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Final Report on the Safety Assessment of 2-Methylresorcinol and Resorcinol

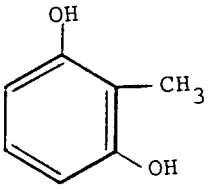
2-Methylresorcinol and Resorcinol are most frequently used in cosmetic hair dye formulations at concentrations between 1 and 5%. The results of cutaneous and oral feeding studies have indicated that both 2-Methylresorcinol and resorcinol are readily absorbed by rodents and are rapidly eliminated. Acute oral toxicity studies indicate that 2-Methylresorcinol is moderately toxic and Resorcinol is slightly to moderately toxic. Subchronic feeding and dermal studies of both ingredients produced no significant effects. A chronic dermal study was uneventful. Significant skin effects were observed in mice, but not in rabbits, following dermal application of Resorcinol at 5%. A 10% Resorcinol solution was not irritating to guinea pigs. A 2.5% 2-Methylresorcinol solution was classified as a primary irritant in rabbits, but 10% 2-Methylresorcinol was not irritating to guinea pigs. 2-Methylresorcinol was not an ocular irritant at 2.5%, but irritation was produced at 5% concentration in unwashed rabbit eyes. Neither 2-Methylresorcinol at 5% nor Resorcinol at 3% produced sensitization in guinea pigs. 2-Methylresorcinol was not photoallergenic to guinea pigs but was a sensitizer at 10%. Resorcinol was not photoallergenic to guinea pigs but was a sensitizer at 10%. Resorcinol and 2-Methylresorcinol were nonmutagenic in microbial and tissue culture assays for mutagenicity. Topically applied hair dyes containing 2-Methylresorcinol and Resorcinol were negative for carcinogenicity. Resorcinol showed no cocarcinogenic potential when tested on mice and rats. 2-Methylresorcinol at 3% concentration produced no evidence of irritation or sensitization in human subjects. Resorcinol was a mild skin irritant and rare sensitizer in clinical testing, but not when tested on nonclinical groups. On the basis of the available animal and clinical data, it is concluded that 2-Methylresorcinol and Resorcinol are safe as cosmetic ingredients in the present practices of use and concentrations.

INTRODUCTION

The major use of 2-Methylresorcinol and Resorcinol in cosmetic products is in hair dyes and colors. This report includes both the published and industry unpublished safety test data on these two ingredients.

CHEMICAL AND PHYSICAL PROPERTIES

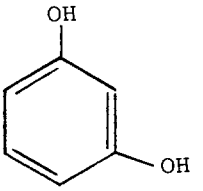
2-Methylresorcinol (CAS No. 608-25-3) has the empirical formula $C_7H_8O_2$ and is the aromatic compound that conforms to the following structural formula[1,2]:



Other names for 2-Methylresorcinol include: 2-methyl-1,3-benzenediol; 2,6-dihydroxytoluene; and 2-methyl-1,3-dihydroxybenzene.[1-3]

2-Methylresorcinol is a white to slightly yellow crystalline powder that is soluble in water, alcohol, ether, and benzene. Its crystalline form in benzene is prismatic. The compound is stable at room temperature but will eventually discolor with exposure to light and air. Solutions become brown due to oxidation when exposed to air.[1,3]

Resorcinol (CAS No. 108-46-3) is one of three possible benzenediol isomers. It is also called 1,3-benzenediol and 1,3-dihydroxybenzene. The structural formula of Resorcinol is as follows[2,3]:



Resorcinol is a white crystalline solid with a faint characteristic aromatic odor and a sweet taste. The crystals are hygroscopic. Resorcinol becomes pink on exposure to light and air or on contact with iron. Its boiling point is 280°C, but it volatilizes at lower temperatures and is slightly volatile with steam. Resorcinol is soluble in water, alcohol, ether, glycerol, carbon tetrachloride, acetic acid, liquid ammonia, liquid sulfur dioxide, liquid hydrogen sulfide, and pyridine, and is slightly soluble in benzene and hot chloroform.[3-6] A summary of the physical properties of 2-Methylresorcinol and Resorcinol is presented in Table 1.

Resorcinol undergoes chemical reactions typical of phenols and may give rise to ethers, monoesters, and diesters. Ring substitutions may be made by halogenation, sulfonation, alkylation, nitration, Kolbe and Reimer-Tiemann reactions, Friedel-Crafts acylation, and condensation with aldehydes, esters, or ketones. Resorcinol may take part in reactions leading to multiring systems.[4,7] Phenols will condense readily with aliphatic and aromatic aldehydes; Resorcinol will combine with formaldehyde in the cold. Resorcinol does not form a qui-

TABLE 1. Physical Properties

	2-Methylresorcinol	*Resorcinol*	*Reference*
Formula	$C_7H_8O_2$	$C_6H_6O_2$	3
Molecular weight	124.15	110.11	3
Specific gravity at			
15/4°C		1.272	4
15°C		1.285	5
–		1.2717	3
–		1.272	6
Melting point (°C)		109.8	4
		110	5
Stable		111	3
Unstable		108.5	3
	119–121		3
		109–111	6
Boiling point (°C) at			
–		281.4	4
–		276.5	5
760 mm Hg		280	6
760 mm Hg	264		3
16 mm Hg	168	178	3
Vapor pressure (mm Hg) at			
108.4°C		1	5
130°C		3.0	4
150°C		8.5	4
170°C		23.5	4
190°C		53.0	4

none.[8] Resorcinol can act as an antioxidant.[4] The autooxidation of Resorcinol at pH 7–9 occurs only to a limited extent.[9]

Several laboratories have investigated the effects of the benzenediols on amine nitrosation. Resorcinol at a concentration of 0.06 M was added to two aqueous solutions with a pH of 4.05 and at a temperature of 37°C that contained diethylamine and sodium nitrite at concentrations of 0.5 M and 0.016 M, respectively. Resorcinol was an effective catalyst in the nitrosation reaction; the rate of nitrosodiethylamine formation was increased approximately 25 times when compared to the noncatalyzed reaction. No further increase in nitrosodiethylamine was formed in the presence of Resorcinol following the depletion of the available nitrite.[10–12]

Qualitative and quantitative determinations of 2-Methylresorcinol are made using gas chromatography,[13] thin-layer chromatography, and photometry.[14] Identification can also be made with infrared and ultraviolet (UV) spectrophotometry. The main maximum in the UV absorption spectrum of 2-Methylresorcinol in cyclohexane is 275 nm; the logarithm of the molar absorption coefficient is 3.02.[3,15]

Qualitative and quantitative determinations of Resorcinol are made by colorimetric methods, gravimetric procedures,[4] spectrophotometric methods including mixed color photometry,[16] ultraviolet spectroscopy,[17] a ring-oven

technique,[18] paper chromatography,[4] thin-layer chromatography,[19,20] gel chromatography,[4,17] high-pressure liquid chromatography,[21] and gas chromatography,[4,17] with flame ionization,[19] or with mass spectrometry.[17,22]

Identification of Resorcinol can also be made by comparison with published infrared and UV absorption spectra, nuclear magnetic resonance, mass, and Raman spectra, and x-ray diffraction patterns.[3,4,19,23]

