SCIENTIFIC LITERATURE REVIEW

DM Hydantoin

May 9, 2007

All interested persons are provided 60 days from the above date to comment on this Scientific Literature Review and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. F. Alan Andersen. This literature review was prepared by Lillian Becker, Scientific Analyst/Writer.

Cosmetic Ingredient Review
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INTRODUCTION

DM Hydantoin (CAS No. 77-71-4; EINECS No. 201-051-3) is a substituted heterocyclic amide infrequently used in cosmetics. It was selected for review because of structure/activity alerts for developmental toxicity and mutagenesis/carcinogenesis.

When further reacted with formaldehyde, DM Hydantoin forms DMDM Hydantoin, a dimethylol dimethyl hetercyclic amide used in cosmetics as a preservative. The Cosmetic Ingredient Review Expert Panel reviewed data relevant to the safety of DMDM Hydantoin (Elder 1988) and concluded that DMDM Hydantoin is a formaldehyde releaser that was safe for use in cosmetics, because, at use concentrations, users of products would not be exposed to levels of formaldehyde greater than 0.2%, a level considered safe.

This scientific literature review presents data relevant to the safety of DM Hydantoin.

CHEMISTRY

DEFINITION AND STRUCTURE

According to the *International Cosmetic Ingredient and Handbook* (Gottschalck and McEwen 2006) DM Hyadantoin (CAS no. 77-71-4) is also know as 5,5-Dimethyl Hydantoin; 5,5-Dimethyl-2,4-Imidazolidinedione; and 2,4-Imidazolidinedione, 5,5-Dimethyl-. Chemical Land 21 (2007) also gives 5,5-Dimethylhydantoin; Dimethylhydantoin; 5,5-Dimethylimidazolidine-2,4-dione; and DMH as synonyms. also . Lonza, Inc./Lonza Ltd. markets a trade name DM Hydantoin called Dantoin DMH (Gottschalck and McEwen 2006).

The structure of DM Hydantoin is shown in Figure 1.

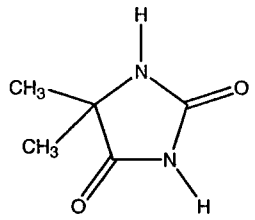

Figure 1. DM Hydantoin (Gottschalck and McEwen 2006)

PHYSICAL AND CHEMICAL PROPERTIES

In the *Kirk-Othermer Encyclopedia of Chemical Technology*, Dantoin DMH is described as a white,

crystalline, odorless solid that is readily soluble in water, ethanol, diethyl ether, and ethyl acetate; moderately soluble in isopropanol, acetone, and methyl ethyl ketone; and insoluble in hydrocarbons and trichloroethylene (Kirk 1977). Chem Land 21 (2007) stated that DM Hydantoin is slightly soluble in water and also provided molecular weight and melting point data. The available physical and chemical properties are provided in Table 1. *Hawley's Condensed Chemical Dictionary* entry for DM Hydantoin stated that it is a white crystalline solid with a melting point of 178°C and that it is soluble in water, alcohol, and ether (Lewis 1997).

Table 1. Physical and chemical properties of DM Hydantoin/Dantoin DMH .

Property	Value	Reference
Molecular Weight	128.13	Chem Land21 2007
Melting point	178-182.5°C	Kirk 1977
	178-182.5°C	Hawley 1981
	175 - 178° C (decomposes)	Chem Land21 2007
pK_a at 23.7°C	9.19	Kirk 1977
pH, 10% aqueous solution	4.5-5.5	Kirk 1977
Solubility in water, wt %		
at 10°C	11.5	Kirk 1977
at 20°C	13.5	Kirk 1977
at 30°C	16.9	Kirk 1977

Pavlovich and Luthy (1988) reported that DM Hydantoin will complex heavy metals. The stability constants found by potentiometric titrations are given in Table 2 and by specific ion electrode data and nonlinear parameter optimization in Table 3. Using polarography, the stability constants for DM Hydantoin and cadmium with the ionic strength = 0.5 mol/l with $NaNO_3$ at 25°C are $\beta_1 = 2.86 \times 10^{3} \pm 0.38$ (absolute standard deviation); $\beta_2 = 2.53 \times 10^{5} \pm 0.28$; and $\beta_3 = 1.89 \times 10^{6} \pm 0.27$.

