Imidazolidinyl urea

39236-46-9

OVERVIEW

This material was prepared for the National Cancer Institute (NCI) for consideration by the Chemical Selection Working Group (CSWG) by Technical Resources International, Inc. under contract no. N02-07007.

Imidazolidinyl urea came to the attention of the NCI Division of Cancer Biology (DCB) as the result of a class study on formaldehyde releasers. Used in combination with parabens, imidazolidinyl urea is one of the most widely used preservative systems in the world and is commonly found in cosmetics.

Based on a lack of information in the available literature on the carcinogenicity and genetic toxicology, DCB forwarded imidazolidinyl urea to the NCI Short-Term Toxicity Program (STTP) for mutagenicity testing. Based on the results from the STTP, further toxicity testing of imidazolidinyl urea may be warranted.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), provided information on the production volumes for this chemical.

Dr. Harold Seifried of the NCI provided mutagenicity data from the STTP.

NOMINATION OF IMIDAZOLIDINYL UREA TO THE NTP

Based on a review of available relevant literature and the recommendations of the Chemical Selection Working Group (CSWG) held on December 17, 2003, NCI nominates this chemical for testing by the National Toxicology Program (NTP) and forwards the following information:

- The attached Summary of Data for Chemical Selection
- Copies of references cited in the Summary of Data for Chemical Selection
- CSWG recommendations to:

(1) Evaluate the chemical for genetic toxicology in greater depth than the existing data,

(2) Evaluate the disposition of the chemical in rodents, specifically for dermal absorption,

(3) Expand the review of the information to include an evaluation of possible break-down products, especially diazolidinyl urea and formaldehyde.

PRIORITY

The CSWG suggested that the recommended testing be conducted with moderate priority.

COMMENTS

The CSWG noted that absorption via the dermal route duplicates human exposure potential from the use of this substance in cosmetics.

The CSWG encourages the NTP to work with the Food and Drug Administration (FDA) to determine study design.

SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

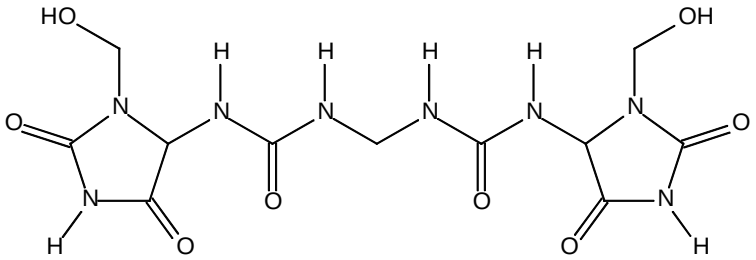
CAS Registry Numbers: 39236-46-9

Chemical Abstracts Service Name: Urea, *N*,*N*''-methylenebis [*N*'-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl] (9CI)

Synonyms and Trade Names: Abiol; Biopure 100; Chemynol I; Germall 115; Gram 1; Imidurea; Imidurea NF; Intersept Plus; Jeecide U-13; methanebis[*N*,*N*'-(5-ureido-2,4-diketotetrahydro-imidazole)-*N*,*N*-dimethylol]; Nipa Biopure 100; Protacide U-13; Sepicide CI; Sept 115; Tri-stat IU; Unicide U-13 (Budavari, 2001; ChemID, 2003; ChemFinder, 2003; Pepe *et al*., 2001)

Structural Class: Heterocyclic substituted urea compound with formaldehyde-releasing activity; urea hydantoin

Structure,



Molecular Formula, and Molecular Weight:

$C_{11}H_{16}N_8O_8$ Mol. wt.: 388.29

Chemical and Physical Properties:

Description: Odorless, white, free-flowing fine powder (Budavari, 2001)

Melting Point: 150 °C (Clariant, 2002)

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Solubility: Soluble in water, ethylene glycol, propylene glycol, glycerine; slightly soluble in methanol; insoluble in ethanol, sesame oil (Budavari, 2001)

Reactivity: Stable at room temperature in closed containers; incompatible with strong oxidants; decomposes in nitrogen oxides, carbon monoxide, and cardon dioxide, among other products (Fisher Scientific, 2003)

Technical Products and Impurities: Imidazolidinyl urea (~95%) is available from Sigma-Aldrich

(Sigma-Aldrich, 2003).