Resorcinol has been found in roasted barley,[24] in cane molasses,[25] in coffee,[26] in cigarette smoke,[17,19] in wood smoke, as a pollutant in filtered surface and ground water at a water-treatment plant, and in the effluents resulting from the production of coal tar chemicals.[19]

Although a variety of methods had been developed for the production of the benzenediols, only a few methods are commonly used in their commercial manufacture. Resorcinol is produced by the fusion of the sodium salt of m-benzenedisulfonic acid with sodium hydroxide, followed by acidification.[4,19]

Resorcinol and other phenylalkylamines decompose following light and UV radiation exposure.[27]

2-Methylresorcinol used in cosmetics should be at least 94% pure, melt at 115°C or above, should be 1% maximum on ignition, and should not contain more than 100 ppm iron. The infrared spectrum should conform to the standard.[1]

The Japan Cosmetic Industry Association standards require Resorcinol to contain a minimum of 99% Resorcinol.[28]

USE

Cosmetic Uses

2-Methylresorcinol is used commonly in dye compositions for hair colorings.[1] Schwartz et al.[29] dyed hair with equimolar parts of 2-Methylresorcinol as a color modifier and 10 primary intermediates. 2-Methylresorcinol produces red tones with *p*-phenylenediamines and O-substituted *p*-phenylenediamines and grayer colors with N-substituted *p*-phenylenediamines. With *p*-aminophenol, an orange-brown color is produced.

Resorcinol is largely used in cosmetics as a coupler in oxidative hair dyeing. In oxidative (permanent) hair coloring systems, the color is produced inside the hair fiber by oxidation of colorless intermediates.[30] To accomplish the color-forming reaction, three classes of chemical reactants are required: the primary intermediates, the oxidant, and the couplers. Frequently employed intermediates are aromatic *o*- or *p*-diamines or aminophenols. Hydrogen peroxide is the most commonly used oxidant.[31,32]

Product types and the number of formulations containing 2-Methylresorcinol and Resorcinol are reported voluntarily to the Food and Drug Administration (FDA) (Table 2). Voluntary filing of this information by cosmetic manufacturers, packagers, and distributors conforms to the prescribed format of preset concentration ranges and product types as described in the Code of Federal Regulations.[34] Some cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, and, therefore, the value reported by the cosmetic formulator or manufacturer may not necessarily reflect the true concentration of

TABLE 2. Product Formulation Data[33]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)		
			>1–5	>0.1–1	≤0.1
2-Methylresorcinol					
Hair dyes and colors	811	104	–	64	40
1981 TOTALS		104	–	64	40
Resorcinol					
Hair shampoos (noncoloring)	909	1	–	1	–
Hair dyes and colors	811	464	20	247	197
Hair tints	15	7	–	–	7
Makeup bases	831	1	1	–	–
Bath soaps and detergents	148	1	–	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	4	–	3	1
Skin fresheners	2601	1	–	1	–
Other skin care preparations	349	3	1	2	–
1981 TOTALS		482	22	255	205

the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Data are only submitted within the framework of preset concentration ranges, which provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a 2- to 10-fold error in the assumed ingredient concentration.

Data submitted to the FDA in 1981 by cosmetic firms participating in the voluntary cosmetic registration program indicated that 2-Methylresorcinol was used in a total of 104 hair dyes and colors (all types requiring caution statement and patch test). 2-Methylresorcinol was used in 64 hair dyes and color products at a concentration of >0.1–1% and in 40 hair dyes and color products at a concentration of ≤0.1% (Table 2).[33] In 1981, Resorcinol was reported as an ingredient in a total of 482 cosmetic formulations at concentrations ranging from ≤0.1% to between 1 and 5% (Table 2).[33]

2-Methylresorcinol and Resorcinol are reported primarily as ingredients of hair dyes and colors (all types requiring caution statement and patch test), although Resorcinol is also used in other hair and skin products. Cosmetic formulations containing 2-Methylresorcinol and Resorcinol may be applied to or come in contact with the skin, eyes, hair, nails, and mucous membranes. They may be applied as many as several times a day and may remain in contact with the skin for variable periods of time following application. Daily or occasional use may extend over many years (Table 2).[32,33]

Noncosmetic Uses

Resorcinol is used for its antiseptic and keratolytic action in acne therapy products[4,35-37] and in products for treating such skin diseases as ringworm, parasitic infections, psoriasis, seborrheic dermatitis, stasis ulcers and eczema, otitis externa, chronic intertriginous dermatitis, and superficial fungal infections.[4,8,35] It has also been used in antidandruff shampoos[38] and in suppositories.[35] In the past, it has been used systemically as an antipyretic and an intestinal antiseptic and externally as a mucous membrane antiseptic.[4]

Resorcinol is currently being evaluated in the FDA over-the-counter (OTC) drug review program[39] (Table 3).

Resorcinol has been classified as Generally Recognized as Safe (GRAS) under conditions of intended use (as a flavoring substance with concentration limits of 5.0–15.0 ppm in food) by the Expert Panel of the Flavor and Extract Manufacturers' Association (FEMA No. 3589).[40,41]

Resorcinol is listed in the Code of Federal Regulations as an indirect food additive. Resorcinol, at a concentration limit of 0.24% by weight, may be used as a reactive adjuvant substance employed in the production of gelatin-bonded card compositions for use in lining crown closures. The gelatin must be technical grade or better. These closures with sealing gaskets may be used on containers intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.[34]

Resorcinol is used as an analytical agent, an antioxidant, and a stabilizer for halogen compounds; in printing and photography; in tanning; as a chemical intermediate; in pharmaceuticals and dyes; in explosives; and in the manufacture of resins, such as Resorcinol-formaldehyde resins that are used as adhesives and are important in the timber, textile, and rubber industries.[4,6,19]

GENERAL BIOLOGY

2-Methylresorcinol has inhibited fungal growth at a concentration of 300 mg/ml.[42] At a concentration of 3.6×10^{-4} M, the compound did not inhibit the beef mitochondrial NADH-oxidase and succinoxidase enzyme systems in vitro.[43]

The antiseptic properties of Resorcinol have been studied extensively.[8,44-47] Some microbial species are not inhibited by Resorcinol but metabolize the compound.[44,48-53]

The destruction of hydrogen peroxide (N/100) by 0.0033% commercial catalase in 1 minute at pH 6.8 and 0°C was inhibited 50% by the addition of 5×10^{-5} M Resorcinol.[54] Concentrations of 1×10^{5} to 1×10^{3} M Resorcinol had no effect on in vitro rat liver catechol-o-methyltransferase activity.[55]

Resorcinol has antithyroid activity.[35,36] The catalysis of the iodination of protein by purified hog thyroid peroxidase was inhibited by 5×10^{-6} to 5×10^{-5} M Resorcinol.[56] Rat thyroid lobes were incubated with labeled iodine. Resorcinol, in concentrations of 1×10^{-6} to 1×10^{-3} M, increased the percentage of labeled iodide within the thyroid.[57] Resorcinol, at a concentration of 1×10^{-3} M

and in the presence of rat plasma, suppressed the in vitro uptake by rat muscle of radioactive thyroxine during a 2-h incubation.[58]

Resorcinol was incubated for 15 minutes at 37°C with nuclei from rat liver and brain cells; 5–35 μg/ml Resorcinol increased RNA synthesis.[59]

