Formaldehyde donors: Human health tier II assessment

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
3,5,7-Triaza-1-azoniatricyclo[3.3.1.13,7]decane, 1-(3-chloro-2-propenyl)-, chloride	4080-31-3
2,4-Imidazolidinedione, 1,3-bis(hydroxymethyl)-5,5-dimethyl-	6440-58-0
Methanol, (phenylmethoxy)-	14548-60-8
Urea, N,N''-methylenebis[N'-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-	39236-46-9
3,5,7-Triaza-1-azoniatricyclo[3.3.1.13,7]decane, 1-(3-chloro-2-propenyl)-, chloride, (Z)-	51229-78-8
Glycine, N-(hydroxymethyl)-, monosodium salt	70161-44-3
Urea, N-[1,3-bis(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-N,N'-bis(hydroxymethyl)-	78491-02-8

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic

data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

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ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group have the common characteristic in aqueous/polar solvents to 'release some or all of the formaldehyde they contain, and they do not remain as a single compound' (SCCNFP, 2002). The hazardous properties of formaldehyde (CAS No. 50-00-0) are therefore expected to dominate the toxicity profile, particularly in consumer products.

Quaternium 15 is listed on the Australian Inventory of Chemical Substances (AICS) in two isomeric forms: CIS (CAS No. 51229-78-8) and mixed isomers (CAS No. 4080-31-3). Both are commonly referred to as quaternium 15; the specific isomeric form is identified in this report by CAS No. where available from the literature source.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening Information Dataset Initial Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; and eChemPortal: OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemicals have reported cosmetic use in:

- preservatives; and
- hair conditioning.

The chemicals have reported domestic use including in:

- adhesive and binding agents;
- cleaning agents; and
- paints, lacquers and varnishes.

The chemicals have reported commercial use including in:

- cutting fluids;
- drilling mud and oil recovery fluids;
- lubricants and additives; and
- hydraulic fluids and additives.

The following non-industrial uses have been identified internationally in:

- pesticides (agricultural and non-agricultural);
- bactericides;
- food additives to preserve adhesives, resins, pulp and paperboard that contact food; and
- pharmaceuticals (antiarrhythmic and anticonvulsant agents).

Restrictions

Australian

No known restrictions have been identified for the chemicals. However, formaldehyde is listed in Schedules 2 and 6 and Appendix C of the *Poisons Standard* (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) as follows:

- in Schedule 2:

'FORMALDEHYDE (excluding its derivatives) for human therapeutic use **except**:

(a) in oral hygiene preparations containing 0.1 per cent or less of free formaldehyde; or

(b) in other preparations containing 0.2 per cent or less of free formaldehyde.'

Schedule 2 chemicals are labelled with 'Pharmacy medicines' and are 'substances, the safe use of which may require advice from a pharmacist and should be available from a pharmacy or, from a licensed person'.

- in Schedule 6:

'FORMALDEHYDE (excluding its derivatives) in preparations containing 0.05 per cent or more of free formaldehyde **except**:

(a) for human therapeutic use;

(b) in oral hygiene preparations;

(c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde;

(d) in nail hardener cosmetic preparations containing 0.2 per cent or less of free formaldehyde when labelled with the statement: PROTECT CUTICLES WITH GREASE OR OIL;

(e) in all other cosmetic preparations; or

(f) in other preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement: CONTAINS FORMALDEHYDE.'

Schedule 6 chemicals are labelled with 'Poison' and are 'substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'.

- in Appendix C:

'FORMALDEHYDE (excluding its derivatives):

(a) in oral hygiene preparations containing more than 0.1 per cent of free formaldehyde;

(b) in aerosol sprays for cosmetic use containing 0.005 per cent or more of free formaldehyde;

(c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde; or

(d) in all other cosmetic preparations containing 0.05 per cent or more of free formaldehyde **except** in preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement: CONTAINS FORMALDEHYDE.'

Appendix C are 'substances, other than those included in Schedule 9, of such danger to health as to warrant prohibition of sale, supply and use'.

International

International restrictions concern the use of the chemicals in cosmetics and food related products.

The chemicals quaternium 15 (CAS No. 4080-31-3), DMDM hydantoin, benzylhemiformal, imidazolidinyl urea, sodium hydroxymethylglycinate and diazolidinyl urea are listed on the following (Galleria Chemica):

- EU Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products—Annex V List of preservatives allowed in cosmetic products, with a maximum authorised concentration of free formaldehyde of 0.2 %; and
- New Zealand Cosmetic Products Group Standard—Schedule 7: Preservatives cosmetic products may contain with restrictions—Table 1: List of preservatives allowed.

The chemicals quaternium 15 (CAS No. 4080-31-3), DMDM hydantoin, benzylhemiformal, imidazolidinyl urea, sodium hydroxymethylglycinate are also listed on the following:

- the ASEAN Cosmetic Directive Annex VI—Part 1—List of preservatives allowed for use in cosmetic products.

The chemical quaternium 15 (CAS No. 4080-31-3) is also listed on:

- New Zealand Cosmetic Products Group Standard—Schedule 7: Preservatives cosmetic products may contain with restrictions—Table 2: List of additional preservatives allowed in New Zealand;
- US FDA Indirect Food Additives: Adhesives and components of coatings—substances for use only as components of adhesives—Adhesives; and
- US FDA List of "Indirect" Additives Used in Food Contact Substances

The chemicals quaternium 15 (CAS No. 4080-31-3 and CAS No. 51229-78-8) and DMDM hydantoin are also listed on the following:

- Europe Substances Listed in EU Directives on Plastics in Contact with Food.

