EVALUATION OF THE HEALTH ASPECTS OF
UREA AS A FOOD INGREDIENT

1978

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C.

Contract No. FDA 223-75-2004
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Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
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NOTICE

This report is one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

Kenneth D. Fisher, Ph.D., Director
Life Sciences Research Office
FASEB

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I. INTRODUCTION

This report concerns the health aspects of using urea as a food ingredient. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1973.* To assure completeness and currency as of the date of this report this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, an announcement was made in the Federal Register of June 13, 1978 (43 FR 25487-25489) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of using urea as a food ingredient. The Select Committee received no requests for such a hearing on urea.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321 (s)], GRAS substances are exempt from the premarking clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (2) [21 CFR 170.3 and 170.30] that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. These sections of the Code also indicate that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA (2) recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety, the Committee, in accordance with

*The document (PB-241 971/1) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. While the Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Committee, there are insufficient data upon which to base a conclusion. The Committee is aware that its conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on urea and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of these substances under the Federal Food, Drug, and Cosmetic Act.
II. BACKGROUND INFORMATION

Urea, CO(NH$_2$)$_2$ is the diamide of carbonic acid. It is a white, odorless, somewhat hygroscopic, crystalline solid. On standing, it may gradually develop a slight ammoniacal odor. It is highly soluble in water, glycerol and hot alcohol, but almost insoluble in chloroform and ether (3). Food grade urea is not listed in the Food Chemicals Codex (4). The U.S. Pharmacopeia specifies a purity of at least 99 percent with not more than 20 ppm of heavy metals, 100 ppm of sulfate, 70 ppm of chloride and 400 ppm of alcohol insoluble matter (5).

Several million tons of urea are produced annually in the United States, the bulk of which is used in agriculture as a slow release fertilizer and as a feed supplement. Its major medical role is to reduce intraocular and intracranial pressure. It has also been used in the treatment of sickle cell anemia, as a diuretic, as a topical antiseptic, and to ammoniate dentifrices (3, 6). It is a basic ingredient in the synthesis of medically important compounds such as barbiturates and urethanes (3).

Urea is used in the manufacture of dyes, fire retardant paints, plasticizers, and stabilizers for explosives. Upon reaction with formaldehyde, it forms resins which have broad applications as plastics and adhesives. These urea-formaldehyde resins are employed as bonding and adhesive agents for plywood, as laminating and protective coatings, and as paper and fabric modifiers. Such resins were the first commercially important products to achieve crease resistance and other desirable properties in cellulosic fabrics. They are used extensively in treating and coating paper to increase the wet strength and the general utility of paper products (7).

Urea appears among substances that are generally recognized as safe in the Code of Federal Regulations (2) for use in cotton and cotton fabrics in dry food packaging (21 CFR 182.70) and in paper and paperboard products (21 CFR 182.90). Unpublished GRAS authorizations include its use in foods, syrups for flavoring milk, chewing gum, vitamin and mineral preparations, as a marker in whiskey, and as a solubilizing agent for riboflavin (8). It is deemed to be generally recognized as safe by the Internal Revenue Service as food for yeast in wine production, with the amount used not to exceed 2 pounds per 1000 gallons (9) [27 CFR 240.1051]. Urea is a regulated food additive for use as a component in cellophane for packaging food (21 CFR 177.1200), in side seam cements for food containers (21 CFR 175.300) and as a plasticizer (in the form of the sodium nitrate-urea complex) in glassine and greaseproof paper for packaging dry foods (21 CFR 176.320).
III. CONSUMER EXPOSURE DATA

Urea is a natural constituent of many common foodstuffs. Oats may contain 4.5 percent of their total nitrogen content as urea and oil seed meals about 0.25 percent. Up to 15 percent of the total nitrogen of young plants and about 5 percent of the mature plants is nonproteinaceous and much is in the form of urea (10). Urea is a normal constituent of animal tissues and fluids and is ingested in small amounts when meat is consumed.

No data are available on the intake of urea resulting from its addition to food. A National Research Council subcommittee investigating the extent to which GRAS substances are added to food did not include urea in its survey of the food industry (11). No listing is shown for urea in the Handbook of Food Additives (12) which gives the usual levels of addition of many GRAS substances to food.