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EXPOSURE INFORMATION

Production and Producers:

Manufacturing Process: Imidazolidinyl urea is produced by the condensation of allantoin and formaldehyde. In this process, allantoin, formaldehyde, and sodium hydroxide are refluxed for an hour and then concentrated acetic acid is added. The final solution is gradually concentrated to a clear viscous liquid. The product is then poured into shallow trays and dried in vacuum at 70 °C (Berke, 1966; Berke & Rosen, 1986).

Producers and Importers: Chemical Sources International (2003) lists four U.S. suppliers of imidazolidinyl urea.

According to recent issues of chemical directories, imidazolidinyl urea is manufactured or distributed by Arrow Chemical Inc.; Bruchem, Inc.; Clariant LSM (America) Inc.; CoKEM Associates, Inc.; International Sourcing Inc.; International Specialty Products (ISP); Sithean Corporation; Spectrum Chemical Mfg. Corp.; Sutton Laboratories; TRI-K Industries, Inc.; and Universal Preserv-a-chem, Inc. (Carroll, 2002; Chemcyclopedia, 2003; Hunter, 2002; Tilton, 2002).

Production/Import Levels:

Imidazolidinyl urea is listed in the Environmental Protection Agency (EPA) Toxic Substances Control Act (TSCA) Inventory (ChemID, 2003).

The 1998 Inventory Update Rule lists the production volume of imidazolidinyl urea in the United States between 1 million and 10 million pounds (EPA, 2003a). The 2002 estimated production volume was between 10,000-100,000 pounds (Walker, 2003).

The Organization for Economic Co-operation and Development (OECD) has listed imidazolidinyl urea as a 2000 high production volume (HPV) chemical (OECD, 2001).

For the 2-month period from July 2003 and September 2003, the Port Import/Export Reporting Service (PIERS) database reported imidazolidinyl urea imports with a cargo weight of 4,128 pounds (Dialog Information Services, 2003).

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Use Pattern:

Imidazolidinyl urea is mainly used as an antimicrobial preservative in cosmetics and other personal care products (INCI, 2003; Lewis, 2000; McEntee, 1995; Ngan, 2003; Nikitakis, 1988; Rieger, 1993).

Imidazolidinyl urea is more active against bacteria than fungi and is often combined with parabens to provide a broad spectrum preservative system. This preservative is one of the most widely used preservative systems in the world (Block, 1993; International Specialty Products, 1999). The Food and Drug Administration (FDA) considers imidazolidinyl urea as one of the most common antimicrobial agents used in cosmetics (Amouroux *et al*., 1999).

Due to its high water solubility, imidazolidinyl urea can be incorporated into almost all water-based cosmetics, toiletries, and cold mix formulations. It is present in a wide range of liquid and powder products such as baby lotion, skin cream, sunscreens, shampoos, eyeliners, blush, perfumes, deodorants, hair dyes, shaving cream, and face masks (Clariant, 2002; International Specialty Products, 1999; NLM, 2003; Pepe *et al*., 2001).

As of November 2003, a total of 1,096 patents using imidazolidinyl urea were filed with the U.S. Patent and Trademark Office since 1976 (U.S. Patent and Trademark Office, 2003).

Human Exposure:

Occupational Exposure: The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 28,769 workers, including 18,644 females, in 1,885 facilities representing 7 industries were potentially exposed to imidazolidinyl urea in the workplace (RTECS, 1997). The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein.

Estimates from the NOES suggest that individuals working as hairdressers and cosmetologists have more exposure to imidazolidinyl urea than any other occupation. In addition, females were exposed more than males (NIOSH, 1990).