Existing Worker Health and Safety Controls

Hazard Classification

The following chemicals are classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Quaternium 15 (CAS No. 51229-78-8):

- T; R63 (reproductive toxicity)
- Xn; R22 (acute toxicity)
- Xi; R38 (irritation)
- R43 (sensitisation).

Imidazolidinyl urea and diazolidinyl urea:

- R43 (sensitisation).

Exposure Standards

Australian

None of the chemicals have specific exposure standards in Australia.

International

None of the chemicals have specific exposure standards.

Health Hazard Information

These chemicals have widespread use as preservatives in cosmetics; the mode of action is formaldehyde release into aqueous solutions. The degree of completeness of formaldehyde release in a cosmetic product will depend on the concentration of the preservative in the product, the percentage of water in the product, the rate of formaldehyde release from the specific preservative, and the length of time since formulation.

Methods have been developed to allow the determination of the free formaldehyde (defined as 'all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol' (SUSMP, 2013)) in the presence of non-dissociated preservative (SCCNFP, 2002).

For skin sensitisation and systemic toxicity, it is considered that the formaldehyde released from the decomposition of these chemicals will be the critical driver of these modes of toxicity. While the toxicity of decomposition products other than formaldehyde is also relevant, the EU SCCNFP considered these were taken into account in some of the test data it used to determine that imidazolidinyl urea, diazolidinyl urea, sodium hydroxymethyl glycinate and benzylhemiformal should be regulated based on free formaldehyde (SCCNFP, 2002).

Acute Toxicity

Oral

The available data for a number of these chemicals (DMDM hydantoin, imidazolidinyl urea and diazolidinyl urea) show that they all have low acute oral toxicity. Quaternium 15 (CAS No. 51229-78-8) is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in HSIS (Safe Work Australia). However, the available data do not support this classification.

No data are available for benzylhemiformal (CAS No. 14548-60-8) and sodium hydroxymethyl glycinate (CAS No. 70161-44-3), but the weight of evidence from the other chemicals suggests that they have low acute oral toxicity.

A median lethal dose (LD50) of 2664 mg/kg was established for quaternium 15 (CAS No. 51229-78-8) in a rat study. Reported signs of toxicity were lethargy, diarrhoea, lacrimation and tremors (EPA, 1995).

A LD50 of 3000–5000 mg/kg in Sprague Dawley (SD) rats was reported for DMDM hydantoin (CAS No. 6440-58-0) (CIR, 1988).

Imidazolidinyl urea (CAS No. 39236-46-9) has reported LD50 values of 5200 mg/kg in Sherman-Wistar rats, 11300 mg/kg in Wistar rats and 7200 mg/kg in mice (CIR, 1990a).

Diazolidinyl urea has reported LD50 values of 3700 mg/kg in CD-1 mice and 2600 mg/kg in Charles River CD rats (CIR, 1990b).

Dermal

The available data for a number of these chemicals (DMDM hydantoin, imidazolidinyl urea and diazolidinyl urea) show that most of them have low acute dermal toxicity. Only Quaternium 15 (CAS No. 4080-31-3 and 51229-78-8) is slightly toxic in rabbits and may require a hazard classification. No data are available for benzylhemiformal and sodium hydroxymethyl glycinate but the weight of evidence from the other chemicals suggests they have low acute dermal toxicity.

A median lethal dose (LD50) of 923 mg/kg was established for quaternium 15 (CAS No. 51229-78-8) in a dermal study on rabbits (EPA, 1995). Two studies in rabbits exposed to a 50 % solution of quaternium 15 (CAS No. 4080-31-3 and CAS No. 51229-78-8) report an LD50 of 605 and 565 mg/kg (CIR, 2010). Dermal application of the chemical as a powder at 3980 mg/kg was non-toxic to rabbits. A dermal study conducted with rats showed no toxic effects and no mortalities (CIR, 2010).

In a rabbit study, the LD50 for DMDM hydantoin (CAS No. 6440-58-0) was estimated to be above the classification limit of 2000 mg/kg (CIR, 1988).

Imidazolidinyl urea has a reported LD50 >8000 mg/kg in a rabbit study (CIR, 1990a).

Diazolidinyl urea was tested at the limit dose of 2000 mg/kg in rabbits without ensuing toxicity (CIR, 1990b).

Inhalation

Data are available for a number of these chemicals (quaternium 15, DMDM hydantoin and imidazolidinyl urea) showing that they all have low acute inhalation toxicity. The weight of evidence suggests that diazolidinyl urea, benzylhemiformal and sodium hydroxymethyl glycinate have low acute inhalation toxicity.

A median lethal concentration (LC50) >4.7 mg/L was established for quaternium 15 (CAS No. 4080-31-3) in an inhalation study on rats (EPA, 1995).

Results from inhalation studies with SD rats exposed to DMDM hydantoin at doses up to 377.8 mg/L revealed no toxicity (CIR, 1988).

Imidazolidinyl urea has a reported LC50 >5 mg/L in inhalation studies on Wistar-Sherman rats exposed for one hour to dust or aerosol of imidazolidinyl urea (CIR, 1990a).

