Data Sources

Data were obtained from the following sources:

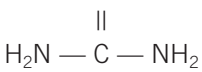
1. OECD (Organisation for Economic Co-operation and Development) (1996) Screening Information Data Set (SIDS) Initial Assessment,
2. IPCS (International Programme on Chemical Safety) (1997) International Chemical Safety Card.

Identity and Physico-Chemical Properties

Information on identity and physical properties was obtained from the OECD SIDS Initial Assessment Report (SIAR) (1996) and the International Chemical Safety Card (1997). Urea is a colourless to white, almost odourless crystalline powder. It has a melting point of 133ºC and a boiling point of 135ºC. It is soluble in water, reacts violently with strong oxidants, nitrates, inorganic chlorides, chlorites and perchlorates causing fire and explosion, and decomposes on heating producing toxic gases.

There are a large number of synonyms for urea available in the literature. Those most frequently cited are provided in Table 1.

Table 1 **Synonyms of Urea**

	Urea
Synonyms	Benural 70B-I-K Carbamide Carbamimidic acid Carbonyl diamide Isourea Nimin Pseudourea UR Urea perhydrate Ureaphil Ureophil Urepearl Urevert Varioform II
Structural Formula	

Import, Manufacture and Use

From HVIC List data, urea is introduced into Australia in large volumes, between 100 000 to 999 999 tonnes per year. However it could conceivably be more than this if urea use in fertilizers (excluded from the HVIC list) is also considered.

Locally urea is used in the chemical industry to synthesise other chemicals; in civil and mechanical engineering applications; in refining and processing of metals; in the pulp and paper industry; textile processing; cleaning/washing agents; colouring agents; explosives and solvents. These uses encompass domestic consumer products such as adhesives, sealers, resins, paints, fragrances, liquid soaps, detergents, cosmetic creams, shampoos, hair conditioners and hair dyes.

Uses listed in the SIDS report in addition to those described above are for flavouring and dehydrating agents, manufacture of some medicines, as a de-icing agent for use on airport runways, household cleaning products.

Other Sources of Urea

Urea is a product of the breakdown of proteins in mammals and therefore occurs in significant concentrations in the blood. It is the main component of mammalian urine. It also enters the human food chain through animal meats and some plants such as oats, grains and possibly other vegetables such as potatoes.

Current Regulatory Status in Australia
Urea is **NOT** listed in:

- the National Occupational Health and Safety Commission (NOHSC) (1995) *Exposure Standards for Atmospheric Contaminants in the Occupational Environment,*
- the NOHSC (1999) *List of Designated Hazardous Substances*
- the National Drugs and Poisons Schedule Committee (May 2003) *Standard for the Uniform Scheduling of Drugs and Poisons*
- the FORS (1998) *Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG Code),* 6th edition

It is the responsibility of manufacturers and importers who supply urea for use at work to determine whether it is a hazardous substance in accordance with the National Occupational Health and Safety Commission's *Approved Criteria for Classifying Hazardous Substances (1999).* If hazardous, the manufacturer or importer has a responsibility to classify and label the substance appropriately.

Data Sources for Human Health Effects
Information on urea was sourced primarily from the OECD SIAR (1996).

The SIDS program is a voluntary cooperative international testing program that began in 1989, operating under the auspices of the chemicals program within the Environment Health and Safety Division of the OECD. The program focuses on developing base level test information on approximately 600 poorly characterised international High Production Volume (HPV) chemicals. Data are used to "screen" the chemicals and set priorities for further testing or risk assessment/management activities. The OECD list of HPV chemicals serves as the overall priority list from which chemicals are selected for the SIDS program. These HPV chemicals include all chemicals reported to be produced or imported at levels greater than 1000 tonnes per year in at least one Member country or in the European Union region, and are compiled by the OECD Secretariat on the basis of regular submissions by Member states.

Health and Safety Information
Urea has been shown to cross the placenta following subcutaneous injection and to be taken up by the foetus in rats. The SIDS report contained no other data on absorption in animals. Urea is rapidly absorbed through human skin. Because of its high water solubility, urea is rapidly absorbed after human oral dosing and is quickly distributed throughout the body. Peak blood levels are achieved after 30 to 90 minutes. About 20-35 g of urea per day is excreted in human urine as a consequence of normal body functions.