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Consumer Exposure: The principal source of human exposure to imidazolidinyl urea occurs from dermal contact when using personal care products containing this compound. These products, especially cosmetics, can remain on the skin for hours providing sufficient time for the absorption of imidazolidinyl urea. Repeated use of these cosmetics could result in chronic exposure to this compound (Agner *et al*., 2001; Cosmetic Ingredients Review Expert Panel, 1980; Ngan, 2003; Vitanet, 2003).

The concentration of imidazolidinyl urea in cosmetics is typically 0.1-0.3 perecent although it has been used as high as 5 percent (Clariant, 2002; Cosmetic Ingredients Review Expert Panel, 1980).

Environmental Occurrence:

Being a component of water-based cosmetics, imidazolidinyl urea has the potential to be introduced into the aquatic environment, however, no ecotoxicity studies identifying or quantifying this compound in the environment were found (Amouroux *et al*., 1999; EPA, 2003b; US Geological Survey, 2001).

In an *in vitro* study, imidazolidinyl urea was found to be slightly cytotoxic to sea urchin eggs by inhibiting H^+-ATPase activity as well as protein and DNA synthesis. However, this compound did not affect ion flux, membrane permeability, or protein phosphorylation (Amouroux *et al*., 1999).

Regulatory Status:

No standards or guidelines have been set by NIOSH or the Occupational Safety and Health Administration (OSHA) for occupational exposure to or workplace allowable levels of imidazolidinyl urea. Imidazolidinyl urea was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) are made.

Imidazolidinyl urea is in list 3 (inerts of unknown toxicity) of the Lists of Other (Inert) Pesticide Ingredients (EPA, 2003c).

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The Federal Food, Drug, and Cosmetic (FD&C) Act defines cosmetics as articles intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting the body's structure or functions (Lewis, 2000).

Under the FD&C Act, cosmetics and their ingredients are not required to undergo approval before they are sold to the public. Generally, the FDA regulates these products after they have been released to the marketplace. This means that manufacturers may use any ingredient or raw material, except for color additives and a few prohibited substances, to market a product without a government review or approval (Lewis, 2000).

The Fair Packaging and Labeling Act requires an ingredient declaration on every cosmetic product offered for sale to consumers (Lewis, 2000).

Although companies are not required to substantiate performance claims or conduct safety testing, if safety has not been substantiated, the product's label must read "WARNING: The safety of this product has not been determined" (Lewis, 2000).

Imidazolidinyl urea is permitted for use in personal care products in the European Union at a maximum concentration of 0.6%. In Japan, imidazolidinyl urea is allowed in rinse-off cosmetics such as shampoo, body wash, and facial cleanser at a maximum concentration of 0.3% (Clariant, 2002; Wu *et al*., 2003).

Imidazolidinyl urea is not listed in the EPA ECOTOX Report or the National Reconnaissance of Emerging Contaminants in U.S. Streams (EPA, 2003b; U.S. Geological Survey, 2001).

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TOXICOLOGY INFORMATION

Human Data:

No epidemiological studies or case reports investigating exposure to imidazolidinyl urea and cancer risk in humans were identified in the available literature.

Contact Dermatitis: Preservatives in cosmetics are the second most common cause of contact dermatitis reactions to cosmetics (Dooms-Goossens *et al*., 1986). The prevalence of positive reactions to imidazolidinyl urea was 1.9 percent and 3.2percent in patients with contact dermatitis in two independent studies (Albert *et al*., 1999; Cohen & Rice, 2001). Concomitant positive reactions have also been reported for imidazolidinyl urea and formaldehyde as well as imidazolidinyl urea and *N*-(3-chloroallyl)hexaminium chloride (Quaternium-15) (Albert *et al*., 1999).

A British study conducted between 1982-1993 showed that the frequency of preservative allergy to imidazolidinyl urea in 5,167 patients with contact dermatitis was 0.99%. Furthermore, the face and the hands were the sites of allergy for 69% and 19% of patients, respectively (Jacobs *et al*., 1995).

