Urea; CASRN: 57-13-6

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Urea

File First On-Line 07/13/2011

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	qualitative discussion	07/13/2011
Inhalation RfC (I.B.)	qualitative discussion	07/13/2011
Carcinogenicity Assessment (II.)	yes	07/13/2011

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name – Urea
CASRN – 57-13-6
Section I.A. Last Revised – 07/13/2011

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the IRIS Guidance Documents Web page for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also

carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

There was no previous oral RfD for urea on the IRIS database.

I.A.1. CHRONIC ORAL RfD SUMMARY

Information regarding the potential toxicity of oral exposure to exogenous urea in humans is limited to accounts of accidental exposure (Steyn, 1961), studies on volunteers with renal disease (Eknoyan et al., 1969), and studies where therapeutic uses of urea were employed (Bensinger et al., 1972). These studies are of limited value in developing a chronic RfD due to the acute nature of exposure to urea, evaluation of high doses, lack of observed toxicity, limited study design, and insufficient exposure characterization (Bensinger et al., 1972; Eknoyan et al., 1969; Steyn, 1961).

Overall, the available studies provide limited information on the potential toxicity of urea following oral exposure. The studies identify the liver and kidney as potential target organs for the toxicity of urea; however, the best available information is from short-term studies (e.g., 28-day exposures) and is insufficient to characterize a dose-response relationship due to a lack of incidence reporting. The 28-day study conducted by Kommadath et al. (2001) is the only available study that could potentially be used for the derivation of an RfD (i.e., a LOAEL of 7.3 mg/kg-day based on degenerative effects in the liver and kidney in male mice), but the reporting of results was very limited, and the observations were of a general nature (e.g., specific types of effects were not identified). This lack of specificity combined with the high degree of uncertainty in extrapolating to chronic exposure to humans precludes its use as a principal study for an RfD. Thus, the available information on the oral toxicity of urea is considered insufficient for the derivation of an RfD.

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Not applicable

I.A.3. UNCERTAINTY FACTORS

Not applicable

I.A.4. ADDITIONAL STUDIES/COMMENTS

Not applicable

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Not applicable

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document - U.S. EPA, 2011

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Urea* (U.S. EPA, 2011). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF).***

Agency Completion Date - 07/13/2011

I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Substance Name – Urea
CASRN – 57-13-6
Section I.B. Last Revised – 07/13/2011

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

There was no previous inhalation RfC for urea on the IRIS database.

I.B.1. CHRONIC INHALATION RfC SUMMARY

Limited information is available regarding the inhalation toxicity of exogenous urea. Four studies (three occupational and one therapeutic) have been identified and are discussed in Section 4.1.2. El Far et al. (2006) compared liver and kidney function as well as carcinogenicity biomarkers in eight workers exposed to urea for an average of 8 years to 15 nonexposed subjects. This study reported elevated AST, ALT, and CEA levels among exposed workers as compared to controls; however, all results were within the normal physiological range. Bhat and Ramaswamy (1993) evaluated lung function in 30 workers at a fertilizer chemical plant. Compared to the 68 controls, exposed workers had decreased PEFR/minute rates, but no change in FVC or FEV_1 was observed. For both studies (El Far et al., 2006; Bhat and Ramaswamy, 1993), no quantitative exposure levels were provided. Marsh et al. (2002) observed a low incidence of bladder cancers deaths—4 in a cohort of 995 workers—among workers at a nitrogen products plant. The mixed chemical exposure limits analyses of the study data in deriving an unbiased estimate of the effect of urea in the presence of known or potential confounders. Cade and Pain (1972) investigated the impact of inhaled urea aerosol (4 M solution from a nebulizer for 10 minutes) on lung function in symptom-free asthmatics. The study authors reported that urea produced mild and variable impairments in VC and FEV_1.

However, a correlation between individual initial and postexposure for VC and FEV_1 was not noted.

No studies of inhaled urea in experimental animals were identified. In summary, the available studies involving possible inhalation exposure to urea are limited, and do not provide concrete evidence of a critical effect or that effects observed are specific to urea exposure. In addition, quantitiative information is lacking to derive an RfC.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Not applicable

I.B.3. UNCERTAINTY FACTORS

Not applicable

I.B.4. ADDITIONAL STUDIES/COMMENTS

Not applicable

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Not applicable

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document - U.S. EPA, 2011

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Urea* (U.S. EPA, 2011). ***To review this appendix, exit to the***

toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)

Agency Completion Date - 07/13/2011

I.B.7. EPA CONTACTS

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II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name – Urea
CASRN – 57-13-6
Section II. Last Revised – 07/13/2011

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per µg/m^3 air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

There was no previous cancer assessment for urea on the IRIS database.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), there is "inadequate information to assess the carcinogenic potential" of urea.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

II.A.2. HUMAN CARCINOGENICITY DATA

The human carcinogenicity potential of urea and urea-containing mixtures has been evaluated in a limited number of studies. One occupational study showed that exposure to urea increased levels of carcinogenic biomarkers (e.g., CEA and PSA), but these changes were within the normal physiologic range (El Far et al., 2006). Marsh et al. (2002) observed a low incidence of bladder cancers deaths—4 in a cohort of 995 workers—among workers at a nitrogen products plant. The mixed chemical exposure limits analyses of the study data in deriving an unbiased estimate of the effect of urea in the presence of known or potential confounders. The available data do not permit a conclusion about human carcinogenicity potential from exposure to urea alone.

