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Final Report on the Safety Assessment of Aldioxa

ABSTRACT

Aldioxa is a heterocyclic organic compound used in cosmetic products as an astringent and skin conditioning agent. The oral LD50 for mice exceeds 23 mg/kg, and 8 g/kg for rats. All of the toxicologic parameters investigated in a 94-day subchronic feeding study in rats were similar in the test and the control group. No significant macroscopic adverse results were obtained in a three generation study in which rats were fed diets containing 10% Aldioxa. A suspension containing 25% Aldioxa was not a sensitizer when applied to the shaved backs of 3 male guinea pigs, nor when 10 animals were given intradermal injections of a 2% Aldioxa suspension on alternating days for a total of 10 applications and challenged after a 10-day nontreatment period. A hydrophilic unguent containing 4% Aldioxa was neither an irritant nor a sensitizer when evaluated on 200 human volunteers. The safety of Aldioxa has not been completely documented and substantiated. It cannot be concluded that this ingredient is safe for use in cosmetic products until the appropriate needed safety data cited in the report have been obtained and evaluated.

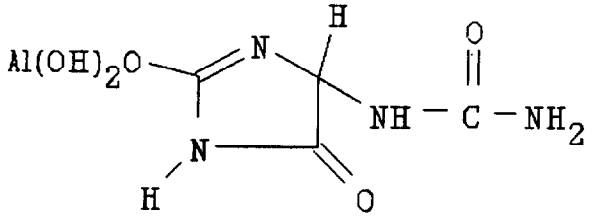
INTRODUCTION

ALDIOXA IS A HETEROCYCLIC organic compound used as a cosmetic astringent and skin conditioning agent. It is an over-the-counter drug ingredient listed as a skin protectant. The Food and Drug Administration (FDA) has ruled Aldioxa as having category III status: the available data are insufficient to establish Aldioxa's safety or efficacy (FDA, 1990). However, this evaluation covers only the drug use of this ingredient and does not apply to its use in cosmetic products (Federal Register, 1983). The following report is a review of Aldioxa as a cosmetic ingredient.

CHEMISTRY

Definition and Structure

Aldioxa (CAS No. 5579-81-7) is a heterocyclic organic compound that conforms generally to the formula (Estrin et al., 1982):



Other names for Aldioxa are Aluminum Dihydroxy Allantoinate; Aluminum, [(2,5-Dioxo-4-Imidazolidinyl) Ureato]Dihydroxy-; and [(2,5-Dioxo-4-Imidazolidinyl) Ureato]Dihydroxyaluminum (Estrin et al., 1982).

Properties

Aldioxa is a white powder that has the following specifications (RONA, 1992): Assay (gravimetric Al_2O_3): 17–27%; Assay (from N, allantoin): 50–60%; Water: 6–12%; Infrared (IR) spectrum conforms to STD; pH (4% suspension): 6.0–8.0.

Aldioxa is insoluble in polar and nonpolar solvents. It was reported that Aldioxa does not absorb in the ultraviolet (UV) range (RONA, 1992).

Method of Manufacture

Aldioxa is formed by the association of allantoin (the H on C_2 is weakly acidic) and aluminum hydroxide (weak base). It is prepared either as a wet slurry or dry blend of these compounds (RONA, 1992).

USE

Cosmetic

United States

Aldioxa is used as a cosmetic astringent and skin conditioning agent (Nikitakis, 1988).

The product formulation data submitted to the FDA in 1992 reported that Aldioxa was used in 42 product formulations (Table 1). Aldioxa is used in eyeliners, eye shadows, mascaras, face powders, and makeup foundations (FDA, 1992). Concentration of use values are no longer reported to the FDA. However, the Cosmetic Ingredient Review was informed by the cosmetic industry that Aldioxa is not used at concentrations over 1% in formulations (RONA, 1992). Additionally, product formulation data submitted to the FDA in 1984 stated that Aldioxa was used at concentrations up to 1% in eyeliners, eye shadow, mascara, and face powders, and up to 0.1% in makeup foundations (FDA, 1984).

TABLE 1. PRODUCT FORMULATION DATA FOR ALDIOXA*

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
Eyeliner	253	6
Eye shadow	512	5
Mascara	247	16
Face powders	313	12
Makeup foundations	398	3
1992 totals		**42**

*CIR requests that the cosmetic industry provide current formulation data on each product category.

Source: FDA, 1992.

International

Aldioxa is approved for use in cosmetic products in Japan (Nikko Chemicals Co., Ltd., 1992).

Noncosmetic Use

Aldioxa has been used in the treatment of diaper rash (Federal Register, 1990). It presently has category III status as an over-the-counter drug ingredient, which means that the FDA found the available data on Aldioxa to be insufficient to establish its safety or efficacy (FDA, 1990).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral Studies

Groups of 10 Swiss Albino mice were administered 5, 10, 15, and 23 mg/kg of an aqueous suspension of Aldioxa via an oral feeding needle. No deaths occurred during the 2-week observation period, and no changes in clinical behavior, feed consumption, or excretion occurred (Meixell and Mecca, 1966).