Imidazolidinyl urea did not induce contact sensitivity in several reports. In a study, 200 subjects were given repeated insult patch tests with a 10% aqueous solution of imidazolidinyl urea three times per week for five weeks. These subjects were challenged for 24 hours after treatment and no evidence of primary irritation or sensitization occurred (Cosmetic Ingredients Review Expert Panel, 1980).

In a separate study, women that used moisturizing cream and hand and body lotion containing 0.5% imidazolidinyl urea daily for 4 weeks showed no evidence of contact or photoallergic sensitivity after reapplying imidazolidinyl urea (Cosmetic Ingredients Review Expert Panel, 1980).

Another repeated insult patch test conducted with a liquid makeup preparation containing imidazolidinyl urea in a 0.5% concentration was applied to the backs of 189 subjects. After

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48 hours, the patches were removed. The patches were reapplied and this process was repeated 11 times with no evidence of primary irritation or allergic contact sensitization at the end of the study (Cosmetic Ingredients Review Expert Panel, 1980).

In 2001, the Cosmetic Ingredient Review (CIR) Expert Panel found no new data contradicting the original conclusions in the imidazolidinyl urea safety assessment conducted in 1980 (Cosmetic Ingredient Review Expert Panel, 2002).

Animal Data:

No 2-year carcinogenicity studies of imidazolidinyl urea in animals were identified in the available literature.

Acute Toxicity: The LC_{50} in rats after continuous inhalation for one hour was >5 mg/l (Cosmetic Ingredients Review Expert Panel, 1980). The LD_{50} values for imidazolidinyl urea are listed in Table 1.

Table 1. Acute Toxicity Values for Imidazolidinyl urea

Species	Route of administration	LD_{50} (mg/kg)
rat	oral	2,599
rat	oral	5,200
rat	oral	>7,500
rat	oral	11,300
mouse	oral	3,701
mouse	oral	7,200
rabbit	dermal	>8,000

Source: Cosmetic Ingredients Review Expert Panel, 1980; International Specialty Products, 1999; NTP, 2001

Subchronic Toxicity: Imidazolidinyl urea was applied in powder form at concentrations of 20, 45, 90, and 200 mg/kg/day to the shaved backs of five male and female albino rabbits for 6 hr/day, 5 d/wk, for three weeks. The only treatment-related effects reported were a slight to mild inflammatory and focal ulcerative effect (Cosmetic Ingredients Review Expert Panel, 1980).

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Seven male and female rats that were fed 6, 28, 130, or 600 mg/kg of imidazolidinyl urea daily for 90 days showed no differences in the hematology, urinalysis, and pathology profiles when compared to controls. However, imidazolidinyl urea induced a decrease in weight gain in males fed diets over 28 mg/kg/day (Sutton Laboratories, 1973a).

A 90-day oral toxicity test in rats using 1,300 mg/kg/day of imidazolidinyl urea reportedly did not produce any observable toxic effects, but experimental details were unavailable (Clariant, 2002).

Short-Term Tests:

Imidazolidinyl urea was mutagenic in *Salmonella typhimurium* strains TA98 and TA100 at concentrations up to 1,500 µg/plate in the presence or absence of rodent liver S-9 fraction (Seifried, 2003).

Metabolism:

No studies on the metabolism of imidazolidinyl urea were identified in the available literature.

Other Biological Effects:

Skin Irritation and Sensitization: Imidazolidinyl urea was described as not phototoxic in female Hartley guinea pigs after intradermal injections of 1-5% doses into the shaved backs and subsequent irradiation with FL20E and FL20BLB light for 30 minutes. The animals were again injected and irradiated 24 and 48 hours after the initial injection with no reaction (Cosmetic Ingredients Review Expert Panel, 1980).

Imidazolidinyl urea sensitized 60-70% of female Dunkin Hartley guinea pigs in a dose-dependent manner. The animals were patch tested with 1, 5, and 10% imidazolidinyl urea in petrolatum and read after 48 hours (Andersen *et al*., 1984).

