Final Report on the Safety Assessment of Pentasodium Pentetate and Pentetic Acid as Used in Cosmetics[1]

Pentasodium Pentetate and Pentetic Acid function as chelating agents in cosmetics. Pentasodium Pentetate is readily soluble in water, but the corresponding free acid is not. Pentasodium Pentetate is used in almost 400 cosmetic products over a wide range of product categories, although it is mostly used in hair dyes and colors at use concentrations of 0.1% to 1.0%. Pentetic Acid is used in 150 cosmetic products, mostly in hair dyes and colors. Chelating agents are used in cosmetics to remove calcium and magnesium cations, which impede foaming and cleansing performance and which can cause a haze in clear liquids. The acute oral LD_{50} of Pentasodium Pentetate in rats was >5 g/kg. The acute dermal LD_{50} of Pentapotassium Pentetate using rats was reported to be >2 g/kg. The intraperitonal LD_{50} of Pentetic Acid was reported to be 585 mg/kg. Short-term studies of the calcium and sodium salts of Pentetic Acid in male mice demonstrated no dose-related toxicity over the dose range of 10, 100, and 250 mg/kg. In a 4-week dermal toxicity study, daily topical application of 0.05% Pentasodium Pentetate to shaved and abraded rabbit skin produced moderate erythema after the first week and throughout the study, but no systemic toxicity. Pentasodium Pentetate or Pentapotassium Pentetate applied to intact albino rabbit skin were not irritating. A 40% solution of Pentapotassium Pentetate was not sensitizing in a guinea pig maximization test. The no observed adverse effect level (NOAEL) for rats given 40% Pentapotassium Pentetate by oral gavage was reported to be 83 mg/kg day^{-1}. Subchronic inhalation evaluation of a bath freshener containing 0.05% or 0.09% Pentasodium Pentetate using albino rats determined that there was no cumulative systemic toxicity attributable to the ingredient at either concentration. The no observed effect level (NOEL) for maternal toxicity in pregnant rats was 400 mg/kg body weight and for fetal toxicity was 100 mg/kg body weight. Another reproductive toxicity study evaluated Pentetic Acid–Zn with and without sodium chloride in pregnant C57/B1 Dougherty mice. No toxicity was found without added sodium chloride. Pentapotassium Pentetate was not mutagenic in an Ames test, with or without metabolic activation. The same material tested in Chinese hamster ovary cells was not clastogenic. Calcium Pentetate at 1.351 μg/ml produced a statistically significant increase in the number of sister-chromatid exchanges. Pentasodium Pentetate is nonirritating to moderately irritating, but not a sensitizer in clinical tests. A human comedogenicity (acne promotion) test using Pentasodium Pentetate found no effect. Although data are lacking on the dermal penetration of these two ingredients, other chelating agents such as EDTA do not penetrate the skin, so it is likely that Pentasodium Pentetate and Pentetic Acid also would not penetrate. The high water solubility of Pentasodium Pentetate and the low water solubility of Pentetic Acid also support that their dermal penetration will be low. Other chelating agents, including EDTA and its salts, have been determined to be safe in the current practices of use in cosmetics. Meta-, Tri-, and Hexametaphosphate salts are chelating agents determined to be safe in the current practices of use in cosmetics. Metasilicate salts were found to be safe as chelating agents in cosmetics when formulated to avoid irritation. Overall, these data were considered sufficient to support the safety of Pentesodium Pentetate and Pentetic Acid as used in cosmetics.

INTRODUCTION

This literature review addresses the safety of the cosmetic ingredients Pentasodium Pentetate (CAS No. 140-01-2) and Pentetic Acid (CAS No. 67-43-6). As described in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), Pentasodium Pentetate and Pentetic Acid function as chelating agents.

Chelating agents have the ability to complex with and inactivate metallic ions in order to prevent their adverse effects on the stability or appearance of cosmetic products. It may be important to complex calcium or magnesium ions, which are incompatible with a variety of cosmetic ingredients. Also, chelation of ions, such as iron or copper, helps retard oxidative deterioration of finished products.

The Cosmetic Ingredient Review (CIR) Expert Panel has reviewed EDTA and its salts, which are structurally similar to Pentasodium Pentetate and are used as chelating agents in cosmetics. The CIR Expert Panel found EDTA and its salts to be safe as used in cosmetic formulations (Andersen 2002). The lowest dose reported to cause a toxic effect in animals was 750 mg/kg/day. EDTA and its salts are cytotoxic and weakly genotoxic, but not carcinogenic. Oral exposures to EDTA produced adverse reproductive and developmental effects in animals.

Clinical tests reported no absorption of an EDTA salt through the skin. EDTA is likely to increase the passage of other chemicals, such as calcium, into the skin. Exposure to EDTA in most cosmetic formulations, therefore, would produce systemic exposure levels well below those found to be toxic in oral dosing studies.

Inhalation exposure to EDTA in cosmetic formulations was evaluated. An exposure assessment done using conservative assumptions predicted that the maximum EDTA dose via

inhalation of an aerosolized cosmetic formulation is below that which has been shown to produce reproductive or developmental toxicity. Because of the potential to increase the penetration of other chemicals, CIR concluded that formulators should be aware of this when combining these materials with ingredients that have been determined to be safe primarily because they were not significantly absorbed.

A safety assessment of three other ingredients, Sodium Hexametaphosphate, Sodium Metaphosphate, and Sodium Trimetaphosphate, whose functions include chelation, was also completed (Andersen 2001). Sodium Hexametaphosphate was reported to be used at concentrations of less than 1% (Sodium Metaphosphate and Sodium Trimetaphosphate were not reported with any uses) and the Expert Panel concluded that they are safe for use in cosmetics when formulated to avoid skin irritation (Andersen 2001). High concentrations of Sodium Hexametaphosphate were demonstrated to be severe irritants, but lower concentrations were, at most, mildly irritating.

In addition, Sodium Metasilicate (used at concentrations ranging from 13% to 18%) was assessed as safe when formulated to avoid irritation in cosmetic formulations (CIR 2001). At high concentrations, Sodium Metasilicate is a severe skin irritant when tested on intact and abraded skin, but other silicate salts were negligible irritants at lower use concentrations.

Data on Pentapotassium Pentetate were available and have been included with the expectation that findings would be similar to the pentasodium salt.

CHEMISTRY

Definition and Structure

Pentasodium Pentetate

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), Pentasodium Pentetate is the pentasodium salt of diethylenetriaminepentaacetic acid, with the formula shown in Figure 1. The structure of Pentasodium Pentetate is similar to the chelating agent EDTA, the structure of which is shown in Figure 2.

Synonyms for Pentasodium Pentetate include

- N,N-Bis[2-[Bis(Carboxymethyl)Amino]-Ethyl]Glycine, Pentasodium Salt;
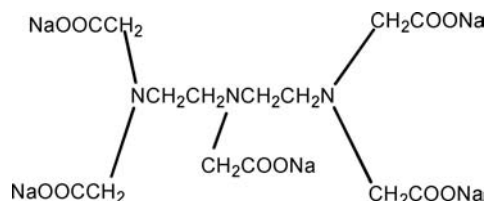- Glycine, N,N-Bis[2-[Bis(Carboxymethyl)-Amino]Ethyl]-, Pentasodium Salt;
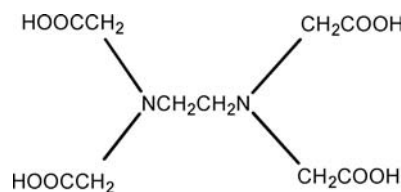

FIGURE 2
EDTA.

- Pentasodium Diethylenetriaminepentaacetate (Pentasodium DTPA); and
- Pentasodium Diethylenetriamine Pentaacetate Solution.

Trade names for Pentasodium Pentetate include AEC Pentasodium Pentetate, Dissolvine D-40, Mayoquest 300, and VERSENEX 80.

Pentetic Acid

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), Pentetic Acid is the substituted amine that conforms to the chemical formula shown in Figure 3.

Synonyms for Pentetic Acid include N,N-Bis[2-[Bis(Carboxymethyl)Amino]-Ethyl]Glycine; Diethylenetriaminepentaacetic Acid (DTPA); Glycine, N,N-Bis[2-[Bis(Carboxymethyl)-Amino]Ethyl]-; and 3,6,9-Triazaundecanedioic Acid, 3,6,9-tris (Carboxymethyl)-. The acronym DTPA is commonly used.

Chemical and Physical Properties

Pentasodium Pentetate

Akzo Nobel Functional Chemicals LLC (2003) stated in a material safety data sheet that Dissolvine D-40 and Dissolvine D-40-L containing 38% Pentasodium DTPA are odorless liquids that have a boiling point of 222.80°F and a freezing point of 5.00°F.

Pentetic Acid

As stated by Lewis (1997), Pentetic Acid is a white, crystalline solid that melts at 230°C and will decompose. The molecular weight of Pentetic Acid is 393.35 Da. It is slightly soluble in cold water and soluble in hot water. Klaassen (1996) stated that the chelating properties of DTPA were similar to that of
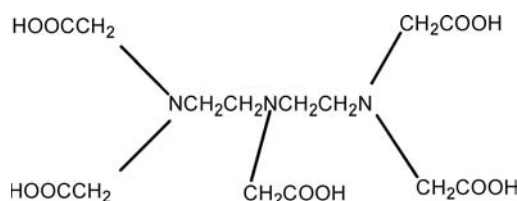

FIGURE 1
Pentasodium Pentetate.

FIGURE 3
Pentetic Acid.

EDTA, in which the calcium salt (CaNa$_2$ DTPA) must be used clinically because of DPTA's high affinity for calcium.

According to the United States Pharmacopeia (USP) National Formulary, Pentetic Acid shall contain not less than 98% Pentetic Acid, leave not more than 0.2% residue on ignition, and contain not more than 0.005% heavy metals (USP 2000).