No membrane damage was observed when human lung fibroblasts were incubated for 30 minutes at 37°C with 0.025 M Resorcinol.[60] Resorcinol, at concentrations of 0.125–0.5%, was incubated with human kidney cells at a pH of 7.4–7.6. Resorcinol protected the cells against irradiation damage but did not protect them against freezing damage.[61]

The dopa reaction of human epidermis was investigated using axillary skin that had been surgically removed for the treatment of osmidrosis. At a pH of 7.4, there was a slight inhibition of the dopa reaction when the epidermis was exposed to concentrations of 0.17×10^{-6} M Resorcinol.[62]

Ciliastasis was observed when air containing approximately 80 to 800 mg/m^3 Resorcinol was passed through a chamber containing a sample of the tracheal mucosa of a rabbit.[63]

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

The cutaneous absorption of 2-Methylresorcinol (1,3-dihydroxy-2-[^{14}C]-methylbenzene) was studied in 8 male and 8 female Wistar rats. A formulation similar to those used for hair dyeing was applied for 30 minutes to the clipped intact skin of the rats. A maximum of 0.48% of 2-Methylresorcinol was absorbed through the rat skin in 24 h. The authors extrapolated from these animal data to an equivalent single human use of a hair dye formulation and concluded that 0.05 mg of 2-Methylresorcinol would be absorbed.[64]

The excretion of 2-Methylresorcinol (1,3-dihydroxy-2-[^{14}C]-methylbenzene) following a single subcutaneous injection or oral dose was studied in Wistar rats.[64] The amount of radioactivity in the urine and feces and in the carcass at the end of the observation period was determined. In addition, in the subcutaneous study, the expired air, and in the oral study, the gastrointestinal tract, were measured for the total amount of the test substance (plus metabolites). In the subcutaneous test, greater than 90% of the administered radioactivity was excreted in the urine and feces within 24 h. No radioactivity was detected in the expired air. No parent compound was present in the urine; the radioactivity was largely excreted as glucuronide or sulfate. The animals that received an oral dose of the radioactive compound excreted approximately 90% of the radioactivity in the urine within 24 h. The excretion was rapid, the major part having been eliminated within 8 h of administration.

Resorcinol was administered orally to rabbits at a dose of 0.4 g/kg, and urine was collected during the following 3 days. A moderate increase in glucuronic acid and organic sulfate conjugates was observed in the urine; it was suggested that measuring these compounds might be a means of monitoring the absorption of Resorcinol.[65] In rabbits given Resorcinol orally, the rate of glucuronide conjugation was proportional to the body concentration of Resorcinol. The rate of organic sulfate formation was approximately constant until almost the whole dose was excreted.[66] Resorcinol, in a dose of 100 mg/kg, was administered

TABLE 3. OTC Drug Review on Resorcinol[39]

Advisory review panel	*Date of action*	*Reference document*[a]	*Recommended category*[b]	or *Final actions and conditions*
Hemorrhoidal drug products	5/27/80	Proposal (45 FR 35661-2)	II	Not safe or effective for intrarectal use as an antiseptic in OTC anorectal preparations
		(45 FR 35663)	III	Safe for external use as an antiseptic but there is insufficient evidence to prove effectiveness for use in OTC anorectal preparations
				Proposed dosage: Adult external dosage is 0.5–2.5% per dosage unit not to exceed 50 mg per dosage unit and not to exceed 6 applications per 24 h; Panel recommends category III labeling for antiseptic active ingredients, pending testing for effectiveness; Panel recommends 2 years for completion of studies
	5/27/80	Proposal (45 FR 35665-7)	I	Safe and effective for external use as keratolytic for relief of itching in OTC anorectal preparations
				Dosage: Adult external dosage is 1–3% per dosage unit not to exceed 6 applications per 24 h
				Panel recommends category I labeling for keratolytic active ingredients
		(45 FR 35668)	II	Not safe or effective for intrarectal use as keratolytic in OTC anorectal preparations

Topical analgesic, antirheumatic, otic, burn, sun and prevention products	12/4/79	Proposal (44 FR 69835-6)	I	Safe and effective for use as OTC external analgesic; Dosage: For adults and children 2 years of age and older: Apply 0.5–3.0% concentration of Resorcinol to affected area not more than 3 or 4 times daily; for children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician; Panel recommends the category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients; Panel also recommends specific labeling
Antimicrobial II	3/23/82	Proposal (47 FR 12459)	II	Safe but not effective as single ingredient for OTC topical use in treatment of acne
		(47 FR 12520)	II	Not safe for OTC topical antifungal use in treatment of athlete's foot, jock itch, and ringworm; there are insufficient data available on its effectiveness for this use
Miscellaneous external drug products	10/5–6/80	OTC Panel (41st meeting)	I	Safe in 1% concentration in treatment of seborrheic dermatitis
			III	For effectiveness in 1% concentration in treatment of seborrheic dermatitis
	11/7–8/80	OTC Panel (42nd meeting)	II	For lack of effectiveness data for use on scalp as keratolytic for seborrheic dermatitis or for psoriasis

[a]FR, Federal Register.
[b]Category I. Conditions under which OTC drug products are generally recognized as safe and effective and are not misbranded.
Category II. Conditions under which OTC drug products are not generally recognized as safe and effective or are misbranded.
Category III. Conditions for which the available data are insufficient to permit final classification at this time as category I or II.

orally to rabbits. The 24-h urine sample contained (as a percentage of dose) 13.5% Resorcinol ethereal monosulfate, 52% Resorcinol glucuronide, and 11.4% free Resorcinol. The researchers did not find any evidence of the oxidation of Resorcinol to any trihydroxybenzenes.[67]

Resorcinol is readily absorbed from the gastrointestinal tract and can be absorbed through human skin. It was excreted in the urine as free Resorcinol and also conjugated with glucuronic, sulfuric, and hexuronic acids.[8,68] Resorcinol appeared to cross excised human epidermis primarily by diffusion through the stratum corneum. The experimental diffusion coefficient for Resorcinol in human epidermis was about 10,000 times less than that for its diffusion in water. Researchers have suggested that since Resorcinol is a polar compound, its diffusion is retarded by a lipid phase barrier of high viscosity in the stratum corneum.[69] Yeung et al.[70] applied topical doses of a 2% Resorcinol ointment for 30 days to human volunteers. After 2 weeks during which 800 mg had been applied to 30% of body surfaces, an average of 1.64% of the dosage was being excreted in the urine as the glucuronide or as the sulfate conjugate. The health status including thyroid function as determined by T_3 and T_4 serum values was not adversely affected. The results in humans correlated well with the pharmacokinetic data observed in rats.[71] In this latter study up to 100 mg/kg was injected daily for 30 days. There were no adverse reactions as determined by body weight, hematology, serum T_3 and T_4 values, and lesions of the thyroid gland and spinal cord. The injected Resorcinol was rapidly eliminated in the urine as the glucuronide without bioaccumulation in the tissues.