METHODS OF MANUFACTURE

Henze and Speer (1942) and Ayabe et al. (1985) described the synthesis of DM Hydantoin by the Bucherer-Bergs synthesis, which is the reaction of aldehydes and ketones with potassium cyanide (2 moles) and ammonium carbonate (4 moles) in 50% aqueous alcohol at 60 - 70°C. Cohen (1957) stated that DM Hydantoin is synthesized commercially by the reaction of acetone, sodium cyanide, and ammonium

carbonate. Lewis (1997) stated that DM Hydantoin's derivation is from either acetone, urea, and ammonium carbonate or acetone, potassium cyanate, and hydrocyanic acid.

Table 2. Stability constants for metals and DM Hydantoin as determined by potentiometric titrations with the ionic strength = .05 mol/l with $NaNO_3$ at 25°C (Pavlovich and Luthy 1988).

Metal	β_1	± Absolute standard deviation	β_2	± Absolute standard deviation	β_3	± Absolute standard deviation
Ag(I)	3.37×10^4	0.51	3.05×10^9	0.23	-	-
Cd(II)	1.43×10^3	0.01	1.48×10^5	0.05	1.31×10^6	0.12
Co(II)	2.60×10^2	0.04	-	-	-	-
Ni(II)	1.11×10^3	0.02	8.62×10^4	0.78	1.50×10^6	0.19
Cu(II)	2.04×10^4	0.07	1.60×10^8	0.15	1.19×10^{11}	0.43
Zn(II)	3.00×10^2	0.22	6.54×10^5	0.57	1.53×10^8	0.26

Table 3. Stability constants for DM Hydantoin-metal complexes as determined by specific ion electrode data and nonlinear parameter optimization (Pavlovich and Luthy 1988).

Metal	β_1	β_2	Variance
Ag(I)	8.71×10^5	1.70×10^9	6.0
Cd(II)	2.29×10^3	2.19×10^5	0.3
Ca(II)	6.61×10^1	-	27

ANALYTICAL METHODS

Reio (1960) used paper-chromatographic separation to identify hydantoin.

Ammann and Lynch (1964) employed the mercuric acetate-diphenylcarbazone spray test to detect hydantoin.

Rhodes and Thornton (1972) found that DM Hydantoin may cause a false positive for barbiturates with the Dille-Koppanyi test but not the Zwikker and multiple microcrystalline tests.

Lau et al. (1973) used gas-liquid chromatography and thin-layer chromatography to assess the amount of an herbicide that breaks down to a compound referred to as 5,5-dimethylhydantoin. However, it was unclear as to whether is was truly DM Hydantoin because the diagram of "DM Hydantoin" included -Cl_3CSCl attached to one of the -CH_3 branches.

IMPURITIES

Chemical LAND21 (2007) states that the purity of its DM Hydantoin is a minimum of 99.0%.

USE

COSMETIC

The function of DM Hydantoin is not reported in the *International Cosmetic Ingredient Dictionary and Handbook* (2006). Lonza, Inc. (2007) describes dimethyl hydantoin as a versatile base molecule which can be derivatized and used for a number of functions such as: biocides, lubricants, coalescing agents, emulsifier, and emollients. For example, de Groot et al. (1988) stated that the cosmetics preservative, DMDM Hydantoin, is formed by the combination of DM Hydantoin and formaldehyde.

DM Hydantoin is used in one "other" skin care product according to data provided by industry to the Food and Drug Administration's (FDA) Voluntary Cosmetic Registration Program (FDA 2006). As noted in the left column in Table 1, there are a total of 915 "other" skin care products reported to FDA, one of which contained DM Hydantoin. The concentration of use is currently unknown, but a survey of current use concentrations will be conducted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) and those data will be added to Table 1 when available.

Table 4. Current cosmetic product uses and concentrations for DM Hydantoin.

Product Category (Total number of products in each category (FDA, 2002))	Ingredient uses in each product category (FDA 2006)	Use concentrations (CTFA 2007) (%)
Noncoloring hair care products		
Shampoos (884)	-	0.6
Tonics, dressings, etc. (598)	-	0.6
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (775)	-	0.3
Body and hand creams, lotions, powders, and sprays (840)	-	0.2
Paste masks/mud packs (271)	-	0.3
Other (725)	1	-
Total uses/ranges for DM Hydantoin	1	0.2-0.6

NON-COSMETIC

DM Hydantoin is used as an intermediate for other hydantoin derivatives such as dibromo dimethyl hydantoin, monomethylol dimethyl hydantoin, and dimethyl hydantoin formaldehyde resin (Cohen 1957; Kirk-Othermer 1977).

Bundgaard and Johansen (1980,1981) investigated the use of DM Hydantion as a pro-drug and

found that it rapidly cleaved to formaldehyde and the parent compounds at neutral pH and 37°C, thus filling the requirements for acting as pro-drugs of the parent drug substances.