Methods of Manufacture

The preparation of amino carboxylic acids and their salts from corresponding amino alcohols was described in a patent by Curme, Chitwood, and Clark (1945). This invention is predicated on the discovery that amino alcohols can be subject to alkaline oxidation to produce the alkali metal salt of the corresponding amino carboxylic acid under conditions that do not substantially oxidize the amino groups (Figure 4). Either sodium hydroxide or potassium hydroxide is the alkaline oxidizing agents of choice. One or the other is selected based on solubility in the amino alcohol to be converted.

A reaction vessel containing the amino alcohol (pentaethanol ethylene triamine as shown below) and, for example, sodium hydroxide, is heated to 230°C to 260°C, preferably in conditions that do not introduce any water into the system. This helps protect the amino groups from oxidation, although the amino group in amino alcohols in which each nitrogen is bonded to three carbons is inherently resistant to alkali oxidation.

Over a period of 12 to 24 h, hydrogen gas evolves and pentasodium carboxymethyl ethylene triamine is formed. This salt is readily soluble in water. Subsequent reaction with an excess of strong hydrochloric or sulfuric acid will produce the amino carboxylic acid form, which has low solubility in cold water (Curme et al. 1945).

Analytical Methods

Pentetic Acid

According to Sillanpaa (1997), early methods for the determination of DTPA included spectrophotometry and titrimetry, which lacked sensitivity and specificity. More recently, DTPA has been analyzed in waste and natural waters by chromatographic (liquid chromatography, gas chromatography, capillary electrophoresis) and electrochemical methods. The detection limits are about 1 μg/L.

USE

Cosmetic

Pentasodium Pentetate

As described in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), Pentasodium Pentetate functions as a chelating agent in cosmetic products. Industry reports provided to the Food and Drug Administration (FDA) total 384 uses across a variety of product categories, including non-coloring hair products, hair-coloring products, and bath products, such as soaps and detergents (FDA 2002) as shown in Table 1. Data on current concentration of use gathered in a survey conducted by the Cosmetic, Toiletry, and Fragrance Association (CTFA 2004) indicate that Pentasodium Pentetate is used at concentrations from 0.008% to 3.0%, with the highest concentration in the hair tonic, dressings, etc. category. Several current concentrations of use were reported in product categories for which no uses had earlier been reported to FDA. In addition, no current use data were available in several product categories in which prior uses had been reported.

According to the Japan Ministry of Health, Labor and Welfare (MHLW) Pentasodium Pentetate is not included on
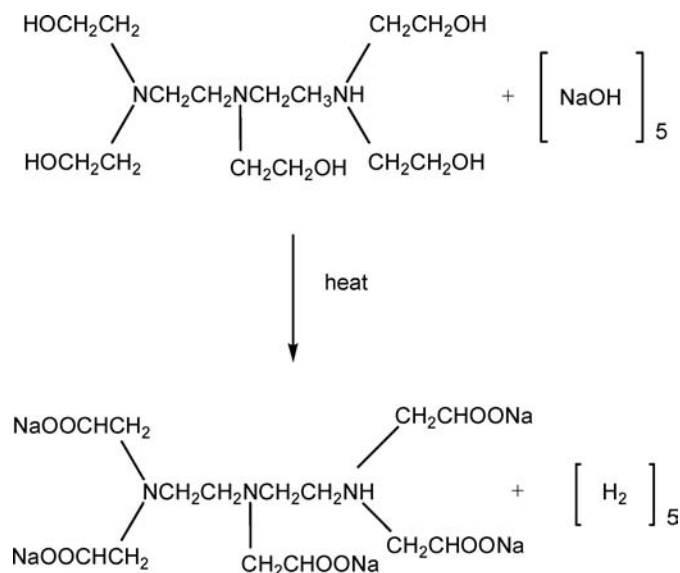

FIGURE 4
Basic reaction to form amino carboxylic acids from amino alcohols.

TABLE 1
Current cosmetic product uses and concentrations for Pentasodium Pentetate and Pentetic Acid.

Product category (total number of products in each category) (FDA 2002)	Ingredient uses in each product category (FDA 2002)	Use concentrations (%) (CTFA 2004)
Pentasodium Pentetate		
Baby products		
Lotions, oils, powders and creams (60)	—	0.06
Other baby products (34)	1	—
Bath products		
Soaps and detergents (421)	53	0.009–1
Other bath products (196)	—	0.02
Fragrance products		
Colognes and toilet waters (684)	9	0.1
Perfumes (235)	—	0.02
Sachets (28)	—	0.02
Other fragrance products (173)	1	0.1
Noncoloring hair care products		
Conditioners (651)	1	0.1–0.2
Sprays/aerosol fixatives (275)	1	—
Straighteners (63)	7	0.008–0.5
Permanent waves (207)	39	0.2–0.5
Tonics, dressings, etc. (598)	5	0.1–3
Wave sets (53)	2	—
Other noncoloring hair care products (277)	2	—
Hair coloring products		
Dyes and colors (1690)	233	0.1
Rinses (20)	—	0.1
Color sprays (5)	1	—
Bleaches (120)	2	—
Other hair coloring products (55)	4	—
Personal hygiene products		
Other personal hygiene products (308)	—	0.01
Shaving products		
Aftershave lotions (231)	8	—
Shaving Cream (134)	—	0.1
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (775)	9	0.06
Body and hand creams, lotions, powders, and sprays (840)	4	—
Skin fresheners (184)	2	—
Total uses/ranges for Pentasodium Pentetate	**384**	**0.008–3**
Pentetic Acid		
Bath products		
Soaps and detergents (421)	—	0.03
Noncoloring hair care products		
Permanent waves (207)	7	—
Shampoos (884)	3	—
Other (277)	1	—
Hair coloring products		
Dyes and colors (1690)	138	—
Rinses (20)	—	0.003
Lighteners with color (5)	1	—
Total uses/ranges for Pentetic Acid	**150**	**0.003–0.03**

the list of ingredients that must not be combined in cosmetic products that are marketed in Japan (MHLW 2001a), or on the list of restricted ingredients for cosmetic products that are marketed in Japan (MHLW 2001b). In addition, Pentasodium Pentetate is not restricted from use in any way under the rules governing cosmetic products in the European Union (European Commission 2002).

Pentetic Acid

Pentetic Acid functions as a chelating agent in cosmetic products (Gottschalck and McEwen 2004). Of the 150 uses reported by industry to FDA (2002), 138 reported uses are in hair dyes and colors (Table 1). No current concentration of use data were provided for the hair dye and color product category, however, an industry survey (CTFA 2004) indicated use in coloring hair rinses at 0.003% and in bath soaps and detergents at 0.03%. No use in this latter category has been reported to FDA.

According to the MHLW, Pentetic Acid is not included on the list of ingredients that must not be combined in cosmetic products that are marketed in Japan (MHLW 2001a), or on the list of restricted ingredients for cosmetic products that are marketed in Japan (MHLW 2001b); nor is its use restricted in the European Union (European Commission 2002).

In a review article, Sillanpaa (1997) stated that there have been no legislative restrictions on the use of DTPA.

General Use of Chelating Agents in Cosmetics

Akzo Nobel Functional Chemicals LLC (2002) reported an overview of literature and patents issued on the use of chelating agents in cosmetics. According to these authors, adding chelating agents to hard water complexes metals like calcium and magnesium and is beneficial for better foaming and cleaning performance. These metal ions also cause a haze in clear liquids, and the chelating agent dissolves the metals, preventing precipitation onto the scales of hair, scalp, and skin. Various patents were described in which chelating agents were said to prevent problems like rancidity of unsaturated oil and fat containing products, discoloration of dyestuffs, or degradation of fragrances (containing aldehydes and ketones). It was suggested that free radical formation can be prevented by adding chelating agents. Other patents were found claiming the prevention of body odor through the application of various chelating agents in deodorant products. The antimicrobial effect is claimed because the growth of microorganisms is inhibited by removal of the metallic co-factor (i.e. iron) by applying chelating agents. In another patent, DTPA and EDTA in a concentration of about 10% were said to be effective in a water-based cream for preventing contact allergic reactions of the skin to metals including cobalt and copper.

Inhalation of Aerosol Cosmetics

Product categories in which Pentasodium Pentetate and Pentetic Acid are being used include potential aerosol applications.

Bower (1999) characterized the typical diameter of anhydrous hair spray particles in the 60 to 80 μm range (typically, <1% are below 10 μm). Pump hair sprays, in contrast, have typical particle diameters of $\geq$80 μm. Johnsen (2004) reported that the mean particle diameter is around 38 μm in a typical aerosol spray. In practice, he stated that aerosols should have at least 99% of particle diameters in the 10 to 110 μm range. For comparison, Jensen and O'Brien (1993) reported a mean aerodynamic diameter of 4.25 $\pm$ 1.5 μm for respirable particles.

Noncosmetic Use

Pentetic Acid

Sillanpaa (1997) reported that some non-cosmetic applications of DTPA include the inactivation of metal ions in the pulp and paper industry and use as a drug in heavy metal poisoning.

Table 2 summarizes studies in which radiolabeled Pentetic Acid was used as a tracer to measure clearance rates.

Table 3 summarizes the many studies that reported the clinical use Pentetic Acid as a chelating agent in treating cases of metal poisoning. The FDA has developed (FDA 2003) and updated (FDA 2004) guidance for industry on submitting a new drug application for Calcium DTPA and Zinc DTPA products used in the treatment of known or suspected internal contamination with plutonium, americium, or curium in two forms: 1 g in a 5-ml aqueous solution for administration by inhalation (with a 1:1 dilution and delivered by nebulization) or intravenous injection. Using these dosing regimens, the FDA concluded that these chelating agents can be found safe and effective for the above use, when produced under specified conditions.

Table 4 summarizes studies in which DTPA is used for diagnosing and/or treating tumors or other disease or in model cellular systems.

GENERAL BIOLOGY

Adsorption

Pentetic Acid

According to Sillanpaa (1997) the adsorption behavior of DTPA and its metal complexes has not received any research attention.