ANIMAL TOXICOLOGY

Oral Studies

Acute Toxicity

The acute oral toxicity of 2-Methylresorcinol has been studied in rats[72] (Table 4). In one experiment, a 2.0–2.75% 2-Methylresorcinol solution was administered orally at three different doses (200–275 mg/kg) to groups of 5 male and 5 female rats. The LD_{50} was 253 mg/kg for male rats and 233 mg/kg for female rats. In a second experiment, a 1% 2-Methylresorcinol suspension was administered at three to four different doses (125–275 mg/kg) to groups of 5 male and 5 female rats. The LD_{50} was 219 mg/kg for male rats and 200 mg/kg for female rats. In the Hodge and Sterner[74] classification of single-dose oral toxicity for rats, 2-Methylresorcinol would be classified as moderately toxic.

The acute oral toxicity of Resorcinol has been studied in rats,[7,73] rabbits,[67,68] and guinea pigs[68] (Table 4). The LD_{50} values for rats were reported as 0.3 g/kg in one experiment and 1.0 g/kg in another experiment. In the Hodge and Sterner[74] classification of single-dose oral toxicity for rats, Resorcinol would be classified as slightly to moderately toxic.

Subchronic and Chronic Toxicity

The subchronic oral toxicity of 2-Methylresorcinol has been studied in rats[75] (Table 5). Five groups of 5 male and 5 female Sprague-Dawley weanling

TABLE 4. Acute Oral Toxicity

Material, concentration and vehicle tested	*Species of animal*	*Method*	*LD_{50} (g/kg)*	*Comments*	*Reference*
2-Methylresorcinol, 2.0–2.75% solution	Rats	3 groups of 5 male rats, given 0.2–0.275 g/kg	0.25	–	72
	Rats	3 groups of 5 female rats, given 0.2–0.275 g/kg	0.23	–	72
2-Methylresorcinol, 1% suspension	Rats	3–4 groups of 5 male rats, given 0.125–0.275 g/kg	0.22	–	72
	Rats	3–4 groups of 5 female rats, given 0.125–0.275 g/kg	0.20	–	72
Resorcinol, in water	Rabbits Guinea pigs	–	0.75 0.37	–	68
Resorcinol, 10% in water	Male rats	4 groups of 5 rats, given 0.147–0.464 g/kg	0.30	Doses of 0.215–0.464 g/kg caused signs of intoxication and death within 4 h; fibrillations, tremors, convulsions, salivation, dyspnea, sedation, and emaciation were observed; dead rats had lung hemorrhages, gastrointestinal tract inflammation, and liver hyperemia; no adverse effects were noted in survivor rats	73
Resorcinol, flake grade	Rats	4 groups of 5 rats, given 0.398–3.16 g/kg by stomach intubation; observed for 14 days	1.0	At dose of 1.58 g/kg 4/5 died within 1 day and at a dose of 3.16 g/kg, 5/5 died in less than 2 h; dead rats had hyperemia and distention of the stomach and intestines; survivors had no gross lesions and body weight gains were similar to controls	7
Resorcinol, in water	Giant chinchilla rabbits	Given by stomach tube in doses of 0.5 and 0.6 g/kg	–	0.5 g/kg had no toxic effect; 0.6 g/kg caused temporary muscular twitching and an increased rate of respiration	67

TABLE 5. Subchronic and Chronic Oral Toxicity

Material tested	*Dose and vehicle*	*Length of study*	*No. and species of animal*	*Results*	*Reference*
2-Methylresorcinol	0–1.0% in diet	4 weeks	5 male and 5 female rats at each of 5 doses	No deaths; no adverse pharmacological or toxicological signs; feed consumption similar to controls; males given 1% had decreased body weight; relative liver weight decreases in males given 0.1 and 0.2% and increases in females given 1%	75
Resorcinol	5% in diet	2 weeks	Rats	Increased in thyroid weight	57
Resorcinol, 2% in corn oil	0–260 mg/kg per day in diet	4 weeks	10 male rats at each of 4 doses	No deaths; no toxicity symptoms and, at necropsy, no lesions; weight gains of treated animals were similar to controls; decrease in adrenal to body weight ratios of all treated rats	73
Resorcinol suspension, in 0.5% (wt/vol) gum tragacanth containing 0.05% (wt/vol) sodium sulfite	2 doses of 250 mg/kg separated by 24 h; gastric intubation	24 h	CFY rats	No deaths up to 6 h after dosing (the animals were then killed)	76

rats were given 0.0, 0.1, 0.2, 0.5, and 1.0% 2-Methylresorcinol in feed for 28 days. At the end of the experiment, all the rats were fasted for 24 h and then were killed and necropsied. All animals survived the 28-day feeding period, and no signs of toxicity were observed. Feed consumption by all the test groups was similar to the feed consumption of the controls. The body weights of the males given 1% 2-Methylresorcinol in the feed were significantly less than the body weights of the controls; the body weights of all other groups were similar to the controls. At necropsy, there were no "remarkable" gross observations. The relative liver weights (compared to body weights) of male rats in the groups given 0.1 and 0.2% 2-Methylresorcinol in the feed were significantly less than in the controls. There was a significant increase in the relative liver weights of females given 1% 2-Methylresorcinol in the feed. No other significant changes in organ weights or relative organ weights were observed (livers, kidneys, and thyroids were examined). The researchers found that relative liver weight decreases were not toxicologically significant.

Groups of 20 male and 20 female Wistar rats were given 0, 20, 60, or 80 mg/kg 2-Methylresorcinol by gavage five times per week for 12 weeks.[77] Body weight gains of the test animals did not differ from controls, and no indication of cumulative toxicity was found in urine, feces, blood, or biochemical studies. Macroscopic and microscopic examination of the internal organs was negative for toxic alterations induced by the test substance.

The subchronic oral toxicity of Resorcinol has been studied in rats[57,73,76] (Table 5). Resorcinol was administered to groups of rats at 5% in the diet for 2 weeks, at 260.7 mg/kg per day in the diet for 4 weeks, and two doses of 250 mg/kg Resorcinol (24 h apart) by gastric intubation. No rats died and no toxic signs were observed. At necropsy, thyroid weights of the rats given the 5% dietary Resorcinol were increased, and adrenal:body weight ratios of the rats receiving up to 260.7 mg/kg per day Resorcinol in the diet were decreased.

Dermal Studies

Acute Toxicity

Fifty μl of a 10% (wt/vol) aqueous solution of 2-Methylresorcinol were applied twice daily for 5 days to 5 adult male hairless mice.[77] During the first 2 days of the application no primary skin irritation was observed. On the third day (fifth application) all animals reacted with mild redness of the skin, which lasted until the end of the study.