Corrosion / Irritation

Skin Irritation

For pure or concentrated forms of these chemicals, there is some variation in skin irritation. Negative results are reported in studies in which only low concentrations of the chemicals were used. Quaternium 15 (CAS No. 51229-78-8) is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). The available data support this classification. No data are available for sodium hydroxymethyl glycinate, but most of the available data show a potential for irritation as detailed below, and it therefore warrants a hazard classification.

A primary skin irritation study on rabbits exposed to quaternium 15 (CAS No. 51229-78-8) reported a very slight oedematous reaction on intact skin (EPA, 1995) while it was reported to be a mild to moderate dermal irritant in rabbit studies (CAS No. 4080-31-3 and CAS No. 51229-78-8) (CIR, 2010).

DMDM hydantoin has shown negative results when a 0.1 % in a moisturising lotion was tested on albino rabbits, but was found moderately irritating when applied to the skin of New Zealand White (NZW) rabbits at 0.4 % in a mascara (CIR, 1988).

Benzylhemiformal is not expected to cause irritation at concentrations up to 0.2 % (SCCNFP, 1999).

Results from skin irritation studies in albino rabbits have showed that up to 5 % imidazolidinyl urea was non-irritant, but at 50 % w/w in water it caused moderate to severe erythema and oedema in all animals. The dry chemical applied to the skin (0.5 g) did not induce any irritation (CIR, 1990a).

Diazolidinyl urea was not irritating to the skin at up to 5 % in albino rabbit studies (CIR, 1990b).

Eye Irritation

For pure or concentrated forms of these chemicals, there is some variation in ocular irritation as detailed below. Sensory irritation from formaldehyde vapour release is not expected from products containing the chemicals as preservatives, given that formaldehyde is unlikely to be volatile at low concentrations. However, if the chemicals are applied directly to the eye, irritation could occur due to the severe irritancy of formaldehyde. No data are available for sodium hydroxymethyl glycinate but the weight of evidence from the available data is sufficient to warrant a hazard classification.

A primary eye irritation study on rabbits exposed to quaternium 15 (CAS No. 51229-78-8) reported slight to moderate conjunctival redness and slight discharge, reversible by 72 hours (EPA, 1995), while it was found mildly irritating in rabbit studies at 0.2 % (CAS No. 4080-31-3 and CAS No. 51229-78-8) (CIR, 2010).

Several irritation tests have shown that DMDM hydantoin was non-irritating to the eyes of albino rabbits at 0.1 and 0.4 %; only transient and minimal irritation was reported in albino rabbits with a concentration of 0.5 % of DMDM hydantoin (CIR, 1988).

Benzylhemiformal is not expected to cause irritation at concentrations up to 0.2 % (SCCNFP, 1999).

Imidazolidinyl urea has proved to be non-irritating up to 20 % in an aqueous solution when applied to the eye of rabbits. When applied as a fine powder, it produced mild transient conjunctival irritation reversible within a few days (CIR, 1990a).

A solution of diazolidinyl urea at 30 % in propylene glycol induced minor conjunctival irritation to the eye of rabbits, reversible within a few days (CIR, 1990b). It was not found to be irritating when tested as a 5 % solution in another rabbit study (CIR, 1990b).

In a low volume eye test (LVET) in rabbits, formaldehyde caused severe irritation after instillation of 10 μL as a 37 % solution. Reported effects were irritation of the cornea, conjunctivae and iris, along with erosion, denudation and oedema to the corneal and conjunctival epithelium (NICNAS, 2006).

Sensitisation

Respiratory Sensitisation

No data are available on the pure chemicals, but formaldehyde is not classified as a respiratory sensitiser, nor is it likely to be volatile from the low concentration solutions present in products containing these preservatives.

Skin Sensitisation

The chemicals quaternium 15 (CAS No. 51229-78-8), imidazolidinyl urea and diazolidinyl urea are classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in HSIS (Safe Work Australia).

The other chemicals are not classified, but due to the presence of formaldehyde, which is a strong skin sensitiser in solutions of these chemicals (NICNAS, 2006), these should also be taken to be skin sensitisers. The available data from animal studies and human data (see **Observations in humans**) support this classification.

In a dermal sensitisation study on guinea pigs, quaternium 15 (CAS No. 51229-78-8) was not found to be sensitising (EPA, 1995). However, a mouse ear swelling study showed that it was a potent sensitiser with positive responses in at least 60 % of animals tested, and that there was sufficient evidence to consider quaternium 15 (CAS No. 51229-78-8) as a sensitiser (NICNAS, 2005).

Imidazolidinyl urea proved to be a strong sensitiser in a guinea pig maximisation test (GPMT), causing sensitisation in 80 % of Dunkin-Hartley guinea pigs tested (NICNAS, 2005). In a local lymph node assay (LLNA) on CBA/Ca mice, imidazolidinyl urea induced a positive response (greater than three-fold increase in thymidine incorporation) at 25 and 50 % in dimethylformamide (NICNAS, 2005).

Diazolidinyl urea was found to be positive in a modified Magnusson-Kligman maximisation test in Dunkin-Hartley guinea pigs, in which 30 % of the animals tested were sensitised at a concentration of 50 % (CIR, 1990b; NICNAS, 2005).

Observation in humans

DMDM hydantoin has shown in a human patch test the potential to cause mild sensitisation at a dose of 1 % (CIR, 1988) in a small number of subjects.