Approximately 4.2 million tons of urea were produced (13) and imported (14) in the United States in 1973, the latest date for which complete data are available. The Select Committee estimates that approximately 90 percent was used as feed supplements or fertilizers, leaving about 400,000 tons (360 million kg) for all other purposes. If all the urea not utilized for animal feed or fertilizer were added to food for human consumption, the per capita addition would be no more than 5 g daily. However, most of the urea not utilized for fertilizer or feed is used for the purposes listed in the previous section, especially for the production of urea-formaldehyde resins. Although no data are available on this point, it is believed that only a very small amount is used as a direct or indirect food ingredient.
IV. BIOLOGICAL STUDIES

Absorption, metabolism and excretion

Urea is extremely soluble in water and oral doses are rapidly absorbed and distributed through the body's tissues and fluids, in proportion to their water content (15, 16). The penetration of urea into fatty tissue such as the brain is lower than for most other tissues (17).

When sheep were fed 40 g of urea with 40 g of glucose, the urea content of portal blood doubled within 15 minutes (18). In man, too, the absorption of urea is very rapid. Archer and Robb (19) found the blood urea concentration to reach a peak, generally within 30 minutes after oral administration. Similar results were obtained by Shannon et al. (20) who reported that the serum urea levels of human volunteers doubled within 20 minutes after receiving 30 g of urea by mouth (about 0.5 g per kg). A maximum level of 94.6 mg per 100 ml (control 36.4 mg per 100 ml) was reached within 40 minutes. Luck and Engle (21) injected pregnant rats subcutaneously with urea and found that it not only penetrated rapidly into maternal tissues and organs but that it also readily passed through the placenta. Within 30 minutes after injection, the urea content of the maternal muscle and liver had increased approximately threefold over the control value and the fetal concentration had doubled. Two hours after injection, the fetus and the maternal liver and muscle contained equal concentrations of urea.

The colon has been reported to be relatively impermeable to urea (22). When urea solutions were introduced into the colon in men, urea concentrations in the blood remained unchanged.

Urea is formed metabolically through a cyclic mechanism first postulated in 1932 by Krebs and Henseleit (23). Free ammonia arising from the oxidative deamination of glutamate in liver mitochondria combines with carbon dioxide to form carbamoyl phosphate. The carbamoyl group is transferred to ornithine to form citrulline, which in turn reacts with aspartate to produce arginosuccinate. This is hydrolysed enzymatically to liberate free arginine and fumarate. The fumarate returns to the pool of tricarboxylic acid cycle intermediates, while the arginine is cleaved by arginase to produce urea and ornithine.

The so-called urotelic animals excrete urea as the major end-product of amino acid metabolism. Included in this group are mammals, elasmobranchs, amphibia, and chelonia (24). Genetic deficiency of any of the enzymes required in the urea cycle produces protein intolerance, elevated amounts of blood ammonia, metabolic disturbances, neurological symptoms and brain damage (25). The development of the urea cycle enzymes in the fetus varies with the species. The pig fetus is able to synthesize urea
at a very early stage, but the rat fetus acquires this ability only at a later period (26).

The normal range of urea in the blood plasma of man is 20 to 30 mg per 100 ml and a 70 kg adult excretes about 30 g daily. An individual consuming a high protein diet will excrete about 90 percent of the dietary nitrogen as urea. The percentage excreted as urea is less with a highly restricted nitrogen intake. The ability of the kidney to remove urea from the blood provides a measure of kidney function, or more specifically, of glomerular filtration capacity (27).

Urea has long been used as a dietary supplement for ruminants (28, 29) and in 1949, Rose et al. (30) demonstrated that it could serve as a nitrogen source in weanling rats as well. Similar utilization of urea has now been shown in the rabbit (31), chick (32), pig (33), horse (34), and man (35-37). Bacterial action in the gastrointestinal tract, particularly in the colon, produces ammonia which is absorbed and mixed with the metabolic pool of nitrogen, where some may be utilized for protein synthesis. Utilization of urea nitrogen has been demonstrated both in malnourished children (36) and adults (37). Gallina and Dominguez (38) report that urea nitrogen can contribute part of the amino acid requirements in man when the diet provides sufficient glucose for nonessential amino acid synthesis. Picou and Phillips (36) estimate that in man the potential contribution of urea or ammonium salts to protein synthesis is less than 10 percent.

Acute toxicity

Ruminants are much more sensitive to urea than are nonruminants. The sudden ingestion of 116 g (about 230 mg per kg) by cattle or 10 g (about 160 mg per kg) by sheep, undiluted by feed, has resulted in labored breathing, tetanic spasms and prostration within 30 minutes (28).

Among nonruminants, the acute toxicity of urea appears to be relatively low. Unfortunately, much of the available data is old and the experimental conditions vague. Acute toxicity data are shown in Table I.