Resorcinol, in doses of 1.0–8.0 g/kg, was applied to the abraded and intact skin of four groups of 4 rabbits for 24 h, and the rabbits were observed for a further 14 days. The acute dermal LD_{50} of Resorcinol was 3.36 g/kg. Skin necrosis was observed in 3 of 4 rabbits of the 2.00 g/kg group and in all the rabbits of the 4.0 and 8.0 g/kg groups. Only slight hyperkeratosis followed moderate to severe irritation in the 1.0 g/kg animals. Most of the survivors of the 14-day observation period gained less weight than the control rabbits. No gross lesions were observed at necropsy of the survivors.[7]

Subchronic and Chronic Toxicity

The chronic percutaneous toxicity of 12 different hair dyes has been studied

in rabbits. One dye contained 1% 2-Methylresorcinol and another 2% Resorcinol[78] (Table 6). The hair dye formulation was mixed with an equal volume of 6% hydrogen peroxide, and 1 ml/kg of the mixture was applied topically twice weekly for 13 weeks to 12 adult New Zealand white rabbits (6 males and 6 females). The hair dye was applied to two clipped, alternating sites on the dorsolateral aspects of the thoracic-lumbar area. Application sites of 3 male and 3 female rabbits were abraded on the first treatment day of each week. After application, the rabbits were restrained for 1 h and then shampooed, rinsed, and dried. There were three control groups of 12 rabbits each. All surviving rabbits were killed at 13 weeks and were necropsied. There was no evidence of toxicity. Body weight gains were normal. Urinalyses were normal, and there was no discoloration of the urine. Slight thickening of treated skin developed due to the frequency of hair dye application. No gross abnormalities were seen at necropsy, and no treatment-related microscopic lesions were found.

A hair dye formulation containing 1.0% 2-Methylresorcinol was diluted 1:1 with hydrogen peroxide and applied twice weekly to the clipped skin of New Zealand rabbits.[77] Six males and six females received 1 ml/kg twice weekly for 13 weeks. Half of the animals were abraded at the site of application on a weekly basis. There was no evidence of compound-induced toxicity with respect to the weight gain, blood or urine values, or changes in internal organs. The treated skin had slight thickening after the 13-week treatment period.

The subchronic and chronic dermal toxicity of Resorcinol has been studied in rats,[79,81] mice,[80,82,84] and rabbits[83] (Table 6). Toxicity to rats was not observed after dermal application of an ointment containing 12.5% Resorcinol two times daily for 3 weeks or a hair dye composite containing 0.75% Resorcinol two times a week for 2 years. A 50% Resorcinol solution was applied to the interior ear of rabbits twice weekly for 180 weeks; toxicity was not observed. Toxicity was not observed in mice after dermal application of hair dye formulations containing 0.40% Resorcinol two times a week for up to 2 years or of a 50% Resorcinol in acetone solution two times a week for 110 weeks; lesions were observed when Resorcinol in acetone solution was applied to the skin of mice.

Primary Skin Irritation

The primary skin irritation of 2-Methylresorcinol has been studied in rabbits.[85] A 2.5% aqueous solution of 2-Methylresorcinol was applied at a dose of 0.5 ml to an area of approximately 1 square inch on the left side of the clipped torso of 6 New Zealand albino rabbits. Erythema and edema were scored at 24 and 72 h following 2-Methylresorcinol applications. No erythema or edema was observed. The Primary Irritation Index (PII) was 0. Five female guinea pigs were treated with 3, 5, and 10% water solutions of 2-Methylresorcinol (0.25 ml/½ inch shaved area) for 14 consecutive days. No skin irritation was observed.[86] In a preliminary screening study, 2-Methylresorcinol was not irritating when tested on guinea pigs at 10, 5, 1, and 0.1%.[87]

Resorcinol, at a dose of 0.5 g, was moistened with saline and placed in contact with the intact and abraded abdominal skin of male albino rabbits for 24 h. The animals were observed for a further 14 days. The PII was 4.4 (max = 8.0); Resorcinol was not a primary irritant on intact skin. The effects observed on abraded skin varied from none to necrosis of the abraded areas. The lesions

were more marked at 72 h than at 24 h. After 14 days, the necrotic areas were still encrusted or scarred; no irritation was observed in any other areas.[7] An aqueous solution of Resorcinol at 10, 5, 1, and 0.1% was not irritating to guinea pigs in a screening study.[88]

Sensitization and Photoallergenicity

The skin sensitization potential of 2-Methylresorcinol has been studied in guinea pigs using the Magnusson and Kligman[89] guinea pig maximization test.[90] Twelve animals received three pairs of intradermal induction injections (0.05 ml) in a clipped area of the dorsal skin in the scapular region. One of each injection pair was injected into each side of the guinea pigs. These injections were of Freund's complete adjuvant diluted with an equal volume of water, 1% 2-Methylresorcinol (wt/vol) in water, and a 1:1 mixture of 1% 2-Methylresorcinol (wt/vol) in water and Freund's complete adjuvant diluted with an equal volume of water (a 1:1 mixture of the other two injections). One week later, the guinea pigs received a topical induction. The same area was clipped, and since 2-Methylresorcinol was not irritating at 25% (determined in a previous experiment), the test site was pretreated for 24 h with 10% sodium lauryl sulfate in water. This was followed by topical induction with a 48-h occlusive patch saturated with 25% 2-Methylresorcinol in propylene glycol. The animals were challenged topically 2 weeks later. The left flank of each guinea pig was clipped, and a 24-h occlusive patch saturated with 25% 2-Methylresorcinol in propylene glycol was applied. Challenge reactions were scored (erythema and edema each scored on a scale of 0 to 4) 24, 48, and 72 h after patch removal. Dermal irritation was observed after intradermal injections of Freund's complete adjuvant alone and mixed with 2-Methylresorcinol and after intradermal injections of 1% 2-Methylresorcinol. No dermal irritation was observed after topical application of 25% 2-Methylresorcinol in propylene glycol. At challenge, no erythema or edema was observed (all scores were 0). Under the conditions of this test 2-Methylresorcinol was not a sensitizer. A second test program using the same procedure was conducted on a group of 20 guinea pigs.[77] Five percent 2-Methylresorcinol was used during the induction phase and for the challenge. The test compound produced no reaction in guinea pigs in this maximization test and was considered a nonsensitizer.

Two test creams, one containing 6% hydrogen peroxide and the second containing both 6% hydrogen peroxide and 2% 2-Methylresorcinol were tested using the same method as previously described.[77] Neither cream produced a positive result.

Resorcinol and 2-Methylresorcinol were separately tested for photoallergenicity on two groups of 20 Hartley albino guinea pigs using identical procedures. Both ingredients were tested at the same concentration (10% aqueous solution for the induction exposure, and 10 and 2% for the challenge exposure). The nuchal area was clipped and gently stripped with pressure-sensitive tape, and 0.3 ml of the test solution was applied using a Hilltop® chamber. Induction sites were covered by occlusive patches for 2 h, uncovered, and exposed to approximately 10 J/cm^2 of UV (320–400 nm) light. The lumbar region was simultaneously shielded from UV exposure. Six induction treatments, on alternating days, were given. Ten guinea pigs were sham-treated as negative controls. After a 9-day nontreatment period, two pairs of sites on the clipped lumbar region of