Human results from a patch test have shown that 14/88 patients tested with imidazolidinyl urea or diazolidinyl urea in a dry form (preventing formaldehyde release) were sensitised, suggesting that both chemicals could be skin sensitisers independently of formaldehyde release. However, it is stated that 'formaldehyde release is likely the primary mode of sensitisation' (NICNAS, 2005).

Repeated Dose Toxicity

Oral

Based on the lack of systemic toxicity of formaldehyde in oral studies (NICNAS, 2006), the chemicals are not expected to be harmful due to formaldehyde release from repeated oral exposure to products containing these preservatives. The available data on some of these chemicals support this conclusion.

In a 90-day feeding study on rats, quaternium 15 (CAS No. 4080-31-3) was administered to groups of rats (n = 10 per sex/group) at 0, 7.5, 15, 30 or 60 mg/kg/day. Reported treatment-related effects were significant decreases in mean body weight in all the treated males and females throughout the study, and in mean food consumption in the treated males, especially at the beginning of the study (females were not as frequently affected as males), and an increase in the incidence of

minimal hepatocellular swelling in the 60 mg/kg/day group males. The EPA (1995) states that 'the major effect of decreased food intake on body weight does indicate that the chemical had a toxic effect on body weight that cannot be accounted for solely by decreased food consumption' (EPA, 1995).

In another 90-day study, quaternium 15 (CAS No. 4080-31-3) was administered in gelatin capsules to beagle dogs (n = 4 per sex/group) at 0, 7.5, 15 or 30 mg/kg/day. Reported toxic effects were significant decreases in haematocrit, haemoglobin and white blood count measurements in the 30 mg/kg/day group males; and histopathological changes, especially in the liver, in the 30 mg/kg/day group males and females including 'obliterative vasculitis and perivasculitis of the hepatic blood vessels; perivascular and pericholangiolar infiltration of mononuclear cells; and hyperplasia of the reticuloendothelial cells lining the hepatic sinusoid' (EPA, 1995).

The administration of a 55 % solution of DMDM hydantoin to SD rats (n = 30 per sex/dose) at 0, 100 200 or 400 mg/kg/day for 13 weeks did not induce any significant toxic effects (CIR, 1988).

In a 90-day feeding study, weanling albino rats exposed to 0, 6, 28, 130, and 600 mg/kg bw/day of imidazolidinyl urea exhibited no signs of toxicity (CIR, 1990a).

A similar negative result was obtained with diazolidinyl urea in a 90-day study on SD rats fed with 10, 25 or 100 mg/kg/day (CIR, 1990b).

Dermal

Based on the available data for some of the chemicals, they are not expected to be harmful after repeated exposure. Formaldehyde has not shown any evidence of systemic toxicity (NICNAS, 2006).

In a 13-week study, New Zealand White rabbits were given daily dermal applications of quaternium 15 (CAS No. 4080-31-3) at 0, 50, 200, or 1000 mg/kg/day. It is reported that 'the only treatment related effect was a dose-dependent increase in ulcerative dermatitis, at the treatment site. This was correlated with the abrasions from clipping. The no observed effect level (NOEL) for systemic toxicity was 1000 mg/kg/day' (EPA, 1995).

A subchronic study on DMDM hydantoin has shown that daily application of 8 or 800 mg/kg of a 55 % solution to the skin of New Zealand White rabbits for four weeks did not induce any pharmacological or toxicological effects (CIR, 1988).

In a chronic study, the dose of 1.2 mg/kg/day of a 55 % solution applied to the skin of New Zealand White rabbits for 90 days did not induce any toxic effects apart from severe dermal irritation (CIR, 1988).

Imidazolidinyl urea did not induce any toxic effects on albino rabbits exposed to 20, 45, 90, and 200 mg/kg/day of undiluted material for three weeks (CIR, 1990a).

Female SD rats exposed to 3140 mg/kg/day of a cosmetic product containing 0.2 % of diazolidinyl urea (~6 mg/kg) for 13 weeks did not exhibit any systemic toxicity (CIR, 1990b).

Inhalation

No data are available on the chemicals. Based on the lack of systemic toxicity of formaldehyde in inhalation studies (NICNAS, 2006) and the low volatility of formaldehyde from the dilute aqueous solutions, the chemicals are not expected to be harmful due to formaldehyde release from repeated inhalation exposure to products containing these preservatives.

Genotoxicity

Genotoxicity concerns arise from the presence of formaldehyde in products containing these preservatives. While some in vivo studies showed positive results for genotoxicity, formaldehyde was not classified as mutagenic in the Priority Existing Chemical (PEC) assessment report (NICNAS, 2006).

Quaternium 15 (CAS No. 4080-31-3) was found to be mutagenic in the in vitro Chinese hamster ovary cell HGPRT forward mutation assay with metabolic activation only, and negative in the rat hepatocyte unscheduled DNA synthesis assay and in the mouse micronucleus test (EPA, 1995). No more details of the studies are available.

The CIR report (1988) explains about DMDM hydantoin that 'because of similar mutagenic potencies and the observation of positive results in the same bacterial strain, it is probable that the mutagenic activity of the product is attributable to formaldehyde release' (CIR, 1988).

Diazolidinyl urea was found non-mutagenic in two Ames tests and a micronucleus assay in vivo in CD1 mice (CIR, 1990b).

Carcinogenicity

While formaldehyde is classified as hazardous (Category 2 carcinogenic substance) with the risk phrase ‘May cause cancer by inhalation’ (T; R49) in HSIS (Safe Work Australia), this applies to inhaled formaldehyde, at high concentrations (NICNAS, 2006). Formaldehyde is not likely to be volatile from the low concentration solutions present in products containing these preservatives. Therefore, there are no carcinogenicity concerns relating to these chemicals in such products. During formulation of the products, formaldehyde gas could be present.