Cytotoxicity

Pentetic Acid

Lucke-Huhle (1976) reported a study that investigated the action of DTPA (Ca-DTPA and Zn-DTPA) on the proliferation of mammalian cells cultured in vitro. Chinese hamster lung cells were incubated until they attained inhibition of growth at approximately 10^6 cells/cm^2 with at least 70% of the cells being in a G$_1$-like phase of the cell cycle. The cells were exposed for different times at various concentrations ranging from 0.1 to 10 mM. A total cell count, survival assay, and

cell cycle analysis were performed on all samples by flow microfluorometry.

A concentration of 0.1 mM Ca-DTPA led to a partial and reversible block in G_1, but higher concentrations brought about a marked G_1 block followed by cell death in the S-phase. Zn-DTPA did not have any effect.

In the case of the cells under non-proliferating conditions, higher doses of Ca-DTPA (≥ 10 mM) are needed to kill the cells; this was also the case for Zn-DTPA (≥ 60 mM). It was stated that the cytotoxicity of Ca-DTPA was caused by interference with the metal requirement of the synthesis of proteins and DNA. It was suggested that the toxic action of both chelating agents

TABLE 2
Uses of ^{99m}Tc-DTPA (Pentetic Acid) as a tracer.

Subjects	Parameters measured	Reference
Animal		
Male Sprague-Dawley rats	Measured changes in lung solute clearance (LSC) in sensitized rats after aerosol challenge with allergen	Sestini et al. 1989
Groups of 8 male ferrets	Measured rate of thoracic clearance of ^{99m}Tc-DTPA after acute exposures to aerosols of $CdCl_2$	Platner and Morrow 1989
Human		
Sarcoidosis patients	Clearance of aerosolized ^{99m}Tc-DTPA and pulmonary function	Dusser et al. 1986
12 males (6 smokers and 6 nonsmokers)	Measured independently the effect of positive pressure and voluntary hyperinflation on the clearance of inhaled ^{99m}Tc-DTPA in smokers and nonsmokers	Nolop et al. 1986
35 patients with respiratory failure	Developed technique for radioaerosol delivery to patients, obtained ventilation images, and measure rate of pulmonary radioaerosol clearance	Jacobs et al. 1987
Patients with AIDS and *Pneumocystis carinii* pneumonia (PCP)	Clearance test to detect lung injury	Mason et al. 1987
11 nonsmoking AIDS patients (9 patients had PCP)	DTPA clearances, gallium scans, and arterial blood gases were compared with those of bronchial alveolar lavage	Picard et al. 1987
7 patients with a history of extrinsic allergic alveolitis	Measured pulmonary clearance of ^{99m}Tc-DTPA to determine whether symptom-free patients with previously diagnosed extrinsic allergic alveolitis had signs of inflammation in the lung	Schmekel et al. 1990
16 children	Measured extracellular fluid volume	Smye et al. 1994
16 healthy subjects	Measured pulmonary clearance of inhaled ^{99m}Tc-DTPA to examine the effects of inhaled iron oxide particles on alveolar epithelial permeability	Lay et al. 2001
Female and male nonsmoking oarsmen	Pulmonary clearance of DTPA	Hanel et al. 2003

TABLE 3
Chelation therapy using Pentetic Acid (DTPA) in metal poisoning cases

Chelating agent	Chelator administration	Results	Reference
Americium			
CaDTPA and ZnDTPA	Intravenous injection of 30 μmol/kg CaDTPA 1 h after exposure followed by administration of 30 μmol/kg ZnDTPA for 64 days through subcutaneous osmotic pumps	Both were effective in dogs	Guilmette and Muggenburg 1988
Cadmium			
DTPA and BAL[a]	50 mg of DTPA and BAL; i.p. 5 days per week for 2 weeks	Injections of DTPA and BAL decreased the amount of cadmium in the total body, and significantly in the liver and kidneys in rats	Cherian 1980
CaNa$_3$DTPA	i.p. administration at dose equal to 1/4 LD$_{50}$ (6.94 mmol/kg)	DTPA was an effective chelator in mice	Cantilena and Klaassen 1981
CaNa$_3$DTPA, with or without vitamin E	0.3 mmol/kg; orally	The chelator plus vitamin E was more effective in reducing levels of Cd in blood, liver, and kidney than vitamin E or the chelator alone in rats	Tandon and Singh 1995
Cobalt			
CaNa$_3$DTPA and EDTA	i.p. administration at dose equal to 1/4 LD$_{50}$ (12.5 mmol/kg)	DPTA and EDTA were effective chelators in mice	Llobet et al. 1986
Curium			
ZnDTPA	ZnDTPA administered as intravenous injections or subcutaneous infusion at either 30 or 120 μmol/kg/d for 64 days	All DTPA treatment methods were effective in dogs	Guilmette and Muggenburg 1992
Lead			
ZnNa$_3$DTPA	i.p. injections of 1 mmol/kg/d for 8 days	The injections caused reductions in lead levels in the kidney and brain in mice	Jones et al. 1994
DTPA	Cultures dosed with 6–24 μmol/L	DTPA increased cellular lead uptake and caused a significant release of lead from preloaded cells, but did not exacerbate lead toxicity in Chinese hamster peritoneal cells	Fischer et al. 1998

TABLE 3
Chelation therapy using Pentetic Acid (DTPA) in metal poisoning cases (*Continued*)

Plutonium

CaDTPA and ZnDTPA	A single injection of CaDTPA (30 μmol/kg), repeated injections of ZnDTPA (30 μmol/kg), or subcutaneous infusion of ZnDTPA 30 or 120 μmol/kg/day) for 64 days	No significant differences in single injection, repeated injection, or subcutaneous infusion efficiency in dogs	Guilmette and Muggenburg 1993
CaDTPA and ZnDTPA	Either weekly injections of 30 μmol/kg CaDTPA or daily injections of 30 μmol/kg ZnDTPA	Weekly treatment in dogs reduced Pu burden significantly, but the daily injection reduced the Pu more, plus prevented continuous deposition of Pu on bone surfaces	Bruenger et al. 1991
CaNa$_3$DTPA	0.25 mmol/kg i.p. and/or intravenous injections	DTPA was not effective in removing plutonium from the liver, although 20% was removed from the skeleton of mice	Guilmette et al. 1979
DTPA, 3,4,3-LIHOPO[b], and 4,4,4-LIHOPO	30 μmol/kg i.p. at 1, 6, and 24 h after contamination	The LIHOPO compounds were effective in rats, but DTPA was less effective	Ramounet-Le Gall et al. 2003

Strontium

CaNa$_3$DTPA	2 equally divided doses at 1/8 LD$_{50}$ (4918 mg/kg); i.p.	DTPA did not significantly enhance urinary elimination of strontium in mice	Colomina et al. 1991
CaNa$_3$DTPA	0.20 ml of 1/4 LD$_{50}$ (4918 mg/kg) in 2 equal doses at 800 and 2000 h; i.p.	DTPA significantly decreased the fecal excretion and urinary elimination of strontium, and increased the concentration of strontium in the blood of mice	Llobet et al. 1992

Uranium

CaNa$_3$DTPA and ZnNa$_3$DTPA	30 μmol/kg in a volume of 100 μl i.p. 2 min and 24 h after contamination	DTPA did not increase the nephrotoxicity induced by uranium in rats	Houpert et al. 2003
CaNa$_3$DTPA	i.p. administration at doses equal to 1/4 LD$_{50}$ (7269 mg/kg); 0, 0.25, 1, 4, and 24 h after contamination	No significant increases in the urinary excretion of uranium after injection in mice	Domingo et al. 1990
DTPA and Tiron[c]	4 i.p. injections of Tiron or DTPA. Doses of DTPA were 250, 500, or 1000 mg/kg	DTPA was less effective than Tiron in protecting against the nephrotoxicity of uranium in rats	Domingo et al. 1997

Zinc

CaNa$_3$DTPA	i.p. administration at doses equal to 1/3 LD$_{50}$ (0.49 mmol/kg); 0, 0.25, 0.5, 2, 12 and 24 h after contamination	Greatest efficacy was observed at 0.50 h after zinc injection in mice; the effectiveness decreased when administered later	Llobet et al. 1989

[a]BAL, for British anti-Lewisite; [b]LIHOPO is a siderophore-analogue chelating agent; [c]Tiron is a bidentate sulphocatechol.