II.A.3. ANIMAL CARCINOGENICITY DATA

Two chronic studies in laboratory animals have evaluated the carcinogenic potential of urea (Fleischman et al., 1980; Shear and Leiter, 1941). Fleischman et al. (1980) observed an increase in malignant lymphomas in the mid-dose group of female mice and interstitial adenomas in the testes in the high-dose group of male rats in a 12-month feeding study. The female mice results were not statistically significant by a trend test, but incidences among the treated groups were higher than in control. A pairwise comparison with control indicated statistical significance ($p = 0.008$) in the mid-dose group only. For the male rats, a statistically significant linear trend and a statistically significant incidence of interstitial adenomas in the testes among the high dose group was noted. However, as discussed in Section 4.2.1.2, there were reporting problems with this study such that the exact number of animals used for histopathological evaluation is unknown. Additional concerns such as the possibility that the statistical significance observed in the high dose group of the male rats may have resulted in the observation of the statistically significant trend for interstitial adenomas, raises uncertainty with the available information. Given the reported findings, an additional year of exposure may have provided a better understanding of the carcinogenic potential as the duration of the

Fleischman et al. (1980) study (i.e., 12 months) is not representative of a lifetime exposure scenario.

The chronic study (11 month treatment period with follow-up to 15 months) by Shear and Leiter (1941) showed no treatment related increase in tumors following subcutaneous administration in mice. As with the Fleischman et al. (1980) study, an additional year of exposure may have aided with understanding the carcinogenic potential of urea. However, the applicability of subcutaneous administration in the evaluation of urea toxicity via oral or inhalation exposure further confounds the conclusions that can be drawn from this study regarding carcinogenic potential.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Urea has been tested for its genotoxic potential and has showed little capacity to produce genotoxic effects in bacterial test strains. Results from in vitro and in vivo studies in mammalian systems were mixed. Genotoxicity and mutagenicity studies in bacterial strains indicate that urea may not be mutagenic in *S. typhimurium* (with or without metabolic activation) or *E. coli* (Hellmer and Bolcsfoldi, 1992; Mortelmans et al., 1986; Shimizu et al., 1985; Ishidate et al., 1981). Based on the results of specific assays that detect DNA strand breaks, urea, at high concentrations, may have the potential to produce single strand breaks in some test systems, but not double strand breaks. It is possible that urea forms ROS resulting in single strand breaks (Zhang et al., 2004; Kultz and Chakravarty, 2001; Garberg et al., 1988). Urea produced CAs in different mammalian cell types and test systems (e.g., mouse lymphoma forward mutation assay and mouse renal inner medullary collecting duct cells evaluated using the alkaline comet assay), generally at high concentrations (approximately 5-38 mg/mL) (Zhang et al., 2004; Garberg et al., 1988; Wangenheim and Bolcsfoldi, 1988, Ishidate et al., 1981; Ishidate and Yoshikawa, 1980; Umeda et al., 1980; Ishidate and Odashima, 1977). However, several of the studies observed effects that were accompanied by a concomitant decrease in cell viability (Garberg et al., 1988; Wangenheim and Bolcsfoldi, 1988; Umeda et al., 1980) or occurred at high concentrations (e.g., 50 mM; Oppenheim and Fishbein, 1965). In vivo, urea produced CAs in bone marrow cells of Swiss albino mice fed high doses of urea (500 mg/kg-day for 5-7 days) but not in mice fed doses of 7.3, 14.6, and 29.2 mg/kg-day for up to 28 days (Kommadath et al., 2001; Chaurasia, 1991; Chaurasia and Sinha, 1987). Additionally, urea did not induce sperm head abnormalities in male mice that received five daily i.p. injections of urea (up to 2,000 mg/kg-day) (Topham, 1980). Based on the available genotoxicity information, even though the studies that detect mutations were negative in *Salmonella* strains, based on the induction of chromosomal aberrations in certain mammalian test systems, the role of genotoxicity in the process of urea-induced carcinogenicity cannot be eliminated.

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not applicable

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not applicable

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

Source Document - U.S. EPA, 2011

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Urea* (U.S. EPA, 2011). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

II.D.2. EPA REVIEW

Agency Completion Date - 07/13/2011

II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. BIBLIOGRAPHY

Substance Name – Urea
CASRN – 57-13-6

VI.A. ORAL RfD REFERENCES

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VII. REVISION HISTORY

Urea
CASRN – 57-13-6
File First On-Line – 07/13/2011

Date	Section	Description
07/13/2011	I., II., VI.	RfD and RfC discussion added; cancer assessment added.

VIII. SYNONYMS

Urea
CASRN – 57-13-6
Section VIII. Last Revised – 07/13/2011

- Carbamide
- Aquacare
- Aquadrate
- Basodexan
- Carbonyldiamide
- Hyanit
- Keratinamin
- Nutraplus
- Onychomal
- Pastaron
- Ureaphil
- Urepearl