Reproductive and Developmental Toxicity

Given that formaldehyde is not considered to be a reproductive or developmental toxin (NICNAS, 2006), most of the chemicals including imidazolidinyl urea, diazolidinyl urea, sodium hydroxymethyl glycinate and benzylhemiformal are not expected to be toxic for reproduction or development. The available data on DMDM hydantoin, dimethyl oxazolidine and imidazolidinyl urea support this conclusion.

However, quaternium 15 (CAS No. 51229-78-8) is classified as hazardous (Category 3 substance toxic to reproduction) with the risk phrase 'Possible risk of harm to the unborn child' (T; R63) in HSIS (Safe Work Australia) and the available data support this classification for both quaternium 15 isomeric forms.

Teratogenicity studies on New Zealand White rabbits showed that the oral administration of a 55 % solution of DMDM hydantoin at 150, 375 or 750 mg/kg/day or dermal applications of 0.6, 1.2 or 2.4 mg/kg/day did not induce any teratogenic effects (CIR, 1988).

Imidazolidinyl urea showed slight foetotoxic effects but no teratogenic effects in albino mice in a teratogenicity study testing 300 mg/kg (CIR, 1990a).

In a dermal developmental toxicity study on Fischer 344 rats, quaternium 15 (CAS No. 4080-31-3) as a 50 % aqueous solution was applied to the dorsal skin on gestation days (GD) 6–15 at 0, 250, or 500 mg/kg/day. No significant adverse effects were found despite the high doses used (EPA, 1995). By the oral route, quaternium 15 (CAS No. 4080-31-3 and CAS No. 51229-78-8) was found teratogenic in Fischer 344 (F344) rats at doses of 25 and 75 mg/kg bw/day and toxic to dams at 75 mg/kg bw/day. Reported teratogenic effects were embryonic malformations (mostly eye anomalies), increased foetal resorption and decreased foetus weights (CIR, 2010).

Risk Characterisation

Critical Health Effects

In general, the critical health hazards relate to the formation of formaldehyde. In cosmetic products containing these chemicals as preservatives, the critical health hazard is skin sensitisation. Quaternium 15 (CAS No. 4080-31-3 and CAS No. 51229-78-8) is also a teratogen.

For formulation workers, health hazards can arise from the presence of formaldehyde gas (NICNAS, 2006); the individual preservative chemicals can also be skin and/or eye irritants.

Public Risk Characterisation

Consumers using these products are at risk of formaldehyde sensitisation unless the concentrations are restricted so that the free formaldehyde present in solution meets the SUSMP limit.

Although use in cosmetic/domestic products in Australia is not known, the chemicals are reported to be used in cosmetic/domestic products overseas with a maximum authorised concentration of free formaldehyde of 0.2 % (SCCNFP, 2002).

Occupational Risk Characterisation

Where these chemicals are handled in a pure or highly concentrated form during formulation, formaldehyde gas could be present and pose unreasonable risks to workers unless adequate control measures to minimise inhalation exposure to the chemicals are implemented. The chemicals should be appropriately classified and labelled and the appropriate risk management measures for formaldehyde (NICNAS, 2006) should be applied in these cases.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemicals in cosmetics and/or domestic products be managed through changes to poisons scheduling, and risks for workplace health and safety be managed through changes to classification and labelling.

The assessment of the chemicals is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

As formaldehyde in cosmetic products is controlled under the SUSMP, and these controls apply to formaldehyde present in cosmetics for any reason, the chemicals are already subject to controls. However, the clarity of this link should be improved.

It is recommended that an amendment to the current listing of formaldehyde in the SUSMP be considered to include the chemicals in the index to the SUSMP with a cross reference to formaldehyde.

Work Health and Safety

The chemicals are recommended for classification and labelling under the current approved criteria and adopted GHS as in the table below. This assessment does not consider classification of physical hazards and environmental hazards.

In addition, quaternium 15 (CAS No. 51229-78-8) is classified as hazardous (Category 3 substance toxic to reproduction) with the risk phrase 'Possible risk of harm to the unborn child' (T; R63) in HSIS (Safe Work Australia). Both isomeric forms of quaternium 15 (including CAS No. 4080-31-3) are recommended to have this hazard classification.

Also, it is recommended that the classification of quaternium 15 (CAS No. 51229-78-8) be amended by removing the risk phrase 'Harmful if swallowed' (Xn; R22) and including the risk phrase 'Harmful if in contact with skin' (Xn; R21) for both isomeric forms of quaternium 15 (CAS No. 51229-78-8 and 4080-31-3).

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Irritating to eyes (Xi; R36) Irritating to skin (Xi; R38)	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing these chemicals should be used according to label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from ocular, dermal and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals— Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemicals has not been undertaken as part of this assessment.

