

Final Report on the Safety Assessment of Dibutyl Adipate¹

Abstract: The diester Dibutyl Adipate functions as a plasticizer and skin-conditioning agent in cosmetic formulations, although it is reportedly used in only one such product. Only limited safety test data were available to the Cosmetic Ingredient Review Expert Panel. The oral median lethal dose in rats was 2 g/kg for a 20% suspension of Dibutyl Adipate. Subchronic dermal exposure of rabbits to 1.0 ml/kg/day caused a reduction in weight gain, which was not seen at 0.5 ml/kg/day. Undiluted Dibutyl Adipate caused mild to moderate skin irritation in rabbits, but it was minimally irritating to the eyes. The fetuses of pregnant rats given intraperitoneal injections of 1.748 ml/kg on days 5, 10, and 15 of gestation showed significant increases in the incidence of gross abnormalities. No effect was seen at lower exposures. The following additional safety test data are needed: (1) the typical concentration at which this ingredient is used, (2) the types of products in which it is found, (3) impurities that may be present in Dibutyl Adipate in cosmetic formulations, (4) ultraviolet radiation absorption data (if there is significant UV absorption, photosensitization data may be needed), and (5) two genotoxicity studies, one using a mammalian system. If these latter studies are positive, a dermal carcinogenesis study using the methods of the National Toxicology Program may be needed. In the absence of this further information, the available data are insufficient to support the safety of Dibutyl Adipate in cosmetics. **Key Words:** Dibutyl Adipate—Cosmetic use—Skin irritation—Safety test data.

Dibutyl Adipate is the diester of butyl alcohol and adipic acid. This report reviews the safety data available on this ingredient.

CHEMISTRY

Definition and Structure

Dibutyl Adipate (CAS NO. 105-99-7) is the diester of butyl alcohol and adipic acid that conforms to the formula shown in Fig. 1. Other names for this ingredient are hexanedioic acid, dibutyl ester, adipic acid dibutyl ester, dibutyl adipinate, and dibutyl hexandioate (Nikitakis et al., 1991; Registry of Toxic Effects of Chemical Substances, 1992) Commercial names for Dibutyl Adipate are Cetiol B and Unitolate B (Nikitakis et al., 1991).

¹Reviewed by the Cosmetic Ingredient Review Expert Panel.

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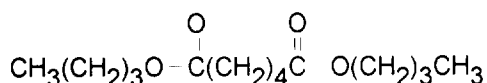


FIG. 1. Chemical formula for Dibutyl Adipate.

Chemical and Physical Properties

Dibutyl Adipate has a molecular weight of 258.36, a boiling point of 165°C, and a melting point of -32.4°C (Weast, 1982). It has a density of 0.962 g/cm³ (Aldrich, 1992) and is soluble in alcohol and ethanol (Weast, 1982). The flash point for Dibutyl Adipate is >230°F (Aldrich Chemical Company, 1992).

USE

Cosmetic

Dibutyl Adipate functions as a plasticizer and skin-conditioning agent in cosmetic formulations (Nikitakis, 1988). The product formulation data submitted to the Food and Drug Administration (FDA) in 1994 reported that it was used in one formulation classified under the category "Other Fragrance Preparations" (FDA, 1994). The concentrations at which Dibutyl Adipate is used are unknown because concentration-of-use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992).

Noncosmetic

Dibutyl Adipate is approved for use as a plasticizer in the manufacture of food packaging materials (Food Chemical News, Inc., 1990).

GENERAL BIOLOGY

Cytotoxicity

Dibutyl Adipate was tested for cytotoxicity in the Metabolic Inhibition Test. A dilution series of Dibutyl Adipate was suspended in HeLa cells. After 24 h, cell viability was determined by microscopy. Viability was also measured after 7 days by looking at the color change of phenol red in the medium. Dibutyl Adipate had no acute toxicity to the cells, which the investigators attributed to its insolubility in water (Ekwall et al., 1982).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Smyth et al. (1951) reported that the oral median lethal dose (LD₅₀) of a 20% dispersion of Dibutyl Adipate in a study with rats was 12.9 g/kg. In another study, the LD₅₀ was 11.26 g/kg for a 20% dispersion of Dibutyl Adipate in 1% Tergitol 7. At greater doses, the authors reported that rats became prostrate and narcotized within 4 h. Death occurred within 24 h, and the liver, kidneys, and gastrointestinal

tract were found to be congested at necropsy (Mellon Institute of Industrial Research, 1950).