TABLE 4

Diagnostic and/or therapeutic uses of DTPA

Test system	Treatment	Diagnostic/thera-peutic/or both	Results	Reference
Animal				
Nude mice bearing BT-20 human mammary tumors	μAB 323/A3 antibody + dual $^{125}I/^{111}In$-labeled DTPA	Diagnostic	Visualization of tumors was effective 2 h after administration	Khaw et al. 1988
New Zealand rabbits with experimental myocardial infarction	Monoclonal antibodies $+^{111}In$-DTPA-Polylysine (PL)	Diagnostic	There was good accumulation of antibody-polymer conjugates in infarcted areas	Torchilin et al. 1993
Nude mice grafted with LS174T human colorectal carcinoma	IgG or F(ab')$_2$ or (BsF(ab')$_2$)$_2$)+ DTPA derivatives $+^{125}I$ or ^{131}I	Both	The IgG was more effective for delivering radiation dose to the tumor than F(ab')$_2$, and both were moderately selective with respect to normal tissues	Gautherot et al. 1998
Tumor-bearing mice	Tumor necrosis factor (TNF) + DTPA + dextran + Cu^{2+}	Therapeutic	Significantly higher tumor accumulation and longer retention period of TNF. Tumor growth was also supressed	Tabata et al. 1999
IC-12 rat tracheal tumors growing in mice	Linear peptides + DTPA or CHX-A DTPA $+^{213}Bi$	Diagnostic	Only small amounts of peptide accumulated at tumor sites	Kennel et al. 2000
LS-174T tumor cells in mice	AntiCD33 antibody + CHX-DTPA ligands $+^{213}Bi$	Both	Tumor growth reduced as a function of higher radiation exposures from the radioisotope	Brechbiel 2001
Tumor-bearing nude mice	CCK-B receptor ligand + DTPA derivatives of Leu[1] and D-Glu[1]+^{111}In or $^{88/90}Y$	Diagnostic	All labeled CCK-B receptor ligands showed fast and specific uptake in CCK-B receptor–positive tissues, such as stomach and tumor	Behe et al. 2003
Athymic mice bearing EGFR-positive human breast cancer xenografts	^{111}In-DTPA-hEGF (human epidermal growth factor)	Both	Strong antitumor effects against breast cancer xenografts overexpressing EGFR	Chen et al. 2003
Rat AS-30 hepatoma cells found in ascites and in implanted tumor	^{153}Sm-DTPA-bis-biotin and ^{99m}Tc-DTPA-bis-biotin	Diagnostic	High uptake in rat AS-30D hepatoma cells in ascites and in implanted tumor	Correa-Gonzalez et al. 2003
Female BALB/d mice injected with murine lung carcinoma cells	Fab' and F(ab')$_2$ or chTNT-3 + DTPA $+^{111}In$	Diagnostic	^{111}In-labeled Fab' and F(ab')$_2$ conjugates were found to have faster whole body clearance times and better biodistribution profiles compared to parental ^{111}In labeled chTNT-3 in tumor-bearing mice	Khawli et al. 2003
Non–tumor-bearing mice	^{111}In-DTPA–labeled pegylated liposomes	Diagnostic	Administration of pegylated liposomes via the i.p. route may result in direct and systemic targeting of both intraperitoneal and distant disease sites	Syrigos et al. 2003

(Continued on next page)

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TABLE 4
Diagnostic and/or therapeutic uses of DTPA (*Continued*)

Human

Subject	Agent	Type	Result	Reference
Male patient with rectal adenocarcinoma	Monoclonal antibody + ^{111}In-DTPA	Diagnostic	Technique was simple and efficient	Epenetos et al. 1984
Two iron-loaded thalassaemic patients—an 11-year-old boy and a 20-year-old woman	Boy treated with ZnDTPA (1 g/day by 12 h s.c. infusion) for a 5-day period, followed by CaDTPA at the same dose for 2 further periods; woman treated with daily oral zinc sulfate and 2 g CaDTPA as a 24-h s.c. infusion	Therapeutic	Daily infusions in the boy produced symptomatic zinc depletion. ZnDTPA proved ineffective as an iron chelator in both, but zinc balance could be maintained in the woman by combining the use of oral zinc supplements and CaDTPA	Pippard et al. 1986
12 patients with known or suspected colorectal carcinoma	Anti-CEA C110 (antibody) + ^{111}In-DTPA	Diagnostic	Imaging showed accumulation of label in suspected lesions	Hnatowich et al. 1990
22 patients with known or suspected colorectal cancer	Rat IgG2a Mab ICR2 (antibody) + ^{111}In-DTPA	Diagnostic	Successful antibody imaging can be carried out despite high levels of circulating antigen	Davidson et al. 1991
11 patients with colorectal carcinoma tumors	Fab'-Fab monoclonal antibody + ^{111}In-labeled DTPA	Diagnostic	Low background images allowed detection of 12 of 13 lesions, 4 and 24 h after hapten injection	LeDoussal et al. 1993
Patients with small cell lung carcinoma	Monoclonal antibody + In-DTPA + ^{131}I	Therapeutic	Toxicity was mainly hematological; tumor dose was 2.6–32.2 cGy/mCi. 9 patients' carcinomas progressed; 2 partial responses, and 1 stabilization	Vuillez et al. 1999
15 males/7 females; 18 with metastatic colorectal cancer, 2 with adenocarcinoma of the lung, 1 medullary thyroid cancer, and 1 pseudomyxoma peritonei	^{111}In-labeled DTPA-cT84.66 (anti-CEA) ^{90}Y-labeled DTPA-cT84.66	Both	No unexpected toxicities; no major responses; the reduction in tumor size in a subset of patients was encouraging	Wong et al. 2000
Breast cancer cells	^{111}In-DTPA-hEGF	Therapeutic	^{111}In-DTPA-hEGF exhibited potent antiproliferative effects towards breast cancer cells at concentrations much lower than chemotherapeutic agents and equivalent to those produced by several Gy of high dose rate γ-radiation	Chen et al. 2002
One healthy subject and 3 patients with metastatic medullary thyroid carcinoma	CCK-B receptor ligand + DTPA derivatives of Leu^1 and $_DGlu^1$ + ^{111}In or $^{88/90}$Y	Diagnostic	Fast stomach and tumor uptake was observed for both ^{111}In-labeled compounds	Behe et al. 2003
Human breast cancer cell lines	Anti-HER2/neu monclonal antibody + CHX-A'-DTPA + ^{111}InCl$_3$ and ^{90}YCl$_3$	Diagnostic	The radioimmunoconjugates were stable and bind significantly to HER2 overexpressing tumor cell lines	Blend et al. 2003
35 female patients with ovarian malignancy	Folate receptor + ^{111}In-DTPA	Diagnostic	The specificity of ^{111}In-DTPA-folate scintigraphy was 76% and 82% for the masked and unmasked analyses, respectively	Siegel et al. 2003

was due to the damage of the cell membrane as a consequence of the removal of Ca^+ by the formation of bimetallic chelates (Lucke-Huhle 1976).

Michaelis et al. (2004) conducted a study based on the premise that chelating agents exhibit antitumor and antiviral effects by complexing with intracellular ions. They examined the cytotoxic effects of DTPA on neuroblastoma (UKF-NB-3) and breast carcinoma (MCF-7) cells. DTPA was covalently linked to soluble gelatin type B (GelB) molecules, to human serum albumin (HSA) molecules, and to nanoparticles made of GelB and HSA.

The antitumor activity of the DTPA conjugates was comparable to that for the free drug in UKF-NB-3 and MCF-7 cells. The anti-human cytomegalovirus (HCMV) activity of the DTPA conjugates was investigated in HCMV-infected human foreskin fibroblasts (HFFs). Cellular uptake of DTPA-HSA-NP occurred in UKF-NB-3 cells and in HFFs as determined by confocal laser scanning microscopy.

DTPA influenced cell viability in all three cell lines tested. In the two tumor cell lines, including neuroblastoma and breast cancer cells, DTPA was about threefold more cytotoxic than in HFFs. The authors concluded that coupling DTPA to HSA, HSA-NP, GelB, and GelB-NP increases the cytotoxicity and anti-HCMV activity of DTPA by five- to eightfold, by mediation of cellular DTPA uptake (Michaelis et al. 2004).

ANIMAL TOXICOLOGY

Acute Toxicity

Pentasodium Pentetate

Batchelder et al. (1980) reported that Pentasodium Pentetate was used in a static water acute toxicity test with Bluegill fish. VERSENEX 80 (40.2% Pentasodium Pentetate) was added with 2 L of water for mixing along with 8 L of water from Lake Huron. Ten fish were exposed to 5 to 10 different concentrations for 96 h; the exact concentrations were not listed. However, the no observed adverse effect level (NOAEL) of VERSENEX 80 was reported as 750 mg/L, the partial kill value was 1000 mg/L, the 100% kill value was 1350 mg/L, and the LC_{50} was 1115 mg/L.

Acute Oral Toxicity

Pentasodium Pentetate

Akzo Nobel Functional Chemicals LLC (2003) stated in a material safety data sheet that Dissolvine D-40 and Dissolvine D-40-L containing 38% Pentasodium DTPA have a low order of toxicity and are considered to be harmless by ingestion. It was noted without any details that the oral LD_{50} for the pentapotassium salt is greater than 5000 mg/kg in rats.

Pentapotassium DTPA

CTFA (2005) stated in a summary that a 40% concentration of Pentapotassium DTPA (similar compound; CAS No. 7216-95-7) was administered by oral gavage at a single dose of 5000 mg/kg to 10 HC/CFT rats. A 15-day observation period followed the dosing. The LD_{50} was greater than 5000 mg/kg.

Acute Dermal Toxicity

Pentapotassium Pentetate

CTFA (2005) stated that a 40% concentration of Pentapotassium Pentetate was administered topically at a dose of 2000 mg/kg to 10 Sprague-Dawley rats. A 15-day observation period followed dosing. The LD_{50} was greater than 2000 mg/kg. No additional details were provided.

Acute Inhalation Toxicity

Pentasodium Pentetate

Akzo Nobel Functional Chemicals LLC (2003) stated in a material safety data sheet that Dissolvine D-40 and Dissolvine D-40-L containing 38% Pentasodium DTPA do not cause any toxic effects caused by inhalation of fumes, vapors, or mists.

Acute and Short-Term Parenteral Toxicity

Pentetic Acid

Morgan and Smith (1974a) reported acute and short-term studies on $CaNa_3$ DTPA injected intravenously. In the acute study, groups of 10 male C3H mice received injections of $CaNa_3$ DTPA solution (250 mg/ml) in doses of 1.0, 2.5, and 5.0 g/kg body weight. The control group received an injection of 0.9% saline. At time intervals of 1, 2, 4, and 24 h post injection, the mice were killed and samples of kidney, liver, and duodenum were removed for histological examination.

In another acute study, groups of male C3H mice received an intraperitoneal injection of $CaNa_3$ DTPA at doses of 100 and 1000 mg/kg body weight. At 10, 20, and 30 min and 1, 2, and 24 h post injection, the mice were killed and samples of liver and kidney were removed for electron microscopy.

In a short-term study, groups of 10 mice were given intravenous injections of $CaNa_3$ DTPA at doses of 10, 100, and 250 mg/kg body weight. The controls received an injection of 0.9% saline. The injections were administered once daily for 5 days, followed by 2 nontreatment days, for a total of 30 treatment days. At the end of the 30 days, the mice were killed and samples of kidney, liver, and duodenum were removed for histological examination.