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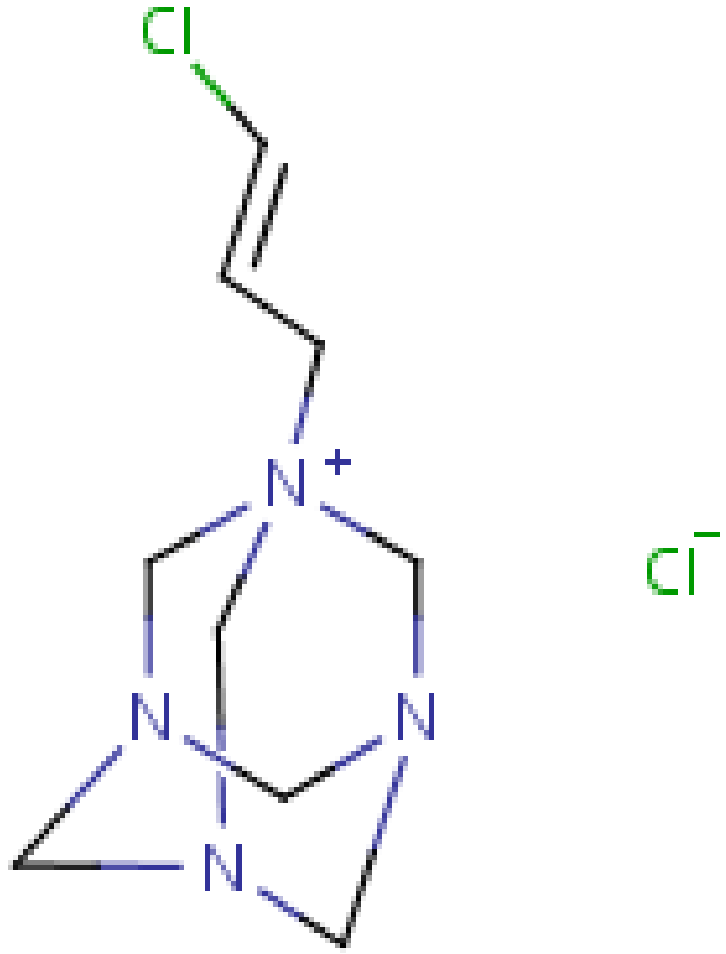
Last Update 04 July 2014

Chemical Identities

Chemical Name in the Inventory and Synonyms	**3,5,7-Triaza-1-azoniatricyclo[3.3.1.13,7]decane, 1-(3-chloro-2-propenyl)-, chloride** 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride hexamethylenetetramine chloroallyl chloride N-(3-Chloroallyl)hexaminium chloride quaternium 15 methenamine 3-chloroallylochloride
CAS Number	4080-31-3
Structural Formula	

	
Molecular Formula	C9H16ClN4.Cl
Molecular Weight	251.159

Chemical Name in the Inventory and Synonyms	**2,4-Imidazolidinedione, 1,3-bis(hydroxymethyl)-5,5-dimethyl-** 1,3-di(hydroxymethyl)-5,5-dimethylhydantoin DMDM hydantoin 1,3-dimethylol-5,5-dimethyl-hydantoin dimethylol-5,5-dimethylhydantoin 1,3-bis(hydroxymethyl)-5,5-dimethyl-2,4-imidazolidinedione
CAS Number	6440-58-0
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	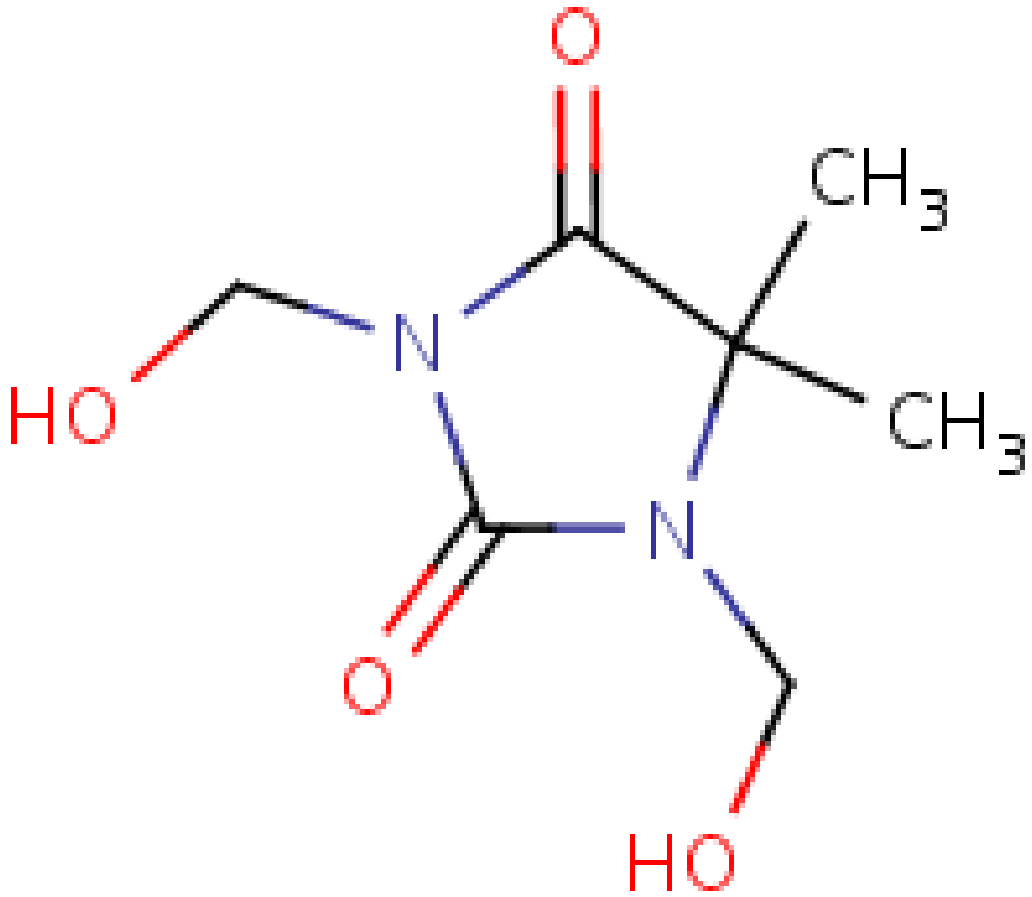
Molecular Formula	C7H12N2O4
Molecular Weight	188.18