Dermal

The dermal LD₅₀ of Dibutyl Adipate (96%) for rabbits was 20 ml/kg (Smyth et al., 1951).

Inhalation

A group of six male albino rats was exposed to a flowing stream of air substantially saturated with Dibutyl Adipate for 8 h. No deaths occurred during exposure (Smyth et al., 1951).

Intraperitoneal

The intraperitoneal LD₅₀ of Dibutyl Adipate (96%) for rats was 5.2441 ml/kg (Singh et al., 1973).

Subchronic Dermal Toxicity

Groups of 10 rabbits were given topical applications of 0.5 and 1.0 ml/kg/day of a 20% dispersion in Tergitol 7 of Dibutyl Adipate five times a week for 6 weeks. A control group of animals was untreated. The rabbits were weighed weekly, and necropsy was performed either at the time of interim death or when the animals were killed at the termination of the study. Five of the rabbits from the 1.0 ml/kg/day group and one rabbit from the 0.5 ml/kg/day group died from causes unrelated to treatment. A significant decrease in body weight gain was observed in the rabbits of the 1.0 ml/kg/day treatment group compared with the control animals. Rabbits in the 0.5 ml/kg/day group also gained less weight, but the reduction was not significantly different from the control group. At necropsy, one of the rabbits from the 1.0 ml/kg/day group that survived the treatment period had slight cloudy hepatic swelling and slight cloudy swelling of the renal convoluted and loop tubules. One rabbit from the 0.5 ml/kg/day group had similar renal lesions (Mellon Institute of Industrial Research, 1951).

In another study, four dogs were soaked with 2 ml/kg of an emulsion containing 6.25% Dibutyl Adipate in water (containing 0.625% of Emulsifier 75 H 14S) twice a week for a total of 28 applications during a 3-month testing period. The retained dosage was estimated as 1 ml/kg of the emulsion. A control group of two dogs was treated with the vehicle emulsifier. No statistically significant changes in body weight were observed during the study. Slight desquamation was found on the skin of three treated dogs and one of the control dogs, but there was no erythema (Mellon Institute of Industrial Research, 1951).

Dermal Irritation

Undiluted Dibutyl Adipate (0.01 ml) was applied to the clipped bellies of albino rabbits (number of animals not stated), and the sites were evaluated after 24 h.

Dibutyl Adipate was given a primary skin irritation score of 2 (maximum possible score: 8) (Smyth et al., 1951). In another study, 0.01 ml undiluted Dibutyl Adipate was applied to the clipped skin of five albino rabbits eight times during a 4-h period. All of the rabbits had moderate erythema at 24 h (Mellon Institute of Industrial Research, 1951). In a 3-day repeated application test, three rabbits were treated with 0.025 ml undiluted Dibutyl Adipate on intact and abraded sites of their abdomens. Applications were made three times a day at 3-h intervals. Erythema and/or capillary injection were observed in all three of the rabbits during the study. Three days following the last application, all of the rabbits had desquamation (Mellon Institute of Industrial Research, 1951).

One-half-square-foot cloth bands impregnated with 1.0 g/sq ft Dibutyl Adipate were placed around the clipped trunks of three rabbits. The bands were kept in contact with skin for 3-day intervals for 3 weeks. Two of the rabbits had moderate erythema on their flanks after the first 3-day interval, but no signs of irritation were observed after 3 weeks of treatment (Mellon Institute of Industrial Research, 1950). In a similar study, bands impregnated with 2.0, 4.0, and 8.0 g/sq ft Dibutyl Adipate were applied to the clipped trunks of groups of five rabbits. New bands were applied to the rabbits twice a week for a total of six applications during the 21-day testing period. No treatment-related progressive damage to the skin was observed (Mellon Institute of Industrial Research, 1951).

Ocular Irritation

Undiluted Dibutyl Adipate was instilled into the conjunctival sac of rabbits (number not specified) for 24 h. The primary irritation score was 1 (maximum possible score: 110) (Smyth et al., 1951).

Reproductive and Developmental Toxicity

In a study by Singh et al. (1973), groups of five pregnant female Sprague-Dawley rats were given intraperitoneal injections of Dibutyl Adipate (96%) in doses of 0.1748, 0.5244, 1.0488, and 1.7480 ml/kg on days 5, 10, and 15 of gestation. Three other groups of pregnant females were injected with distilled water, normal saline, and cottonseed oil. The data obtained from these animals were pooled to determine a 95% confidence interval for an injected volume control. Another group of females was "blunt needle injected" (i.e., a needle was inserted, but no substance was actually injected). On day 20 of gestation the females were killed, and the uterine horns, ovaries, and fetuses were examined.