In the acute studies, mice receiving $CaNa_3$ DTPA at doses between 1.0 and 5.0 g/kg had glomerular tuft swelling in the kidney. There were no other histological changes in the kidney as determined by light or electron microscopy. In the liver there were definite morphological changes (vacuolization) at higher doses in the acute study. There were no histological changes in the duodenum at any dose for the acute studies. The authors did note that the liver appeared to be more sensitive to acute exposures than the kidney and stated that although there were transient cellular changes after acute exposures in the kidney and liver, the doses tested were well above the doses approved for therapeutic uses.

In the short-term study, there were no histological changes in kidneys. In the liver there were definite morphological changes (vacuolization) at 100 mg/kg in the short-term study. There were no histological changes in the duodenum at any dose. The authors stated that although there were transient cellular changes after short-term exposure in the kidney and liver, the doses tested were well above the doses approved for therapeutic uses (Morgan and Smith 1974a).

Morgan and Smith (1974b) further studied the effect of acute and short-term CaNa$_3$ DTPA exposures at and above the recommended therapeutic doses that could possibly impair hepatic cell function. Two sensitivity indices of hepatic cell function are sulphobromophthalein (BSP) retention and plasma glutamic pyruvic aminotransferase (GPT) concentration. Groups of 10 adult, male C3H mice received CaNa$_3$ DTPA (250 mg/ml) by intraperitoneal injection at doses of 1.0, 10, 100, and 1000 mg/kg body weight. The control group received similar doses of 0.9% saline. There were three different treatment schedules: a single acute injection; one injection daily for 5 days; and one injection daily for 30 days. The tests for hepatic function were carried out 24 h after the final dose.

At all doses of CaNa$_3$ DTPA between 1.0 and 1000 mg/kg, blood concentrations of [^{35}S]BSP did not exceed the control values for the groups that received the chelating agent for one single injection and for the groups receiving the chelating agent once daily for 30 days. There was a slight increase in the blood concentration of [^{35}S]BSP in the group that received an injection daily for 5 days at a dose of 10 mg/kg, but not at any other doses. The authors stated that, because this increase was not observed at any other doses (higher or lower), it was not due to the DTPA ligand. There were no statistically significant increases in plasma GPT concentrations at any dose.

The authors concluded that, because the chelating agent did not cause elevated levels in either test, CaNa$_3$ DTPA does not cause measurable cell injury at the doses used. It was also concluded that the fatty vacuoles previously observed do not adversely affect hepatic cell function (Morgan and Smith 1974b).

Srivastava et al. (1986) reported that female albino rats received a single injection, intraperitoneally, with the following doses of DTPA: 266, 400, 500, 600, 700, and 1000 mg/kg. The LD$_{50}$ was recorded as 587 mg/kg.

Short-Term Parenteral Toxicity
Pentetic Acid

Doolan et al. (1967) noted that the tubular vacuolization produced in the rat (Sprague-Dawley and Long-Evans) by intraperitoneal injection of Ca-DTPA daily for 10 days was not accompanied by significant increases in serum creatinine or urea nitrogen. Also, there was no impairment in renal excretion of the chelating agent or in the ability of slices of the renal cortex to accumulate p-aminohippurate.

Dalvi et al. (1980) reported the in vivo and in vitro effects of certain chelating drugs on rat liver microsomal enzymes. DTPA

was one of the five chelating drugs tested using Sprague-Dawley rats. The rats were divided into seven groups, three rats in each. Five groups received, intraperitoneally, 0.11 mmol/kg of a different chelating agent, and two groups served as controls. The injections were administered daily for 7 consecutive days. At 24 h after the last injection, the animals were killed, the livers excised, and microsomes isolated. In order to examine the in vitro effect of the chelating agents on drug metabolizing enzyme system, an equimolar (1.0 mM) concentration of each chelating agent was incubated with liver microsomes, isolated from phenobarbital-pretreated rats, and the concentration of microsomal cytochrome P450 was determined.

All of the treatment groups (in vivo) had a significant decrease in hepatic microsomal benzphetamine N-demethylase activity. There was no appreciable change in the microsomal cytochrome P450 concentration. In vitro incubation of the chelating agents with liver microsomes isolated from rats caused no significant loss of the hemopoeitin. There was a slight increase in the amount of cytochrome P450 in the incubations containing CaNa$_2$EDTA and DTPA attributed to the antioxidant properties of the compound. The authors concluded that the chelating drugs used in this study do not appear to be biotransformed by liver drug metabolizing enzymes (Dalvi et al. 1980).

Planas-Bohne and Ebel (1975) reported that when Ca-DTPA is administered intraperitoneally in fractions rather than as a single daily injection, the LD$_{50}$ value changes. Adult Heiligenberg female rats received injections (daily dose varied depending on which group) of Ca-DTPA. A different schedule was used for each treatment. The first group (50 rats) received Ca-DTPA in a single injection. The second group (40 rats) received one injection per day for 5 consecutive days. The third group (73 rats) received two injections per day for 5 consecutive days. The fourth group (104 rats) received five injections per day for 5 consecutive days. The LD$_{50}$ of groups 1, 2, 3, and 4 were 6.80, 11.52, 8.93, and 5.15 mmoles/kg, respectively.

Short-Term Dermal Toxicity
Pentasodium Pentetate

In a report submitted by CTFA (1975), 50 New Zealand albino rabbits were used in a 4-week dermal toxicity study to evaluate the dermal irritation potential of a hand and body lotion containing 0.05% Pentasodium Pentetate. There were five groups of 10 rabbits each; one group was the untreated control group and the four test groups each received 1.0 ml/kg of the hand and body lotion.

The hair was clipped off the back of the rabbits and the area was abraded at weekly intervals in four of the animals per group. The test material was applied by gentle inunction to the skin of each rabbit daily, 5 days a week for a total of 20 applications. Daily observations were made for gross signs of dermal irritation and systemic toxicity.

After 24 days of treatment, blood samples were taken from the rabbits and the following parameters were determined:

hematocrit, hemoglobin concentration, erythrocyte count, total and differential white blood cell count, blood urea nitrogen concentration, serum alkaline phosphatase activity, and serum glutamic pyruvic transaminase activity. All animals were killed and the internal organs were examined for any abnormalities. After review of gross necropsy observations, only the liver, kidney, and bone marrow were submitted for histopathology.

The authors stated that there were no adverse trends in body weight data, physical appearance, behavior, or survival for all animals in the study that could be attributed to the hand and body lotion. There were no signs of dermal irritation in the control group. There were signs of slight to moderate erythema in the test groups after the first week of application. Moderate erythema with some wrinkling, cracking, and drying of the skin was noted throughout the rest of the study. The mean hematocrit of male rabbits treated with the hand and body lotion were significantly lower than that of the controls.

At necropsy, there were no findings that could be attributed to the test material. There were no significant changes in organ weights. A focal mononuclear cell infiltration of the liver and kidney appeared sporadically in all groups. The authors interpreted these findings as manifestations of an intracolony subclinical inflammatory process well within the historical frequency. It was concluded that there are no systemic effects attributed to the hand and body lotion containing 0.05% Pentasodium Pentetate at 1.0 ml/kg (CTFA 1975).

Subchronic Oral Toxicity

Pentapotassium DTPA

CTFA (2005) summarized a study in which a 40% concentration of Pentapotassium DTPA was administered by oral gavage to CD rats (25/sex/dose) at doses of 83, 333, or 1330 mg/kg day^{-1} for 28 consecutive days. Four high dose males died; a contracted spleen was found in these animals. Changes in unspecified clinical chemistry parameters were observed in mid and high dose males and females. The NOAEL was 83 mg/kg/day.

Subchronic Inhalation Toxicity

Pentasodium Pentetate

CTFA (1983) reported a safety evaluation of an after bath freshener containing 0.05% Pentasodium Pentetate. Albino rats were exposed for five days per week for 65 days to 21 mg/m^3 of the after bath freshener. The treatment was discharged for 1 second every 5 to 6 min in the inhalation chamber for 4 h. Survival, general appearance and behavior, body weight gain, and skin reactions were closely monitored. Blood and urine samples were obtained from the rats for analysis after 8 and 13 weeks of treatment. At necropsy, organ weights were obtained for all animals and a record made of any gross pathologic observations. Histopathologic evaluation of tissues from all animals was also performed.

Body weight gain, blood and urine data, and organ weight values were all within normal limits. No cumulative systemic toxic effects attributable to the after bath freshener containing 0.05% Pentasodium Pentetate were noted (CTFA 1983).

CTFA (1986) reported a 13-week subchronic inhalation toxicity study that evaluated the effect of an aerosol room freshener containing 0.09% Pentasodium Pentetate in albino rats. Male and female Sprague-Dawley rats were repeatedly exposed by the inhalation route for 5 days per week for 13 consecutive weeks to the aerosol room freshener. The chamber concentration was 100 mg/m^3. The control group was held in a chamber as well, however they were not exposed to a test material. During the exposure period or at the necropsy the following parameters were evaluated: survival, general appearance and behavior, body weight gain, hematology, blood chemistry, urinalysis, and gross and microscopic pathology.

All of the rats survived the study (one rat escaped its cage and was not counted). All rats in both the control and treatment groups were found to have an essentially normal appearance throughout the study.

There were no statistically significant differences between the treatment and control groups on any of the hematology or clinical chemistry parameters, except for the blood urea nitrogen (BUN) values, which were significantly lower than that of the corresponding value for the control group at week 8, but had returned to normal by week 13.

The only statistically significant differences in the urinalysis data was the protein value, which was significantly decreased in the treatment group as compared to control group for weeks 8 and 13. However, these values were within the range normally observed, so the difference was not considered toxicologically significant.