DM Hydantoin is used in the processing of pulp and paper products (Sweeny 2006).

DM Hydantoin and its derivatives are used in the preparation of textile softeners, lubricants, resins, and agrochemicals. They have bacteriostatic and bactericidal capabilities that are useful preservatives against bacteria and fungi. They also have antibacterial, antifungal, antiprotozoal, and anthelmintic activity. DM Hydantoin and its derivatives are used in the manufacture of pharmaceuticals, especially anticonvulsant drugs such as phenytoin, ethotoin, and methyphenytoin (Chemical LAND21 2007).

GENERAL BIOLOGY

CENTRAL NERVOUS SYSTEM EFFECTS

The Condensed Chemical Dictionary entry for DM Hydantoin stated that it is a central nervous system depressant, but no published studies were found to support that statement (Hawley 1981) .

ANIMAL TOXICOLOGY

No animal toxicology studies were found.

GENOTOXICITY

No genotoxicity studies were found.

CARCINOGENICITY

Griswold et al. (1968) examined the carcinogenic effects of DM Hydantoin in young female Sprague-Dawley rats that are sensitive to chemical carcinogens. The rats (n = 20) were orally administered ten doses of 300 mg DM Hydantoin dissolved in sesame oil (3,000 mg total) at 3-d intervals starting at 45 d of age. Controls were the vehicle (n = 132) and 7,12-dimethylbenz[a]anthracene (n = 40). The rats were weighed and examined weekly. Abnormalities, particularly masses in the breast region, were noted. After 9 months, the rats were killed and necropsied. There was no mortality during the experimental period. One rat in the treatment group had a fibroma at necropsy; no other mammary lesions were observed. The positive control group had 29 rats with mammary lesions (75 carcinoma, 10 fibroadenoma, and 47 hyperplasia). The

negative control group had 5 rats with mammary lesions (3 carcinoma, 1 fibroadenoma, and 5 hyperplasia).

In a second experiment, the authors compared the effects of a single dose and multiple doses of DM Hydantoin. The rats were administered either a single dose of 150 mg at 50 to 55 d of age or a total of 10 doses of 100 mg every 3 d at 40 to 70 d of age (n = 20). The rats were killed and necropsied after 6 months (single dose) or 9 months (multiple doses) and the incidences of mammary carcinomas, fibroademomas, or adenomas were determined. In both dose protocols, one rat was found to have a tumor. Using sesame oil control, there were no tumors in the single dose group (n = 89) and 2 tumors in the multiple dose group (n = 132; Griswold et al. 1968).

CLINICAL ASSESSMENT OF SAFETY

de Groot et al. (1988) patch tested 35 patients allergic to formaldehyde with DM Hydantoin at 1.0%, 3.0%, and 10.0% (w/w). The time frame of exposure and readings were not given. There were no reactions observed to DM Hydantoin.

SUMMARY

DM Hydantoin is a substituted heterocyclic amide infrequently used in cosmetics. One trade name version, called Dantoin DMH is marketed to the cosmetics industry. Dantoin DMH is a white, crystalline, odorless solid that is soluble in water, ethanol, diethyl ether, and ethyl acetate; moderately soluble in some organic solvents; but insoluble in others. DM Hydantoin will complex heavy metals. DM Hydantoin is synthesized commercially by the reaction of acetone, sodium cyanide, and ammonium carbonate. As supplied, the purity of its DM Hydantoin is a minimum of 99.0%.

The company that makes Dantoin DMH describes it as a versatile base molecule which can be derivatized and used for a number of functions such as: biocides, lubricants, coalescing agents, emulsifier, and emollients. DM Hydantoin is used in one "other" skin care product.

DM Hydantoin is used: as an intermediate for other hydantoin derivatives; in the processing of pulp and paper products; and its derivatives are used in the preparation of textile softeners, lubricants, resins, and agrichemicals.

Hawley's Condensed Chemical Dictionary entry for DM Hydantoin stated that it is a central nervous system depressant, but no published studies were found to support that statement. No animal toxicology

studies were found.

No genotoxicity studies were found, but one carcinogenicity study was conducted using rats. Dosing regimens included repeated oral administration (10x) of 300 mg of DM Hydantoin at 3-day intervals, beginning at day 45; single dose of 150 mg around day 50; and repeated doses (10x) of 100 mg at 3-day intervals, beginning on day 40. No differences between control and treated animals were reported.

Individuals allergic to formaldehyde patch-tested with DM Hydantoin exhibited no sensitization reactions.

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