The number of corpora lutea was comparable between the experimental and control groups. Resorptions occurred in all of the groups, ranging from 2.9 to 9.4% in the test groups and 3.7 to 12.3% in the pooled-volume control group. The rate was 6% in the blunt-needle group. Dead fetuses were found only in the experimental groups; one fetus from the 1.0488 ml/kg Dibutyl Adipate dose group and two fetuses from the 1.7480 ml/kg treatment group died. In general, the body weights of the fetuses were lower than those of the control groups, but they were not significantly different. No gross, skeletal, or visceral anomalies were found in the 0.1748 ml/kg Dibutyl Adipate group. Gross abnormalities were found in the

higher-dose groups, but the incidence was increased significantly only in the group receiving 1.7480 ml/kg (5.4%) compared with both control values (0% for the blunt-needle group and 0.7–3.1% for the pooled-volume control). The types of abnormalities were not specified. However, this study investigated the effects of a number of other adipic acid esters, and the authors stated that the most common gross abnormalities observed among these esters were hemangiomas on various parts of the fetus, twisted hind legs, and compact head and neck. No visceral anomalies were found among the control groups, but one anomaly each was found in test groups treated with 0.5244 and 1.7480 ml/kg Dibutyl Adipate. Two skeletal malformations (6.7%) were found in the 1.7480 ml/kg Dibutyl Adipate group, and one (3%) occurred in the blunt-needle group. The 95% confidence interval for these types of anomalies in the pooled-volume control group ranged from 1.0 to 12.6% (Singh et al., 1973).

SUMMARY

Dibutyl Adipate is the diester of butyl alcohol and adipic acid, which is used as a plasticizer and skin-conditioning agent in cosmetic formulations. The oral LD₅₀ for a 20% dispersion of Dibutyl Adipate is 12.9 g/kg for rats, and the dermal LD₅₀ for undiluted Dibutyl Adipate is 20 ml/kg for rabbits. In a subchronic dermal toxicity study, 1.0 ml/kg/day Dibutyl Adipate caused a significant reduction in body weight gain in rabbits. A dose of 0.5 ml/kg/day Dibutyl Adipate was without effect. In a study with dogs, no adverse effects were observed from an emulsion containing 6.25% Dibutyl Adipate when it was applied to the entire body twice a week for 3 months. When undiluted Dibutyl Adipate was tested for dermal irritation using rabbits, it received a primary irritation score of 2, of a maximum possible score of 8. Undiluted Dibutyl Adipate caused moderate erythema in rabbits following repeated exposure. However, material impregnated with Dibutyl Adipate was not irritating to the skin of rabbits. Dibutyl Adipate was minimally irritating to the eyes of rabbits. In a developmental study in which pregnant female mice were intraperitoneally injected with Dibutyl Adipate, a significant increase in fetal gross abnormalities was observed only with the largest dose tested.

DISCUSSION

Section 1, paragraph (p), of the Cosmetic Ingredient Review (CIR) Procedures states that "a lack of information about an ingredient shall not be enough to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the Procedures, the Expert Panel informed the public of its decision that the data on Dibutyl Adipate are insufficient to determine whether Dibutyl Adipate, under each relevant condition of use, is either safe or unsafe. The Expert Panel released a "Notice of Insufficient Data Announcement" on November 30, 1993, outlining the data needed to assess the safety of Dibutyl Adipate. The types of data required included:

- (1) Types of cosmetic products in which Dibutyl Adipate is used and the typical concentrations of use in each of these products;

- (2) Impurities;
- (3) UV absorption data and, if absorbed in the UVA or UVB range, possibly photosensitization data; and
- (4) Two genotoxicity assays (one using a mammalian system) and, if positive, possibly a dermal carcinogenicity assay by National Toxicology Program standards.

No offer to supply the data was received. In accordance with Section 45 of the CIR Procedures, the Expert Panel issues a Final Report—Insufficient Data. When the requested new data are available, the Expert Panel will reconsider the Final Report in accordance with Section 46 of the CIR Procedures, Amendment of a Final Report.

CONCLUSION

The CIR Expert Panel concludes that the available data are insufficient to support the safety of Dibutyl Adipate as used in cosmetics.

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