Chemical Name in the Inventory and Synonyms	**Methanol, (phenylmethoxy)-** benzyl hemiformal (phenylmethoxy)methanol (benzyloxy)methanol
CAS Number	14548-60-8
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	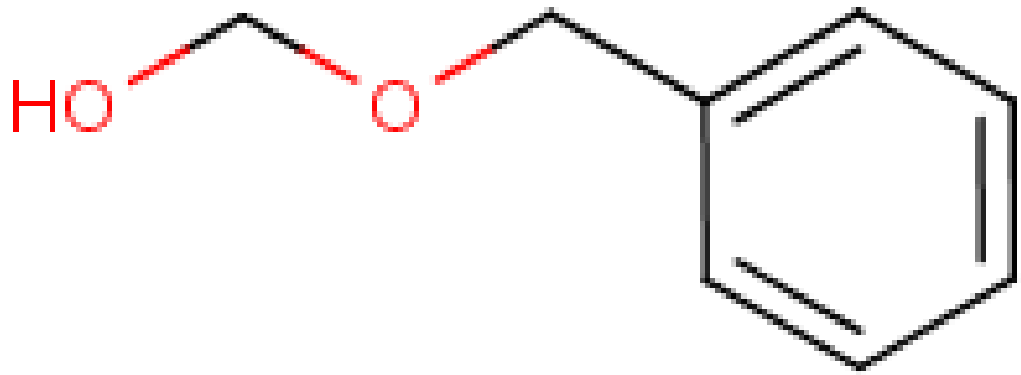
Molecular Formula	C8H10O2
Molecular Weight	138.165

Chemical Name in the Inventory and Synonyms	**Urea, N,N''-methylenebis[N'-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-** imidazolidinyl urea 1,1'-methylenebis(3-(3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl)urea imidurea methanebis(N,N'-(5-ureido-2,4-diketotetrahydroimidazole)-N,N-dimethylol) N,N''-methylenebis(N'-(3-(hydroxymethyl)-2,5-dioxo-4-imidazolidin- yl)urea
CAS Number	39236-46-9
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	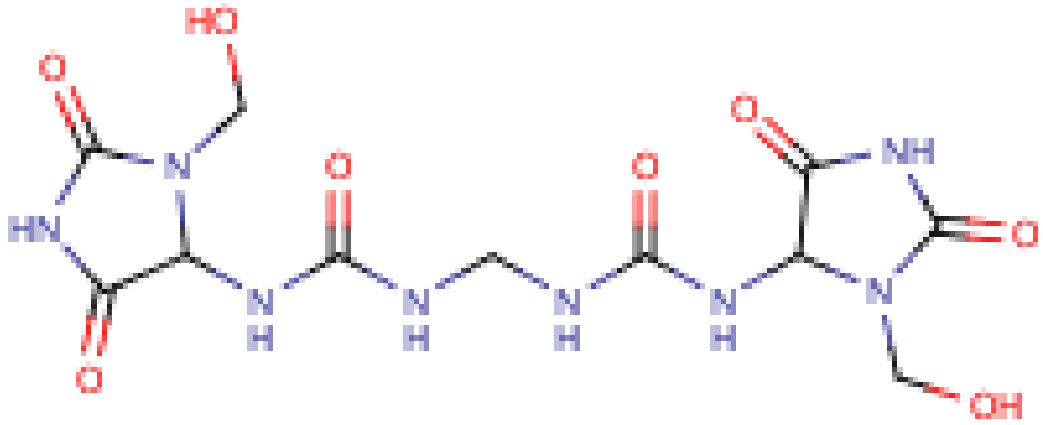
Molecular Formula	C11H16N8O8
Molecular Weight	388.295