Mottling and/or scattered red foci on all lobes of the lung were detected grossly in the control and treatment groups. A few rats in the treatment and control groups exhibited microscopic changes of the lung and trachea, which the authors stated were not treatment related. It was concluded that the aerosol room freshener containing 0.09% Pentasodium Pentetate did not cause cumulative systemic toxicity (CTFA 1986).

Ocular Irritation

Pentasodium Pentetate

Spielmann et al. (1993) reported on the use of the alternative HET-CAM test on 136 known irritants in place of the Draize eye irritation test. Pentasodium Pentetate was included as a known irritant. The authors stated that of the 36 chemicals that cause irreversible ocular damage and have been classified as a severe irritant, the HET-CAM test correctly classified 15 of them as severe irritants. The authors did not state whether Pentasodium Pentetate ocular toxicity was confirmed by the HET-CAM test.

Akzo Nobel Functional Chemicals LLC (2003) stated in a material safety data sheet that Dissolvine D-40 and Dissolvine D-40-L containing 38% Pentasodium DTPA are not expected

to cause ocular irritation. It was noted that these products do not produce any irritation in rabbit eyes (no further details were provided).

Merrill and Wilt (2003) reported an ocular irritation screening assay using the EpiOcular human cells for Soap-25-0 containing 0.067% Pentasodium Pentetate. Approximately 100 μl of the soap was administered to the assay medium at 10% (w/v). Exposure times of 0.17, 4, 8, and 24 h were tested in duplicate. Duplicate cultures of the positive control, 100 μl of 0.3% Triton[®] X-100, were exposed for 15 and 45 min. Soap-25-0 had an ET$_{50}$ of 2.9 h. The positive control had an ET$_{50}$ of 28.3 min.

CTFA (2005) provided a summary of a Draize test in which a 40% concentration of Pentasodium DTPA was applied to the left eye of six New Zealand white rabbits. After an observation period of 7 days, slight ocular irritation occurred in all animals. No further details were provided.

Pentapotassium DTPA

CTFA (2005) summarized a study in which a 40% concentration of Pentapotassium DTPA was applied to the left eye of three New Zealand white rabbits. After 14 days of observation, reversible corneal opacity occurred in two animals. The test material was considered moderately irritating.

Dermal Irritation
Pentasodium Pentetate

Akzo Nobel Functional Chemicals LLC (2003) stated in a material safety data sheet that Dissolvine D-40 and Dissolvine D-40-L containing 38% Pentasodium DTPA is not expected to cause irritation when exposed to the skin. The product was not irritating to albino rabbit skin (no details provided).

CTFA (2005) stated in a summary that a 40% concentration of Pentasodium DTPA was applied to three New Zealand white rabbits. Following a 4-h exposure period and 24- and 72-h observation periods, there was no irritation.

Pentapotassium DTPA

CTFA (2005) stated in a summary that a 40% concentration of Pentapotassium DTPA was applied to three New Zealand white rabbits. Following a 4-h exposure period and 24- and 72-h observation periods, there was no irritation.

Dermal Sensitization
Pentapotassium DTPA

CTFA (2005) stated in a summary that a 40% concentration of Pentapotassium DTPA was tested in a guinea pig maximization study. The test material applied to 20 Dunkin/Hartley guinea pigs was non-sensitizing.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY
Pentasodium Pentetate

BASF Corporation (1994) studied the prenatal toxicity of Trilon[®] C Liquid (41% w/w solution of diethylenetriaminepen-

taacetic acid, pentasodium salt) in Wistar rats. Sexually mature virgin females were mated with untreated males. Groups of 22 pregnant rats were treated via stomach tube with 100, 400, or 1000 mg/kg body weight Trilon[®] C Liquid solution during days 6 to 15 of gestation. The standard dose volume of 10 ml/kg body weight was administered. A control group of 23 pregnant rats was dosed with doubly distilled water vehicle. Throughout the study, food consumption, body weight, and clinical signs were monitored daily.

No mortalities occurred during the treatment and recovery periods. On day 20 post coitum, the dams were killed and assessed by necropsy. The uteri were weighed and fetuses were removed, sexed, weighed, and examined for external, soft tissue, and skeletal abnormalities. Early and late resorptions, number of viable and nonviable fetuses, and number of dead implantations were noted.

Dams that received 1000 mg/kg day^{-1} had statistically significant decreased food consumption during the first half of the treatment period, decreased body weight at days 17 and 20, impairment in body weight gain, decreased mean gravid uterus weight, and decrease mean number of live fetuses per litter. This group also experienced dark-yellow discoloration of feces during treatment and the first days of the recovery period.

The fetuses of this group had lower mean body weights and a statistically significant increase in malformation rates (including skeletal malformations) and increase in rates of skeletal variation and retardation. Fetuses of the dams that received 400 mg/kg/day also had a statistically significant increase in skeletal variation and retardation.

No substance-related effects were observed in the dams or fetuses of the 100 mg/kg day^{-1} treatment group. The no observed effect level (NOEL) for maternal toxicity was reported at 400 mg/kg body weight, and the NOEL for fetal toxicity was reported at 100 mg/kg body weight (BASF Corporation 1994).

Pentetic Acid

Calder et al. (1979) studied the reproductive and developmental effects of Zn-DTPA in C57/B1 mice. Two virgin female mice were placed in a cage with one male mouse, for a total of 79 female mice studied. The males were allowed to stay in the cages for 11 days. At day 4, the females received subcutaneous injections of one of the four solutions daily: Zn-DTPA containing no NaCl; Zn-DTPA containing NaCl; hypertonic saline with 81 g NaCl/L; or bacteriostatic isotonic saline with 9 g NaCl/L.

Female mice received treatment injections in doses of 0.2, 0.4, or 0.8 ml, according to whether the daily dose level was 2880, 5750, or 11,500 μmole Zn-DTPA/kg, respectively. Hypertonic saline was injected in volumes of 0.4 or 0.8 ml, equivalent to 23,000 or 46,000 μmole NaCl/kg day^{-1}. Female mice were treated until they bore pups or had received 29 injections. The mice were examined daily for any adverse reactions to the injections, and the pups were externally examined for any evidence of gross malformation.

Viable offspring were produced by dams in every injection group. The number of births per litter were similar to that of the isotonic saline controls, except that only two of seven dams bore live young in the group that received 11,500 μmol Zn-DTPA/kg + 23,000 μmole NaCl/kg). This compared with at least five dams bearing young per injection group among those given various other doses of Zn-DTPA or saline. Fifteen of 16 control group dams gave birth to live young.

Acute effects of the chelating agent occurred only among dams at the highest daily dosage of Zn-DTPA with NaCl (11,500 μmol Zn-DTPA/kg + 23,000 μmole NaCl/kg). In this group, three dams died (on days 19, 30, and 32) as a result of severe damage to the proximal and distal tubules of the kidney.

The pups from the highest level of the Zn-DTPA plus NaCl and the Zn-DTPA groups had a significant weight deficiency at birth. No congenital malformation was noted among pups in any of the groups. It was concluded that, whereas Zn-DTPA with NaCl proved toxic to both dams and pups at 11,500 μmole/kg day^{-1}, Zn-DTPA (no NaCl) is not toxic to mice or their offspring at doses of 11,500 μmole/kg day^{-1}. This dose was estimated to be just over 6 g/kg day^{-1} (Calder et al. 1979).

GENOTOXICITY

Pentapotassium DTPA

CTFA (2005) stated in a summary that a 40% concentration of Pentapotassium DTPA was tested in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. The test material was not mutagenic with and without metabolic activation. This source also stated that a 40% concentration of Pentapotassium DTPA was tested in Chinese hamster ovary cells. The test material was not clastogenic with or without metabolic activation.

Pentetic Acid

Prosser (1978) reported that sister-chromatid exchange (SCE) induction is a screening test in which a drug can be tested for possible mutagenic side effects. The ability of Ca-DTPA and a lipophilic DTPA derivative to induce SCEs in human lymphocytes was investigated using a differential staining procedure, in which the base analogue bromodeoxyuridine (BrdU) was incorporated into the deoxyribonucleic acid (DNA) of cultured human blood lymphocytes.

Approximately 0.1 ml of solution of Ca-DTPA was added to the test cultures at 3 different concentrations: 0.77, 0.077, and 0.0077 mg/ml, resulting in a final concentration in the culture medium of 13.51, 1.351, and 0.135 μg/ml, respectively. The 1.351 μg/ml concentration corresponded approximately to that in blood after a single intravenous injection.

The mean number of SCEs per cell in the control, 0.135, 1.351, and 13.51 μg/ml concentrations were 9.17, 10.14, 12.41, and zero, respectively for Ca-DTPA.

The highest concentration inhibited the production of metaphase cells, hence the "zero" result.

At the other two DTPA concentrations, an increase in the number of SCEs above the control value was observed. For the lower concentration of DTPA, the increase was not significant, but for the higher one it was significantly higher than that of the control value.

The authors concluded that the limited ability to induce gross structural abnormalities in chromosomes is probably not a major hazard of DTPA. It was also concluded that the absence of mitotic figures at higher concentrations of both materials suggests some further toxic effect, possibly associated with the removal of metal ions from the culture medium or even from cell membranes (Prosser 1978).

CARCINOGENICITY

No data were available on the carcinogenicity of Pentasodium Pentetate or Pentetic Acid.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

Pentasodium Pentetate

A facial toner containing 0.21% Pentasodium Pentetate was evaluated by a single-insult patch test using 23 subjects; however, no procedural information was provided. All subjects showed a 0 score. The conclusion was that there were no significant differences in irritancy observed between the test material and the control (CTFA 2001).