TABLE 6. Subchronic and Chronic Dermal Toxicity

Material tested	*No. and species of animal*	*Length of study*	*Dose of material*	*Method*	*Results*	*Reference*
2-Methylresorcinol						
Hair dye, 1% 2-Methylresorcinol (23 other ingredients)	6 male and 6 female New Zealand rabbits (3 control groups)	13 weeks	0.5 ml/kg	Mixed with 6% H_2O_2 and applied topically 2 times weekly to clipped, alternating sites in the thoracic-lumbar region; restrained 1 h, shampooed, rinsed, and dried; one half of rabbits abraded each week	No toxicity; normal body weight gains; "unremarkable" urinalysis; slight thickening of treated skin	78
Resorcinol						
12.5% Resorcinol ointment (contained glycerin, wool fat, and yellow soft paraffin)	6 albino rats (6 controls)	3 weeks	–	Shaved bellies; rubbed with ointment 15 min 2 times daily; controls received ointment base only	No differences in final thyroid weights of rats	79
2 hair dye formulations, 0.40% Resorcinol (8 other ingredients)	28 male and 28 female Swiss-Webster mice per group (76 male and 17 female controls)	2 years	0.05 ml	Mixed with 6% H_2O_2 and applied weekly to clipped intrascapular region; dried with hair dryer	Body weight gains similar to controls; no skin irritation or other adverse effects; erratic survival rate	80
0.75% Resorcinol and other hair dye ingredients in a carboxymethyl-cellulose slime with ammonia and sodium sulfite	50 male and 50 female Sprague-Dawley rats (50 male and 50 female controls)	2 years (and observed additional 6 months)	0.5 g	Mixed with 6% H_2O_2 and applied 2 times a week to shaved dorsal skin for 30 min; washed and dried	Normal behavior, body weight changes, feed intake; no skin irritation; hematological data within normal ranges; no liver function impairment; similar to controls in mean lifespan and mortality rate; at necropsy no pathological changes attributed to treatment	81

5, 25, 50% Resorcinol in acetone	50 female Swiss mice per group (150 females untreated, 50 females treated with acetone)	110 weeks	0.02 ml	Dropped onto shaved dorsal skin between flanks 2 times a week	Skin lesions with ulceration, inflammation, and hyperplasia; survival rates similar to the controls; all mice died by 110 weeks	82
5, 10, 50% Resorcinol solutions	5 New Zealand rabbits (9 controls)	180 weeks	0.02 ml	Applied to interior left ear 2 times a week	No treatment-related decrease in survival rates or local changes; all rabbits died by 180 weeks	83
3 oxidation hair dye formulations, 0.40% Resorcinol (up to 10 other hair dye intermediates and ingredients)	6 groups of 100 mice (250 untreated, 2 groups of 100 received hair dye base–no intermediates, Resorcinol)	18 months	0.05 ml	Hair dyes mixed with 6% H_2O_2 and applied to shaved midscapular area; each hair dye and the base alone was applied to one group weekly and one group fortnightly	For first 5 months, moderate alopecia in 50% mice receiving hair dye weekly; by 11 months hair growth appeared normal; at necropsy, skin and appendages were normal (microscopically); no signs of systemic toxicity; body weights similar to controls; liver:body weight ratios and hematological data within normal limits; survival varied from 58 to 80%; similar to controls	84
Hair dye, 2% Resorcinol (23 other ingredients)	6 male and 6 female New Zealand rabbits (3 control groups)	13 weeks	0.5 ml/kg	Mixed with 6% H_2O_2 and applied topically 2 times weekly to clipped, alternating sites in the thoracic-lumbar region; restrained 1 h, shampooed, rinsed, and dried; one half of rabbits abraded each week	No toxicity; normal body weight gains; "unremarkable" urinalysis; slight thickening of treated skin	78

each guinea pig were challenged with 0.3 ml of the 10 and 2.0% solutions, respectively, and covered by occlusive patches for 2 h. The left side and the induction area were subsequently shielded while the right side was exposed to approximately 10 J/cm^2 of UV (320–400 nm) light. Sites were scored at 24 and 48 h. Two of 20 animals receiving induction treatments of 10% Resorcinol were positive for sensitization when challenged at 10% but not when challenged at 2.0%. One additional animal was positive for sensitization when separately treated areas were exposed to UVA and challenged with 10% Resorcinol. The severity of response in the sensitized animals was not increased by exposure to UVA. No animals showed hypersensitivity or photoallergenicity when challenged at 2.0% Resorcinol. All controls were negative.

Six of 20 animals receiving induction treatments of 10% 2-Methylresorcinol were positive for sensitization when challenged at 10%, but only 1 of 20 animals was sensitized when challenged at 2.0%. The number of positive responses, as well as the severity of the reaction, were not increased when the separately treated areas were exposed to UVA. All controls were negative.[87,88].

A guinea pig sensitization test, using the open epicutaneous method, was conducted with 3% Resorcinol.[91] None of the 19 animals tested reacted to the application of Resorcinol.

Ocular Irritation

The ocular irritation of 2-Methylresorcinol has been studied in rabbits.[92] The left eyes of 4 female New Zealand albino rabbits were used in the experiment, and the right eyes served as controls. A 2.5% aqueous solution of 2-Methylresorcinol, in a dose of 0.1 ml, was instilled into the conjunctival sac, and the eyelids were held together for 1 second and then released. The eyes of 2 of the rabbits were washed with 20 ml distilled water 20 seconds after 2-Methylresorcinol administration. The eyes were examined 1 h and 1, 2, and 3 days after administration of the compound. Two of the rabbits (1 with unwashed eye, 1 with washed eye) had some ocular discharge, and in 2 of the rabbits (both with washed eyes) conjunctival redness was observed at 1 h. There were no other adverse reactions. No positive reactors were observed; 2-Methylresorcinol was not an ocular irritant.

When 100 μl of a 5% water solution of 2-Methylresorcinol (pH 8–10) were instilled without washing into the conjunctival sac of 6 New Zealand rabbits, no irritation of the cornea and iris was observed in all test animals.[77] The conjunctivae of all animals reacted 24 h after instillation with mild to severe redness, mild edema, and exudation. The observed signs disappeared in 7 days.

Two groups of 5 New Zealand rabbits were used to evaluate the acute eye irritation of a basic cream used in hair dyeing.[77] One preparation contained the cream mixed 1:1 with hydrogen peroxide, and the other was the same preparation in which 2-Methylresorcinol was added to a final concentration of 2%. Both preparations were classified as "slightly irritating," but mixtures containing hydrogen peroxide are normally slightly irritating. The addition of 2-Methylresorcinol did not change the acute eye irritation produced by the cream.

Resorcinol, 100%, was an eye irritant in rabbits.[7]

A product formulation containing 1.4% Resorcinol was tested in 9 rabbits.[93] One-tenth milliliter of the test material was instilled into the conjunctival

sac of one eye of each rabbit; the contralateral eye served as control. The eye was held shut for 1 second. In 3 rabbits the treated eyes were washed after 30 seconds. The test material produced corneal damage and conjunctivitis in all animals (washed and unwashed eyes) and iritis in 5 of 9 animals at 24 h (2 of 3 washed, 3 of 6 unwashed eyes). By day 7, corneal opacity, iritis, and conjunctivitis were noted in 1 animal, and corneal stippling and conjunctivitis in another, of the 6 animals exposed without washing. Three of the remaining 4 animals of this group had only conjunctivitis by day 7. For the 3 animals with washed eyes, 1 had corneal opacity and conjunctivitis, and the remaining 2 had conjunctivitis by day 7.

Intraperitoneal, Intravenous, and Subcutaneous Studies

Resorcinol has been administered intraperitoneally (ip) to mice[94] and rats,[95] intravenously (iv) to dogs,[68] and subcutaneously to rats[79,81] (Table 7). Ip administration to mice and rats and subcutaneous administration to rats resulted in convulsions. Dogs were killed by iv doses of 0.7–1.0 g/kg Resorcinol. Subacute subcutaneous administration resulted in rat thyroid gland hypertrophy. A single subcutaneous dose did not affect thyroidal uptake of iodine. Subcutaneous administration to rats of a hair dye formulation containing 0.75% Resorcinol did not result in methemoglobin formation, but a few Heinz bodies were found.