Chemical Name in the Inventory and Synonyms	**3,5,7-Triaza-1-azoniatricyclo[3.3.1.13,7]decane, 1-(3-chloro-2-propenyl)-, chloride, (Z)-** 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride, cis- chloroallyl methenamine chloride cis-1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride hexamethylenetetramine cis-chloroallyl chloride quaternium 15
CAS Number	51229-78-8
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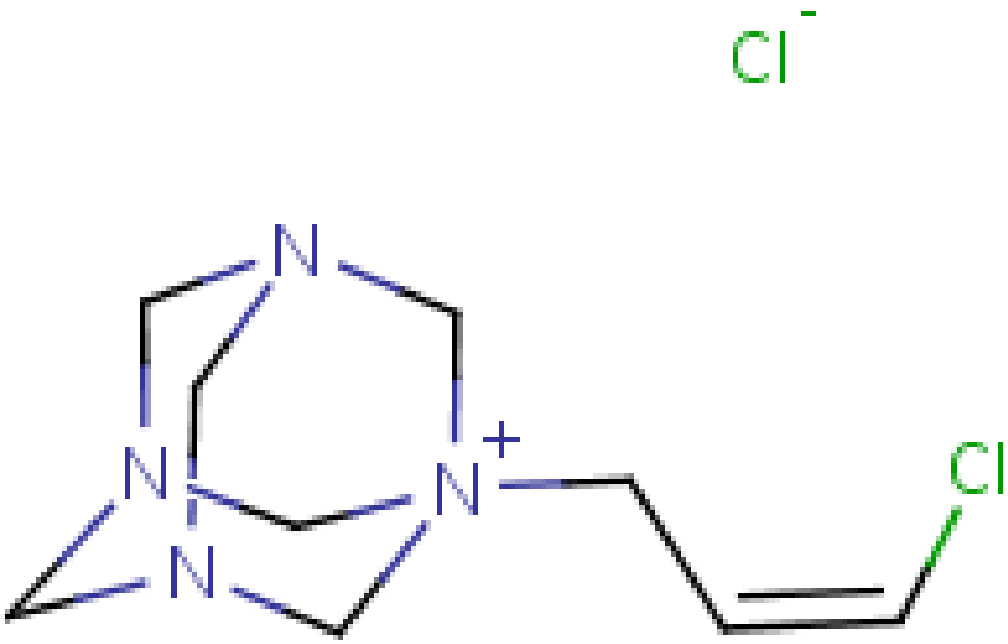
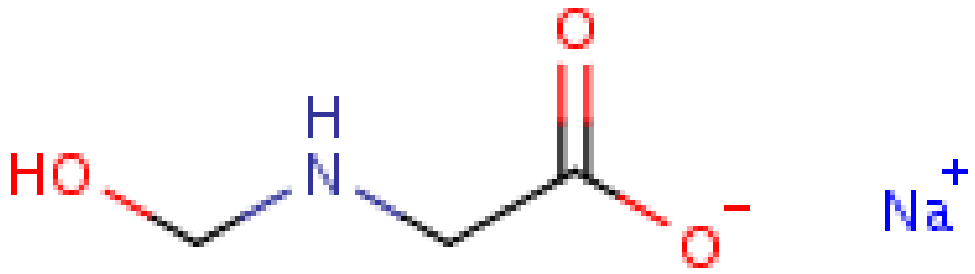
	
Molecular Formula	C9H16ClN4.Cl
Molecular Weight	251.159

Chemical Name in the Inventory and Synonyms	**Glycine, N-(hydroxymethyl)-, monosodium salt** N-carboxymethyl-N-hydroxymethylamine, sodium salt sodium hydroxymethylglycinate hydroxymethylaminoacetic acid, sodium salt sodium N-(hydroxymethyl)glycinate suttocide A
CAS Number	70161-44-3
Structural Formula	

	
Molecular Formula	C3H7NO3.Na
Molecular Weight	127.074

Chemical Name in the Inventory and Synonyms	**Urea, N-[1,3-bis(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-N,N'-bis(hydroxymethyl)-** 1-(1,3-bis(hydroxymethyl)-2,5-dioxoimidazolidin-4-yl)-1,3-bis(hydroxymethyl)urea N-(1,3-bis(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl)-N,N'-bis(hydroxymethyl)urea N-(hydroxymethyl)-N-(1,3-dihydroxymethyl-2,5-dioxo-4-imidazolidinyl)-N'-(hydroxymethyl)urea diazolidinyl urea diazolidinylurea
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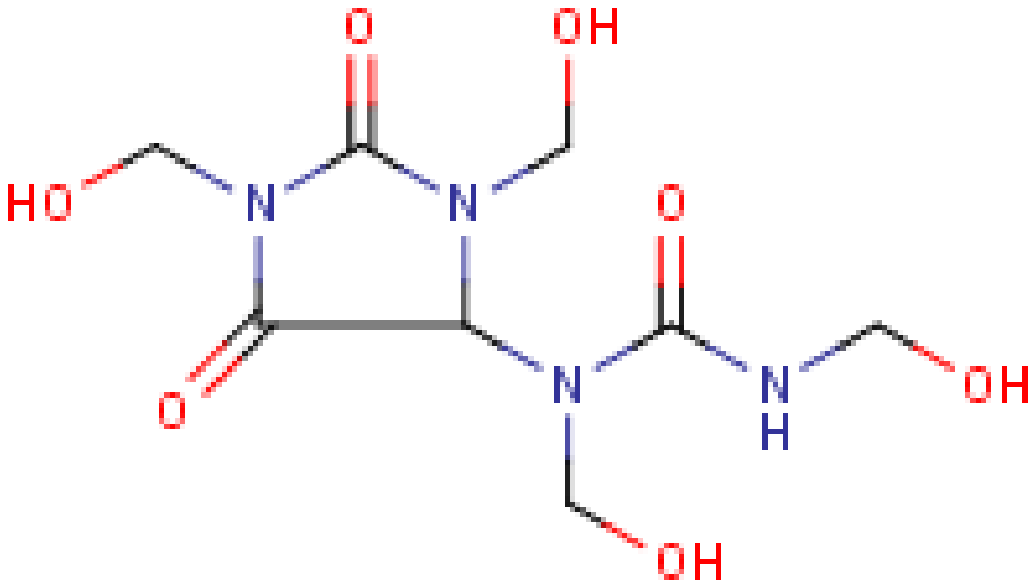
Structural Formula	

	
Molecular Formula	C8H14N4O7
Molecular Weight	278.22

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