TKL Research Inc. (2002a) reported a 2-week cumulative irritation patch study in 29 subjects conducted on a 1.0% aqueous dilution of a soap bar that contained 0.1177% Pentasodium Pentetate. A dose of 0.2 ml of the test material was applied to the patch, and the patch was applied to the infrascapular area of the back. A 0.2% w/v sodium lauryl sulfate (SLS) aqueous solution was patched occlusively to serve as a positive control. The second positive control was a 0.75% w/v SLS aqueous solution, and was patched semiocclusively. The 0.2% SLS solution and the test material was applied everyday over a 2-week period, except that patches applied on Friday were not removed until Monday. The 0.75% SLS solution was applied on study day 4 and continued for 3 days beyond the test material and 0.2% SLS application. All subjects completed the study.

There was no significant irritation for the soap bar that contained 0.1177% Pentasodium Pentetate. The two positive controls were found to be moderately irritating (TKL Research Inc. 2002a).

TKL Research Inc. (2002b) reported a 21-day cumulative irritation patch study conducted in 33 subjects using a 1.0% aqueous dilution of a soap bar containing 0.1177% Pentasodium Pentetate. A dose of 0.2 ml of the test material was placed on an occlusive patch and applied to the subject's back. Sodium lauryl

sulfate, 0.2% *w/v* aqueous solution, served as a positive control, which was also placed on the subject's back. The patches were applied daily and removed every 24 h, although the patches applied on Friday were removed on Monday. This study extended over a 22-day period with 21 evaluations. Thirty subjects completed the study.

The authors concluded that the soap bar containing 0.1177% Pentasodium Pentetate was moderately irritating, whereas the SLS was highly irritating (TKL Research Inc. 2002b).

CTFA (2003) reported a product tolerance test on Soap-25-0 that contained 0.067% Pentasodium Pentetate. There were 24 men enrolled in the study, 23 of whom completed it (1 man was dismissed due to failure to show up for follow-up visit). All subjects were instructed to use Soap-25-0 along with two other products (shave gel and after-shave cooling gel) regularly at home; however, the Soap-25-0 was the only one that contained Pentasodium Pentetate in its formulation. After 14 days of use, the author stated that Soap-25-0 was well tolerated by the population with no increased erthema, dryness, or stinging noted between days 1 and 14.

Dermal Sensitization
Pentasodium Pentetate

Ivy Laboratories (1993) reported a study that assessed the skin sensitizing potential of a facial foundation containing 0.1% Pentasodium Pentetate. Twenty-five subjects were enrolled in the study. The study was conducted with a pretesting phase, induction phase, and challenge phase.

In the pretesting phase, 0.1 ml of the testing material was applied to an occlusive patch and placed on the subject's upper outer arm, volar forearm, or back to determine whether the testing material was irritating and whether SLS was required. The patch was left in place for 48 h, and the site was examined for irritation.

None of the subjects had any evidence of irritation, so the induction phase was then conducted with SLS pretreatment.

In the induction phase, 0.1 ml of aqueous SLS (1.0%) was applied to an occlusive patch. The patch was removed after 24 h, and 0.1 ml of the facial foundation containing 0.1% Pentasodium Pentetate was applied to the same site, covered with an occlusive patch. This patch was left in place for 48 h, or for 72 h when the patch was placed over a weekend.

If no irritation was present, a 1.0% aqueous SLS patch was reapplied to the same site for 24 h, followed by the test material patch. This cycle (24 h SLS pretreatment followed by 48 h of test material application) continued for a total of five induction exposures.

After a rest period of 10 days, a challenge phase was introduced. Approximately 0.1 ml of a 10% aqueous SLS solution was applied to an occlusive patch and was left in place for 1 h. After removal of the patch, another patch containing the test material (amount not specified) was applied to the same location for 48 h.

All reactions were scored on a scale of 0 to 3 (no sensitization to strong sensitization-large vesiculo-bullous reaction). All 25 subjects completed the study, in which during the induction phase no adverse or unexpected reactions occurred.

During the challenge phase, no instances of contact allergy were recorded at either 48 or 72 h after the application. It was concluded that the facial foundation containing 0.1% Pentasodium Pentetate does not possess a detectable contact-sensitizing potential and is not likely to cause contact sensitivity reactions under normal use conditions (Ivy Laboratories 1993).

RCTS Inc. (2002a) conducted a human repeat-insult patch test (HRIPT) using a 1.0% aqueous diluted solution of a soap bar containing 0.1177% Pentasodium Pentetate. One hundred twenty-two subjects volunteered for the study; 104 subjects completed the test.

The induction phase consisted of an occlusive patch containing 0.2 ml of test material applied to the subject's back. The patches were applied every Monday, Wednesday, and Friday until nine applications of the test material had been made. After 2 weeks of rest, the challenge patch was applied to a previously unpatched test site. The site was scored 24 and 72 h after the application.

Sixty-nine of 104 showed a barely perceptible (+) to moderate (2-level) responses (occasionally accompanied by mild to moderate dryness, mild edema, mild papular responses, and scab formations) during the induction and/or challenge phases. The authors stated that neither the incidence nor level of peak severity (moderate) of these responses were considered evidence of clinically meaningful irritation for a 1.0% dilution of a surfactant-based wash-off product tested under repetitive, occlusive patch conditions. The authors concluded that there was no evidence of induced allergic contact dermatitis in human subjects (RCTS Inc. 2002a).

Education & Research Foundation, Inc. (2005) reported a HRIPT for Soap-25-0 that contained 0.067% Pentasodium Pentetate using 53 male and female volunteers; 50 completed the test. The subjects were patched for a total of nine times in the induction phase and once in the challenge phase. Approximately 0.2 g of the Soap-25-0 was applied to the semiocclusive patches. The induction patches were worn for 24 h and scored every 48 h (except for Friday's patch, which was scored every 72 h). During the challenge phase, the sites were scored 48 and 72 h after the application.

During the induction phase of the study, there were several ± reactions and one subject had a grade 1. For the challenge phase, one subject had a grade ± reaction that fell to 0, and another subject had a grade 1 that fell to 0. It was concluded that the product was not a sensitizer nor an irritant (Education & Research Foundation, Inc. 2005).

Comedogenicity
Pentasodium Pentetate

RCTS Inc. (2002b) conducted a human comedogenicity (acne promotion) test using a 1.0% aqueous diluted solution of

a soap bar containing 0.1177% Pentasodium Pentetate. Twenty subjects volunteered for this test in which 0.2 ml of the test article and the positive control (Acetulan® Cetyl Acetate and Acetylated Lanolin Alcohol) were placed on an occlusive patch and then applied to the subject's back. The negative control consisted of an untreated occlusive patch.

Each patch was placed on the subject's back every Monday, Wednesday, and Friday. The patches were worn for 48 h with the exception after Friday, they were worn for 72 h. The sites were scored prior to the next patch application. There were a total of 12 patch applications.

At the 13th visit, follicular biopsies were collected for all sites using the cyanoacrylate follicular biopsy technique. Biopsies were scored on a 5-point scale (0 to 4). Nineteen subjects completed the study for the test material and negative control; 18 subjects completed the study for the positive control.

The authors stated that the soap bar containing 0.1177% of Pentasodium Pentetate did not produce significantly greater comedogenicity scores than did the negative control (blank patch). Both the test material and the negative control produced significantly fewer comedones than the positive control.

It was concluded that since the soap bar containing 0.1177% Pentasodium Pentetate did not produce significantly greater comedones than the negative control, it was considered non-comedogenic (RCTS Inc. 2002b).

Clinical Test

Pentetic Acid

Wohrl et al. (2001) reported a randomized, double-blind study demonstrating that DTPA is effective in preventing allergic contact dermatitis to nickel sulfate, cobalt chloride, and copper sulfate. Over a period of 1 year, 45 subjects with positive patch tests to nickel, cobalt, copper, palladium, and/or chromium were enrolled in the study.

DTPA was used at a concentration of 10% in an oil-in-water emulsion. Hydrocreme® (HY) was used as a vehicle and as a physical barrier against these metals. There were eight circular areas tested on each subject. The six different treatments were randomized along with two negative controls. The treatments consisted of: Ni 5%, Ni 5% + HY, Ni 5% + HY-DTPA, Ni 2.5%, Ni 2.5% + HY, and Ni 2.5% + HY-DTPA. The negative controls were HY alone and HY-DTPA. The readings were done 3 days after the patches were applied. This same procedure was carried out for the remaining metals (cobalt, copper, palladium, and chromium).

The negative controls, HY alone and DTPA-HY, did not provoke skin irritation. DTPA-HY reduced the number of positive patch test reactions to nickel. When the skin was pretreated with Ni 2.5% + DTPA-HY, only 1/28 subjects had a positive reaction to the nickel. The patch containing Ni 2.5% + HY did not serve as a protective barrier; 24/25 subjects had positive reactions to the nickel. When subjects were pretreated

with Ni 5% + DTPA-HY, 7/32 subjects had a positive reaction. The patch containing Ni 5% + HY did not protect the subjects; 28/32 had a positive reaction.

DTPA-HY also reduced allergic skin reactions to cobalt and copper; however, it was not effective with chromium and palladium (Wohrl et al. 2001).

Case Studies

Khokhryakov et al. (2003) reported a case study that took place in 1975. A worker broke a chemical retort containing a solution of ^{239}Pu nitrate. The solution covered the front surface of his shin, and burned the skin. It was rinsed with water, but he complained of pain in his knee. An examination revealed edema with smaller and larger bubbles filled with turbid liquid on the surface of the shin. Lymphangitis was also noticed around the area. Immediately 1 g of DTPA was injected intravenously because 120 Bq of plutonium was detected in 340 ml of urine. The patient was treated with chelation therapy of intraperitoneal (i.p.) injections: 0.5 g twice a day from days 2 to 4, 0.5 g once a day from days 6 to 20, and 0.25 g once a day from days 21 to 33. This therapy allowed 96% of absorbed plutonium to be excreted.