Inhalation Studies

No deaths occurred when groups of 6 female Harlan-Wistar albino rats inhaled Resorcinol-water aerosols for 1 h at concentrations of 2130 and 7800 mg/m^3 or for 8 h in concentrations of 2000–2800 mg/m^3. Normal weight gains were made over a 14-day observation period, and no treatment-related lesions were seen at necropsy at the end of the 14 days. Rats, rabbits, and guinea pigs inhaled Resorcinol at a concentration of 34 mg/m^3 for 6 h a day for 2 weeks. The animals were maintained several months, and periodically some were killed. No toxic effects were observed. No damage to the lungs and trachea and no evidence of an allergic reaction in the respiratory tract were noted.[7]

Rats and guinea pigs received three daily throat sprayings with 1% Resorcinol in water for 2 weeks and were observed for a further 10 weeks. During the 2 weeks of exposure, the throats of the animals appeared irritated, but this disappeared after exposure was discontinued.[7]

Special Studies

Animal Reproduction and Teratology

A series of hair dyes, one containing 1% 2-Methylresorcinol and four containing 1.7, 1.7, 1.0, and 2.0% Resorcinol, have been tested for teratological and reproductive effects in two separate studies using rats.[78,96] Two different hair dyes each containing 1.7% Resorcinol were tested in mice.[97,98] The procedures used in these four studies have been previously described.[32,99] The results were negative. The teratological effects of Resorcinol as a pure ingredient have also

TABLE 7. Intraperitoneal, Intravenous, and Subcutaneous Toxicity

Material tested	*Method*	*Results*	*Reference*
Resorcinol, in 0.9% saline	Given ip to groups of 6 urethane-anesthetized male albino mice	Produced myoclonic convulsions (short-lasting muscular jerks with no evidence of prolonged tetanic activation of the muscles) in 50% of the mice at 0.92 mmol/kg; time to peak effect was 12 min	94
Resorcinol	Given ip to Sprague-Dawley rats in doses of 150 and 200 mg/kg	Produced convulsions	95
Resorcinol	Given iv to dogs	Dogs were killed at doses of 0.7–1.0 g/kg	68
Resorcinol, in water	Given subcutaneously to 5 rats; 3 h later, labeled iodine was administered ip; 2 h later, rats killed and thyroid uptake of iodine determined	Thyroid uptake of labeled iodine was not different in treated and control rats	79
Resorcinol, 1.5 g in 100 ml arachis oil	Given subcutaneously 2 times a day (in doses of 0.14 mmol/kg Resorcinol) for up to 69 days to 4 rats; 1 rat killed at 10, 31, 47, and 69 days	At 10 and 31 days the thyroid was macroscopically normal; at 47 days, the thyroid had typical goitrogen-induced changes of hyperemia, gross cellular hyperplasia, and widespread depletion of colloid; at 69 days, moderate thyroid hyperplasia	79
Resorcinol, 10 g in 100 ml arachis oil containing 5 g beeswax	Given subcutaneously 2 times a day (in doses of 0.45 mmol/kg Resorcinol) to 6 rats	Was toxic; convulsions; killed rats after a "few" days	79
0.75% Resorcinol and other hair dye ingredients in a carboxymethyl-cellulose slime with ammonia and sodium sulfite	Mixed 1:1 with H_2O_2 and given subcutaneously to groups of 2–4 Wistar-Elberfeld rats	No pathological methemoglobin formation; very small number of Heinz bodies found	81

been tested in rabbits and mice.[100,101] The results were negative in both testing programs. These experiments are summarized in Table 8.

Three related but separate reproduction studies have been conducted using Resorcinol (pure ingredient): a teratology dose-range study in rats,[90] a full study in rats at 40, 80, or 250 mg/kg per day,[100] and a study in rabbits of 25, 50, or 100 mg/kg per day.[101] Distilled water was given to the negative control group in each study. The second and third studies also included a positive control group treated daily with vitamin A (15 mg/kg in rats and 6 mg/kg in rabbits). Intragastric intubation with the compound began on day 6 of pregnancy and continued to day 15 in the dose-range study and through day 18 of gestation in the second and third studies. For the two studies using rats, the animals were killed on day 20 in the dose-range study and on day 19 in the second study. The rabbits in the third study were maintained without treatment from day 19 to day 28 of gestation when they were killed and examined. The dose-range study included 5 pregnant rats per treatment group, 23 mated rats at each dose in the second study, and 18–26 mated rabbits at each dose in the third study. In the dose-range study, the mean numbers of implants and live fetuses were significantly higher in the 475 mg/kg dose group than in the controls. No other significant deviations from control values were noted for mean number of implants, live fetuses, resorptions, or dead fetuses for any of the dose groups. No effects were observed in the rats of the second study during the treatment period, and no embryotoxicity, embryolethality, or teratogenicity due to the administration of Resorcinol was observed. In the study using rabbits, no evidence of maternal toxicity, embryotoxicity, or teratogenicity at any treatment was observed.

Mutagenicity

The mutagenic activity of 2-Methylresorcinol has been investigated in the Ames *Salmonella*/mammalian-microsome mutagenicity tests.[102,103] 2-Methylresorcinol, doses of 50–2500 μg, was negative in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, and TA98 with metabolic activation. (Metabolic activation was from 9000 × *g* liver homogenates from Aroclor 1254-induced rats.) At a dose of 2500 μg *S. typhimurium* strains TA1537 and TA1538 were inhibited or partially inhibited by 2-Methylresorcinol. All strains were inhibited or partially inhibited at 5000 μg 2-Methylresorcinol. A similar study at doses of 50–5000 μg, both with and without activation, was negative. There was no cell inhibition at these doses[104] (Table 9).

2-Methylresorcinol was nonmutagenic when tested in vitro in cultured Chinese hamster ovary cells and in vivo in CD-1 mice.[104]

Resorcinol has been studied in the Ames mutagenesis assay both with and without metabolic activation; it was generally negative in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100[95,102,105–112] (Table 9). Resorcinol was not mutagenic for the tryptophan auxotrophs, *Escherichia coli* strains WP2 and WP2 uvrA$^-$, with or without metabolic activation.[110] Concentrations of 50–500 μM Resorcinol were negative in an *E. coli* DNA cell-binding assay.[113] Aneuploid production in the fungus, *Neurospora crassa*, with Resorcinol was similar to the control results.[114]