In another study, groups of 12 Wistar rats were orally administered 1, 2, 4, and 8 g/kg of Aldioxa. No deaths occurred during the 10-day observation period (RONA, 1992).

Intraperitoneal Studies

Intraperitoneal toxicity studies were conducted with Swiss mice and Wistar rats. Groups of six female mice were injected intraperitoneally with 0.5, 1, 2, and 4 g/kg of Aldioxa, and groups of 12 male rats were injected with 1, 2, and 4 g/kg of Aldioxa. All of the rats survived the 3-day observation period, but 1 mouse in the 4 g/kg dose group died (RONA, 1992).

Subchronic Oral Toxicity

Groups of 10 white Wistar consanguineous rats were given feed containing 2.5, 5, and 10% Aldioxa for 94 days. A control group of animals was fed the diet alone. Body weight gain was monitored regularly, and a complete hematological examination was conducted after 50 days. At the end of the study, half of the rats were necropsied and microscopic examinations were performed on the major organs and glands. No deaths occurred during the study and all of the toxicologic parameters investigated were similar to those of the control group (RONA, 1992).

Chronic Toxicity

Four groups of consanguineous rats were fed diets containing 0, 2.5, 5, and 10% Aldioxa for 117 days. After this period, the rats were paired and allowed to mate. The resulting offspring were weaned to the treated feed at the age of 21 days. A third generation of rats was obtained from this group using the same methods. Thus, the first generation was exposed to Aldioxa for a total of 311 days, the second generation for 167 days, and the third generation for 94 days. A representative group of first-generation rats was necropsied after 213 days, and the others after 311 days. Similarly second-generation rats were killed on either day 67 or 167. All of the third-generation rats were killed on day 94. No deaths occurred during the study, and there were no significant effects either on growth, feed consumption, blood characteristics, or reproduction. No macroscopic alterations were found in the major organs examined (RONA, 1992).

Dermal Irritation and Sensitization

A suspension containing 25% Aldioxa in 5% Dupanol was applied to the shaved backs of three male guinea pigs. The suspension was rubbed for 1 min on a 4-inch square area of skin on alternating days for 8 days, for a total of 4 applications. In order to rule out effects of the vehicle, 5% Dupanol was applied under similar conditions in preliminary studies. One week following the last application, a challenge application was given. The test animals appeared normal throughout the experiment, and there was no evidence of immediate or delayed hypersensitivity (Mecca, 1959; Meixell and Mecca, 1966).

Negative results were also obtained when a diaper cream containing 0.75% Aldioxa was tested using the same methods (Mecca, 1959; Meixell and Mecca, 1966).

Ten guinea pigs were given intradermal injections (0.1 cc) of a 2% Aldioxa suspension on alternating days for a total of 10 applications. After a 10-day nontreatment period, a final injection was administered. There was no evidence of primary irritation or sensitization (Mecca, 1963).

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

Two-hundred women had 4% Aldioxa in a hydrophilic unguent applied under occlusive patches to their backs for 48 h. A challenge application was made after a 14-day nontreatment period. None of the women had any signs of irritation during the study (Mecca, 1963).

A modified Draize technique of repeated insult predictive patch testing was used to determine the dermal irritation and sensitization potential of a perfumed body powder containing 0.2% Aldioxa. Patches containing this formulation were applied to the backs of 194 subjects for 48 h. The sites were scored at the time of patch removal, and before the next application 1–2 h later. A total of 10 applications were made following this sequence. A challenge application was made after a 2-week nontreatment period and a second challenge was administered 1 week after the first challenge. No signs of primary irritation, skin fatiguing, or sensitization were observed (Orentreich Research Corporation, 1985a).

An eye makeup formulation containing 0.4% Aldioxa was tested on 600 subjects using the same testing procedures. No evidence of irritation was observed at any time during the study (Orentreich Research Corporation, 1985b).

SUMMARY

Aldioxa is a heterocyclic organic compound used as an astringent and skin conditioning agent in cosmetic formulations. It did not appear to be toxic in acute, subchronic, and chronic studies, and both animal and clinical studies indicate that it is neither a skin irritant nor sensitizer.

DISCUSSION

Section 1, paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be sufficient 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 Aldioxa were not sufficient for determining whether the ingredient, under relevant conditions of use, was either safe or unsafe. The Panel released a Notice of Insufficient Data on February 12, 1992, outlining the data needed to assess the safety of Aldioxa. Data on the concentration of use and human irritation and sensitization data were received in response to the Panel's request. However, the following data were not submitted and are required to make a safety assessment: (1) Chemistry (UV spectral analysis, impurities, and method of manufacture); (2) 28-day dermal toxicity; (3) Ocular irritation (nonanimal studies will be considered); (4) At least two genotoxicity tests; (5) Photosensitization, only if Aldioxa absorbs UV light; and (6) Carcinogenicity, if the genotoxicity tests are positive.

CONCLUSION

The safety of Aldioxa has not been documented and substantiated. The CIR Expert Panel cannot conclude that this ingredient is safe for use in cosmetic products until the appropriate safety data have been obtained and evaluated.

ACKNOWLEDGMENT

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[1]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, N.W., Suite 310, Washington, DC 20036.