Bailey et al. (2003) reported a case study where a 45-year-old male worker wounded his thumb at a work site that was previously contaminated with plutonium and americium. A radiation survey was conducted that confirmed that he had been contaminated with Pu and Am. He was immediately administered 1 g of inhaled Ca-DTPA, and a chelation ointment was applied. Because the wound was not healing, he was instructed to have five daily treatments (not specified) of Zn-DTPA; however, he only received three. The worker needed to have a surgical excision procedure due to the extensive contamination. About 70% of the initial wound activity was removed by surgical procedure and less than 1% of the wound activity was removed by chelation therapy.

SUMMARY

Pentasodium Pentetate and Pentetic Acid function in cosmetics as chelating agents. Other chelating agents, including EDTA and its salts, and Meta-, Tri-, and Hexametaphosphate salts have been determined to be safe in the current practices of use as chelating agents in cosmetics. Metasilicate salts were found to be safe as chelating agents in cosmetics when formulated to avoid irritation.

Pentasodium Pentetate is readily soluble in water, but the corresponding free acid is not. The salt is produced by reacting the corresponding amino alcohol with an alkali such as sodium hydroxide at elevated temperatures, releasing hydrogen. The free acid is produced from the salt by reaction with a strong mineral acid such as hydrochloric acid.

Pentasodium Pentetate is reportedly used in 384 cosmetic products over a wide range of product categories, although it is mostly used in hair dyes and colors (233) at use concentrations of

0.1% to 1.0%. Overall, use concentrations range from 0.008% to 3.0%, with the highest concentration in the hair tonics, dressings, etc. category.

Pentetic Acid is used in 150 cosmetic products, with hair dyes and colors accounting for 138 of those uses. No current concentration of use data are available for the hair dye and color product category; however, an industry survey indicated use in coloring hair rinses at 0.003% and in bath soaps and detergents at 0.03%.

Chelating agents are used in cosmetics to remove calcium and magnesium cations, which impede foaming and cleansing performance and which can cause a haze in clear liquids.

Pentetic Acid is reported to be used as a chelating agent in metal poisonings, including those involving radioactive substances. The FDA has approved Pentetic Acid for treatment of accidental ingestion of plutonium, americium, and/or curium. Radiolabeled Pentetic Acid has also been used as a tracer to measure pulmonary clearance and as a diagnostic/therapeutic agent in visualizing/treating tumors.

In an acute static water toxicity test using Bluegill fish, a solution containing 40.2% Pentasodium Pentetate had a NOAEL of 750 mg/L. The acute oral LD_{50} of Pentasodium Pentetate in rats was >5 g/kg. A 40% solution of Pentapotassium Pentetate given by oral gavage to rats also had an LD_{50} of >5 g/kg. The acute dermal LD_{50} of Pentapotassium Pentetate administered topically at 2000 mg/kg to rats was reported to be >2 g/kg. The intraperitonel LD_{50} of Pentetic Acid was reported to be 585 mg/kg.

Short-term studies of the calcium and sodium salts of Pentetic Acid in male mice demonstrated no dose-related toxicity over the dose range of 10, 100, and 250 mg/kg, although morphological changes (vacuolization) were seen in the liver at the intermediate dose. Further study confirmed the absence of a dose-response and identified that there was no hepatocellular damage.

In a 4-week dermal toxicity study, daily topical application of 0.05% Pentasodium Pentetate to shaved and abraded rabbit skin produced moderate erythema after the first week and throughout the study, but no systemic toxicity. Pentasodium Pentetate or Pentapotassium Pentetate (40% solutions) applied to intact albino rabbit skin were not irritating. A 40% solution of Pentapotassium Pentetate was not sensitizing in a guinea pig maximization test.

Rats given 40% Pentapotassium Pentetate by oral gavage at doses up to 1.33 g/kg for 28 consecutive days had 4/25 deaths in the high dose group, with a contracted spleen found at necropsy. The NOAEL was reported to be 83 mg/kg day^{-1}. Subchronic inhalation evaluation of a bath freshener containing 0.05% or 0.09% Pentasodium Pentetate using albino rats determined that there was no cumulative systemic toxicity attributable to the ingredient at either concentration.

Reversible moderate ocular irritation was observed in a Draize test of 40% Pentapotassium Pentetate. A soap containing 0.067% Pentasodium Pentetate was screened using the EpiOcular test *in vitro* tests. Compared to the positive control, 0.3%

Triton® X-100 with an ET_{50} of 28.3 min, the sample had an ET_{50} of 2.9 h.

A prenatal toxicity study of Trilon® C Liquid (41% w/w solution of Pentasodium Pentetate) in pregnant Wistar rats resulted in a NOEL for maternal toxicity at 400 mg/kg body weight and for fetal toxicity at 100 mg/kg body weight. Females that received 1000 mg/kg/day exhibited decreases in food consumption, body weight, and number of live fetuses. Fetuses in the dams that received 400 and 1000 mg/kg/day were noted to have increased rates of skeletal variation and retardation. Another reproductive toxicity study evaluated the effects of Zn-DTPA with and without NaCl in pregnant C57/B1 Dougherty mice. Daily dose levels were 2880, 5750, or 11,500 μmole/kg. Pure Zn-DTPA was not toxic to the females or their offspring, but Zn-DTPA coupled with NaCl produced toxic effects in females and pups.

Pentapotassium Pentetate at 40% was not mutagenic in an Ames test, with or without metabolic activation. The same material tested in Chinese hamster ovary cells was not clastogenic. Calcium Pentetate was evaluated in a sister-chromatid exchange (SCE) screening protocol. At the highest concentration, production of metaphase cells was inhibited. At 1.351 μg/ml for Calcium Pentetate, a statistically significant increase in the number of SCEs above the control value was found.

Pentasodium Pentetate at 0.21% was not an irritant in a single insult patch test. A 1% aqueous dilution of a soap containing 0.1177% Pentasodium Pentetate was not an irritant in one cumulative irritation patch study of 29 individuals, but was moderately irritating in another cumulative irritation patch study of 30 subjects. A product tolerance test of a soap containing 0.067% Pentasodium Pentetate resulted in no adverse effects in 23 men.

A sensitization test of 0.1% Pentasodium Pentetate in 25 subjects resulted in no irritation during induction and no sensitization reactions at challenge. An HRIPT in 104 subjects using 1.0% Pentasodium Pentetate produced no evidence of sensitization. Another HRIPT of a soap containing 0.067% Pentasodium Pentetate in 50 subjects gave the same result.

A human comedogenicity test using a 1.0% aqueous dilution of a soap containing 0.1177% Pentasodium Pentetate in 20 subjects did not produce a statistically significant increase in comedones compared to controls. Both the control and test subjects had a statistically significant decrease in comedones compared to the positive control.

A clinical test of 45 subjects with allergic contact dermatitis to nickel sulfate, cobalt chloride, and copper sulfate who were treated with Pentetic Acid in an oil/water emulsion resulted in reduced skin reactions to nickel, cobalt, and copper, but not to chromium and palladium. Case studies reported the use of Pentetic Acid or Calcium Pentetate in successful treatment of radioisotope poisoning.

DISCUSSION

The CIR Expert Panel recognized that there are data gaps regarding use and concentration of Pentasodium Pentetate and

Pentetic Acid. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicate a pattern of use, which was considered by the Expert Panel in assessing safety.

The CIR Expert Panel considered that the safety test data in earlier safety assessments of chelating agents used in cosmetics were relevant to the assessment of the safety of Pentasodium Pentetate and Pentetic Acid. For example, data are lacking on the dermal penetration of these two ingredients, but data are available demonstrating that EDTA, a structurally similar chelating agent, does not penetrate the skin, so it was considered likely that Pentasodium Pentetate and Pentetic Acid also would not penetrate. The high water solubility of Pentasodium Pentetate and the low water solubility of Pentetic Acid also supported the view that their dermal penetration will be low.

Acute, short-term, and subchronic oral and dermal toxicity studies supported the safety of Pentasodium Pentetate and Pentetic Acid with respect to systemic toxicity endpoints. Neither significant skin irritation or skin sensitization were demonstrated in animal studies at concentrations well above those actually used in cosmetic products, and clinical use tests of products containing these chemicals further supports their safety.

The CIR Expert Panel noted that, in one oral reproductive and developmental toxicity study, pure Zn-DTPA was not toxic to the females or their offspring, but Zn-DTPA coupled with NaCl produced toxic effects in females and pups. In another oral study of a trade name product with 41% w/w Pentasodium DTPA, fetuses in the dams that received 400 or 1000 mg/kg/day were noted to have increased rates of skeletal variation and retardation. Given the absence of significant skin penetration of these chelating agents, these oral data did not suggest that their use in cosmetics presents any reproductive or developmental toxicity risk.

The CIR Expert Panel also noted the absence of carcinogenicity studies. Genotoxicity studies in bacterial and mammalian test systems were negative. In addition, there were no structural alerts in these agents. The Expert Panel considered it unlikely that Pentasodium Pentetate and Pentetic Acid would present any carcinogenic risk.

Inhalation toxicity data were not available for these ingredients. However, due to their structural similarity to EDTA and the availability of relevant toxicity data concerning the safety of EDTA, the CIR Expert Panel determined that these ingredients can be used safely in aerosolized products when packaging and use ensure that particulates are not respirable (are greater than 10 μm). The Panel reasoned that the particle size of aerosol sprays (60 to 80 μm) and pump sprays (>80 μm) is large compared to the median aerodynamic diameter of 4.25 $\pm$ 1.5 μm for a respirable particulate mass.

The CIR Expert Panel further noted that the safety of chelating agents in cosmetics was supported by guidance for industry developed by FDA on submitting new drug applications for Calcium Pentetate and Zinc Pentetate products used in the treatment of known or suspected internal contamination with plutonium,

americium, or curium in two forms: 1 g in a 5-ml aqueous solution for administration by inhalation (with a 1:1 dilution and delivered by nebulization) or intravenous injection. Using these dosing regimens, the FDA concluded that these chelating agents can be found safe and effective for the above use, when produced under specified conditions.

CONCLUSION

The CIR Expert Panel concluded that Pentasodium Pentetate and Pentetic Acid are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment.

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