Animal Data

Acute Toxicity
Acute toxicity is low by the oral route in mammals except for ruminants. Rats and mice given urea subcutaneously and intravenously exhibit low acute toxic effects. Oral LD50 values for rats were 14 300 mg/kg body weight for females and 15 000 mg/kg body weight for males. In mice, oral LD50 values were 13 000 mg/kg body weight for females and 11 500 mg/kg body weight for males.

Irritation
Urea showed no irritant properties to rabbit eyes in a study undertaken to OECD guidelines. Poorly documented skin studies in animals showed no irritant effects.

Skin Sensitisation
Studies in animals showed no skin sensitising potential.

Effects from Repeated Exposure
Robust long term toxicity studies were limited to dermal exposure. Although the quantities of urea applied were not known, rats exposed to urea ointment rubbed into the back skin for 4 and 24 weeks showed no consistent treatment related effects. It was concluded that repeat dose toxicity of urea by the dermal route was low.

Genotoxicity
Bacterial mutagenicity studies were considered adequate and showed that urea had no effect. It caused DNA strand breakage in mammalian cells in laboratory tissue culture and when administered to animals, but only at concentrations around 50-100 times higher than those found normally in human blood.

Carcinogenicity
Mice and rats administered 4500, 9000 or 45 000 ppm in their diet for up to 12 months showed no treatment related effects to any of the organ systems studied, including reproductive organs.

Reproductive toxicity
Based on the lack of toxic effects seen in the gonads of test animals in carcinogenicity studies, urea is not expected to display a significant potential for adverse effects on fertility. No information on urea's effects on the developing foetus is available in mammals.

Human Data

Irritation
Urea has been used for some time at concentrations up to 10% in creams and ointments to treat dry skin. One human study showed that urea was slightly irritating at 7.5% and markedly irritating at 30% when applied to skin.

Effects from Repeated Exposure
Long term follow-up studies have indicated that the substance is non-allergenic and virtually free of side effects. It is assumed that humans are well adapted to deal with urea even in high doses. This is supported by clinical evidence in cases where patients have received long term urea treatment for endocrine disorders. One patient is reported to have suffered no side effects following treatment with urea at levels of about 470 mg/kg body weight/day for five years.

Outcome of the SIDS OECD Initial Assessment (1996)

The OECD SIDS report (1996) concluded that: *"Based on the available information, the initial assessment gave no concern for the human health and the environment.*

Urea is an important endogenous product of mammalian metabolism. This may partly explain why it has not been rigorously studied with toxicological tests. Nevertheless, urea appears to cause little or no toxicity to most mammalian species (ruminants are more sensitive because of microbial ammonia production) and humans at reasonable dose levels.

Urea should be of low current concern to human health".

Overall, there are no data in the OECD SIDS report on urea to indicate urea to be a skin sensitiser, carcinogenic, or a reproductive toxicant. Urea has not been rigorously examined with respect to reproductive and developmental toxitity, however chronic toxicity and carcinogenicity studies have suggested a no observed adverse effect level of 2000-6000 mg/kg bw/day in rats and mice. Though it does appear to have genotoxic properties, this occurs at doses far in excess of what a person would normally expect to be exposed to. The toxicity of urea appears to be restricted to skin irritation, which was reported in a single human study. The risk to humans from urea will depend on the amount of exposure to the chemical. The bulk of human exposure to urea comes from food and occupational exposure adds little to the amounts received orally. Despite the human health effects associated with urea together with data indicating potentially extensive use in both industrial and consumer areas, it appears that for consumers and workers, the human health hazards are low.

References

1. FORS (Federal Office of Road Safety) (1998) Australian Code for the Transport of Dangerous Goods by Road and Rail 6th ed., Canberra, Australian Government Publishing Service.
2. IPCS (1997) Urea: International Chemical Safety Card 0595. International Programme on Chemical Safety, World Health Organisation http://www.inchem/org/ documents/icsc/icsc/eics0502.htm
3. National Drugs and Poisons Schedule Committee (2003) Standard for the Uniform Scheduling of Drugs and Poisons. Canberra, ACT, Australian Government Publishing Service
4. NOHSC (1995) Exposure Standards for Atmospheric Contaminants in the Occupational Environment. Canberra, ACT, Australian Government Publishing Service
5. NOHSC (1999) Approved Criteria for Classifying Hazardous Substances. Sydney, NSW, National Occupational Health and Safety Commission.
6. NOHSC (1999) List of Designated Hazardous Substances. Sydney, NSW, National Occupational Health and Safety Commission.
7. OECD (1996) OECD Screening Information Data Set (SIDS), Initial Assessment, Volume 3, Part 1: Urea Paris, OECD.