Imidazolidinyl urea was found to be a sensitizer after topical applications of 25 µl of 10, 25, or 50 percent to CBA/Ca mice daily for three days induced significant radiolabelled thymidine incorporation into local lymph nodes four days after the last treatment with imidazolidinyl urea (Basketter & Scholes, 1992).

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Imidazolidinyl urea was non-irritating after an application of 0.1 ml of a solution containing 5, 10, or 20 percent of this compound in the right eye of albino rabbits. In another study, imidazolidinyl urea did not produce any irritation after application to the shaved backs of albino rabbits at concentrations of 0, 1, 2.5, and 5 percent (Cosmetic Ingredients Review Expert Panel, 1980).

Imidazolidinyl urea was not a sensitizer in male guinea pigs after 24 hours of the last of 11 intracutaneous injections of a dose of 0.1%. The first injection of 0.05 ml was followed by nine 0.1 ml injections on alternate days into the same area. The final dose of 0.05 ml was given two weeks after the 10^{th} injection (Cosmetic Ingredients Review Expert Panel, 1980).

Reproductive and/or Developmental Effects: Imidazolidinyl urea induced a slight increase in the number of resorptions and/or fetal deaths *in utero* on day 17 in female albino mice that were orally intubated with 30, 95, and 300 mg/kg from day 6 to 15 of gestation. However, no different abnormalities in soft or skeletal tissue with respect to controls were found. This compound was found to be slightly fetotoxic but not teratogenic in mice (Sutton Laboratories, 1973b).

Cytotoxicity: Imidazolidinyl urea induced a significant dose- and time-dependent decrease in cell viability of HL60 cells after 3, 6, or 24 hours of incubation at a concentration range of 0.01-1%. Apoptotic markers of cell death, DNA subdiploid content, internucleosomal DNA fragmentation, and caspase activation were observed in HL60 cells treated with low concentrations of imidazolidinyl urea (0.01% and 0.1%). However, at higher concentrations (0.5-1%), the mechanism of cell death was necrosis (Anselmi *et al*., 2002).

Imidazolidinyl urea was not cytotoxic to normal human fibroblasts after incubation with 1-30% solutions for up to 30 minutes (Rivalland *et al*., 1994).

Formaldehyde Releaser: Imidazolidinyl urea releases formaldehyde into cosmetics at temperatures above 10 ºC. A 1974 study found formaldehyde release occurs at the non-physiological conditions of 60 ºC and a pH of 6. In water-containing cosmetics like shampoos, formaldehyde release increases with a rise in pH and temperature of the solution as well as a longer storage period (Cosmetic Ingredients Review Expert Panel, 1980; Organic & Natural Enterprise Group Ply Ltd, 2003; Scientific Committee on Cosmetic Products and Non-Food Products, 2002).

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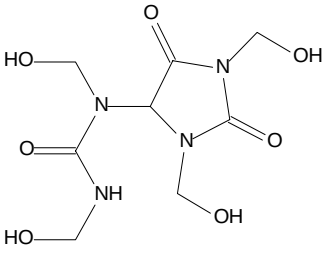
A Taiwanese study revealed that eight domestic and imported cosmetic products, labeled as containing imidazolidinyl urea and purchased between 1995 and 1996, had a total and free formaldehyde content of 50-390 ppm and 7-79 ppm, respectively (Wu *et al*., 2003).

Structure-Activity Relationships:

One compound structurally related to imidazolidinyl urea, diazolidinyl urea [CAS No. 74891-02-8], was selected for review. No information on the carcinogenicity of this chemical was identified in the available literature.



Diazolidinyl Urea

Diazolidinyl urea was mutagenic in *Salmonella typhimurium* strains TA98, TA100, and TA102 with and without metabolic activation. This compound induced micronuclei in Chinese hamster V79 cells with and without metabolic activation. Diazolidinyl urea also inhibited the formation of microtubuli at 3 mmol/l (Pfuhler & Wolf, 2002). In contrast, the Cosmetic Ingredients Review Expert Panel (1990) found that diazolidinyl urea was not mutagenic in *S. typhimurium* and that this compound did not induce micronuclei; however, no technical details were available.

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