In man, the recommended dose to reduce intraocular and intracranial pressures is 1 g per kg body weight administered intravenously. Nausea, vomiting, mental confusion, hyperthermia, nervousness, and tachycardia may result but can be minimized by slow infusion. Urea may also be used orally as a diuretic in daily doses of 40 to 100 g (0.7 to 1.6 g per kg) (49). Two to 3 g per kg body weight have been given orally to normal volunteers with no reported untoward effects (50).
<table>
<thead>
<tr>
<th>Animal</th>
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<th>Dose (mg/kg)</th>
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<tr>
<td>Rabbit</td>
<td>oral (?)</td>
<td>LD₅₀</td>
<td>5000</td>
<td>40</td>
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<tr>
<td></td>
<td>gavage</td>
<td>LD</td>
<td>5000</td>
<td>41</td>
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<td></td>
<td>I.V.</td>
<td>LD</td>
<td>7320</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>I.V.</td>
<td>LD</td>
<td>6310</td>
<td>44</td>
</tr>
<tr>
<td>Cattle</td>
<td>oral</td>
<td>MLD</td>
<td>510</td>
<td>18</td>
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<tr>
<td></td>
<td>oral</td>
<td>MLD</td>
<td>600-1080</td>
<td>47</td>
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<tr>
<td>Pony</td>
<td>gavage</td>
<td>LD</td>
<td>3310-3610</td>
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<td>Dog</td>
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<td>LD</td>
<td>3000-9000</td>
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<td></td>
<td>I.V.</td>
<td>LD</td>
<td>3000</td>
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<tr>
<td></td>
<td>I.V.</td>
<td>MLD</td>
<td>&gt;10,000</td>
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<td>42</td>
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<td>LD</td>
<td>16,000</td>
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The therapeutic effectiveness of urea in sickle cell anemia is still controversial, but its use provides additional data on its possible acute toxicity. Massive doses of urea have been injected intravenously into patients during sickling crises. The total dose of urea varied from 2.6 g per kg body weight injected over a 10-hour period (51) to a maximal dose of 6.0 g per kg administered within 12 to 24 hours (52). The injection fluid was 10 or 15 percent urea dissolved in 10 percent invert sugar solution. The investigators concluded that the rapid infusion of large amounts of urea was not superior to invert sugar alone in shortening the crisis episodes. The side effects were not serious, consisting mainly of diuresis, headache, and vein irritation. The diuresis was considerable. In one instance, the urinary output over an 18-hour period was more than 28 liters.

**Short-term studies**

Chronic toxicity to urea is dependent on species, body size, nutritional status, rate of feeding and nature of the diet. Most of these studies have been conducted with ruminants. The American Feed Control Officials (53) recommend that the amount of urea fed to cows not exceed 3 percent of the total grain ration, which represents about 0.45 g per kg per day. Various reports indicate that sheep can ingest 50 to 100 g (about 0.8 to 1.6 g per kg) urea daily with no harmful effects when properly mixed with feed (54).

Richet and Maret (55) fed rats for periods up to 190 days with rations containing from 2 to 25 percent urea (about 2 to 25 g per kg body weight daily). Even at the lower levels of urea ingestion, weight loss and suppression of sexual function resulted. Rats receiving 14 percent urea in their diet and deprived of water died within a few days. If water were allowed, they survived for 20 to 76 days at the 20 percent level and 12 days with the 25 percent supplement. Anemia and renal hypertrophy were also observed in some animals. It is difficult to evaluate these findings for the number of animals in each series was small (often 1 to 3) and no data are given on the actual food intake. The extreme weight loss of the rats suggests that inanition was likely.

Balestri et al. (56) injected subcutaneously 3000 to 4000 mg urea per kg into 12 unilaterally nephrectomized dogs every 8 hours for a period of 45 days. Plasma urea levels were maintained between 200 and 700 mg per 100 ml. Hematocrit and platelet counts were made in some animals, electroencephalographic recordings in some and measurements of spontaneous movement in others. Except for a mild drowsiness and increased diuresis, the results of all measurements were essentially normal.

Grollman and Grollman (57), however, claimed that many of the signs encountered in uremia were due to the effect of accumulated urea. They believed the presence of high urea levels induced changes in tissue electrolytes which were at least partly responsible for the observed toxic
effects. The investigators maintained concentrations of 540 to 1690 mg urea per 100 ml extracellular fluid in nephrectomized dogs by means of intermittent peritoneal lavage. The first signs of toxicity were weakness and anorexia soon followed by vomiting, retching, diarrhea, drop in body temperature and culminating in deep torpor or coma. The animals were killed after 4 to 10 days at a time when they exhibited severe signs of uremia. This technique allowed the other constituents in the extracellular fluid to be kept constant while the amounts of urea were varied.

Employing a somewhat similar technique, Johnson and coworkers (58) maintained high blood urea concentrations by intermittent dialysis in three patients suffering from advanced renal failure. Blood concentrations of 181 to 600 mg urea per 100 ml were maintained for periods of 7 to 90 days. When the urea concentration was kept below 300 mg per 100 ml, no untoward effects were noted although this level is about 10 times greater than normal. Concentrations above 300 mg per 100 ml were associated with malaise, vomiting, bleeding tendency, and headache. However, the more severe gastrointestinal, cardiovascular, mental and neurologic changes of uremia were not observed.

Bensinger et al. (59) administered by mouth 40 to 120 g (0.6 to 2.0 g per kg) urea daily in divided doses to eight patients with sickle cell disease for periods of 3 weeks to 9 months. The blood urea concentrations of the patients approximately doubled during the test periods. While the patients were ingesting urea, there was a slight decrease in blood volume, probably resulting from the chronic osmotic diuresis induced by the urea. The life span of the red cells did not change. There was no demonstrable improvement in the patients. The most obvious effects of the urea intake were thirst and diuresis. Two patients were unable to complete the study because of nausea and vomiting.

Long-term studies

Reports of long-term studies of urea were not available to the Select Committee.

Carcinogenesis, teratogenesis, mutagenesis

Urea was injected subcutaneously into 20 Strain A and 10C57 black male mice (60). The dose was progressively increased from 10 to 50 mg (0.5 to 2.5 g per kg body weight). Repeated injections were given over a period of 11 months until a total of 800 mg (40 g per kg body weight) was given. Nineteen mice survived one year and five were killed after 15 months. No induced tumors were observed.

Weekly intraperitoneal injections of 400 mg urea per kg body weight for 13 weeks produced no increase of lung tumors in Strain A mice, a strain sensitive to carcinogenic substances (61).
Immersion of frog eggs in 1.25 percent urea at various times after fertilization produced various embryonic abnormalities, especially of the central nervous system (62). Abnormalities were also produced in chick embryos with relatively small doses of urea (63, 64). Fifty to 900 mg urea dissolved in egg albumin were injected into eggs between the 7th and 20th hour of incubation. Among 132 embryos subjected to this treatment, 78 showed neural, vascular or cardiac abnormalities.

Pregnant rats received a daily dose of 50 g per kg of urea by gastric intubation for an average of 14 days (65). During this period the blood urea levels ranged from 1000 mg per 100 ml one hour after urea administration to 100 mg per 100 ml 12 hours later and just before the next intubation. Within 48 hours, the newborn rats were killed and the kidneys examined. No hypertrophy or other kidney changes were detected nor were any teratogenic effects reported.

Intraruminal administration of 0.44 g urea per kg body weight caused the death of pregnant cows within 4 hours (66). However, when 2 and 1 moles acetic acid per mole urea were injected into the rumen 15 and 180 minutes, respectively, after the urea, the cows survived despite high levels of blood ammonia. When 29 pregnant cows (stage of pregnancy not stated) were treated in this manner only one death resulted. The treatment had no effect on the number of calves born, their birth and weaning weights, and the rebreeding performances of the cows. No abnormalities were reported among the calves.

Urea had no effect on cultured human leukocytes at physiological concentrations (1mM) (67). At a concentration of 50 mM, however, it caused severe chromosome fragmentation and "moderate" cell damage. The authors suggest that these changes may be nonspecific effects of high molarity solutions on cell division.
V. OPINION

Urea is a normal body constituent and is constantly being produced during amino acid and protein metabolism. It is a natural constituent in commonly consumed foods. Several grams per kilogram of body weight can be ingested by nonruminants, including man, without untoward effects. Most of the nitrogen consumed in food is excreted in the form of urea. A 70 kg individual consuming a normal diet will excrete an average of 25 g urea daily. While urea appears to be teratogenic in chick and frog embryos, no teratogenic effects were observed after ingestion of large doses of urea by pregnant rats and cows.

If all urea not used in animal feed and fertilizer were utilized in human food, it would amount to about 5 g per capita daily. However, it is known that the majority of this urea is used for the production of urea-formaldehyde resins and other non-food uses. Therefore, the per capita intake of urea as a direct or indirect food ingredient is much less than 5 g daily.

In the light of the foregoing, the Select Committee concludes that:

There is no evidence in the available information on urea that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future.
VI. REFERENCES CITED


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OCT 27 1978

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