Resorcinol, at a concentration of 50 mM, did not cause sex-linked recessive

TABLE 8. Teratology and Reproductive Studies

Ingredient	*Hair dye formulation*	*Ingredient in hair dye (concentration – %)*	*Dose*	*Test animal*	*No. of animals*	*Method of delivery*	*Results*	*Reference*
2-Methylresorcinol								
	P-21	1	2 ml/kg of 1:1 dye: H_2O_2 dilution	Rat	20F	Topical	No embryotoxic or teratogenic effects	78
	P-21	1	0.5 ml/animal of 1:1 dye: H_2O_2 dilution	Rat	20F, 20M	Topical	No treatment-related effects	96
	Pure ingredient	–	0.1 0.4 1.5	Rat	35	Feed	Significant weight loss in male and female adults and in weanlings; no teratological effects	77
Resorcinol								
	7401	1.7	2 ml/kg of 1:1 dye: H_2O_2 dilution	Rat	20F	Topical	No embryotoxic or teratogenic effects	78
	7402	1.7		Rat	20F	Topical		
	7404	1.0		Rat	20F	Topical		
	7405	2.0		Rat	20F	Topical		

7401 7402 7404 7405	1.7 1.7 1.0 2.0	0.5 ml/animal of 1:1 dye: H_2O_2 dilution	Rat Rat Rat Rat	20M, 20F 20M, 20F 20M, 20F 20M, 20F	Topical Topical Topical Topical	No treatment-related effects	96
2773 2774	1.7 1.7	0.05 ml/animal of 1:1 dye: H_2O_2 dilution	Mice Mice	30F 30F	Topical Topical	No teratogenic effects; possible retarding of ossification process	97
2773 2774	1.7 1.7	2 ml/kg of 1:1 dye: H_2O_2 dilution	Rabbit Rabbit	24F 24F	Topical Topical	No teratogenic effects; possible embryotoxicity in slightly lower fetal survival	98
Pure ingredient	–	25, 50, 100 mg/kg groups	Rabbit	≥ 20F/dose level	Gavage	No embryotoxicity or teratogenic effects	100
Pure ingredient	–	40, 80, 250 mg/kg groups	Rat	23F/dose level	Gavage	No embryotoxicity, embryolethality, or teratogenicity	101

TABLE 9. Ames *Salmonella* Mutagenesis Assay[102]

Material tested	Dose and solvent	Results without metabolic activation[a]					Results with metabolic activation[a]					Comments	Reference
		TA1535	*TA1537*	*TA1538*	*TA98*	*TA100*	*TA1535*	*TA1537*	*TA1538*	*TA98*	*TA100*		
2-Methylresorcinol													
	50–2500 μg	...	...	...	...	...	(–)	(–)	(–)	(–)	...		103
	50–5000 μg	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)		104
Resorcinol													
	4.0–2500 μg/plate, dimethyl sulfoxide (DMSO)	...	...	...	...	...	(–)	...	(–)	(–)	(–)		105
	Up to 5.5 mg/plate	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)		95
	0.5–2.0 mg	...	...	....	(–)	...	...	...	...	(–)	...		106
	3 μmol/ plate, ethanol	(–)	(–)	...	(–)	(–)	(–)	(–)	...	(–)	(–)	Spot tests	107
	0.03–30 μmol/ plate, ethanol	...	...	...	...	(–)	...	...	...	...	(–)	Spot tests	107

Up to 60 μmol/plate	(−)	(−)	(−)	(−)	(±)	(±)	(−)	(−)	(−)	(−)	Used two minimal media, was positive on one medium for TA100 − S − 9 and TA1535 + S − 9	108
	...	...	...	...	...	(−)	(−)	...	(−)	...		109
	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	Concentration gradient plates; also negative ± S − 9 in strains G46, C3076, and D3052	110
0.1–1000 μg/plate	...	...	...	...	(−)	...	...	...	...	...		111
5–1000 μg/plate, DMSO	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)		112

[a](−), nonmutagenic; (±), weakly mutagenic; ..., no data.

lethal mutations in the F_2 and F_3 generations of the fruit fly, *Drosophila melanogaster*.[108]

Resorcinol, at concentrations up to 1000 nmol/ml, did not induce unscheduled DNA synthesis in primary cultures of adult rat hepatocytes; this assay measures the repair of chemically induced DNA damage.[110] Increased chromatid breaks and exchanges were observed in Chinese hamster ovary cells after exposure to 1.6 mg/ml Resorcinol with and without metabolic activation.[115] Resorcinol, in concentrations of $0.5–2.0 \times 10^{-5}$ M, was negative for sister chromatid exchanges (SCE) in cultured Chinese hamster V79 cells.[116] Darroudi and Natarajan[117] confirmed these latter findings but reported that 0.002% Resorcinol increased the frequency of chromosomal aberrations in lymphocytes from cultures of heparinized human whole blood samples.

Rats were given Resorcinol ip in doses of 1–100 mg/kg or orally by stomach tube in doses of 0.8–100 mg/kg; no increase was observed in SCE in bone marrow cells. Resorcinol was applied topically for 20 minutes to a shaved area on the necks of rats and then was washed off. The Resorcinol was applied in single doses of 0.2–200 mg/kg several hours apart. No increase in the frequency of SCE was observed in bone marrow cells.[95]

An oral dose of 100 mg/kg Resorcinol to male mice did not inhibit testicular DNA synthesis.[118] Resorcinol was negative in the mouse sperm-head abnormality test after ip administration of 0.5–2.0 mmol/kg.[116]

Resorcinol was negative in the mouse bone marrow micronucleus test after ip administration of 0.5–2.0 mmol/kg Resorcinol.[116] Resorcinol was also negative in this test after the ip administration of two doses of up to 2.0 mmol/kg (220 mg/kg) Resorcinol 24 h apart.[108] Rats were given two oral doses of 250 mg/kg Resorcinol as a suspension in 0.5% (wt/vol) gum tragacanth containing 0.05% (wt/vol) sodium sulfite 24 h apart; Resorcinol was negative in the rat bone marrow micronucleus test.[76]

Carcinogenicity

The carcinogenic potentials of five hair dyes, one containing 2-Methylresorcinol (1.0%), and four dyes containing 1.7, 1.7, 1.0, or 2.0% Resorcinol, were investigated in a combined study using 60 male and 60 female Charles River CD weanling rats obtained from the first mating (F_{1A}) of a multigeneration reproduction study.[119,120] The procedures used in these three experiments have been previously described.[32,99] The results were negative.

Resorcinol as a pure ingredient has been tested for carcinogenicity. Three groups of 50 female Swiss mice were topically treated with 0.02 ml of 5, 25, and 50% solutions of Resorcinol in acetone two times a week for 100 weeks. The Resorcinol solutions were applied to the shaved dorsal skin between the flanks. The experiment also included 150 untreated mice, 50 mice treated with acetone alone, and 50 positive controls treated with 7,12-dimethylbenz(a)anthracene (DMBA). Approximately half the mice treated with Resorcinol were alive after 75 weeks. The percentage of tumor-bearing animals was similar in the Resorcinol-treated, untreated, and acetone-treated groups. Most of the tumors were lymphomas, pulmonary adenomas, and hepatic hemangiomas. Two, three, and two mice had skin tumors in the Resorcinol-treated, untreated, and acetone-treated groups, respectively. Resorcinol was not carcinogenic in this experiment.[82]

Groups of 5 New Zealand rabbits were topically treated with 0.02 ml of 5, 25, and 50% solutions of Resorcinol two times a week for 160 weeks. The Resorcinol solutions were applied to the interior of the left pinna. A group of untreated rabbits and a positive control group treated with DMBA were included in the experiment. No tumors were seen in the Resorcinol-treated groups and Resorcinol was considered noncarcinogenic.[83]

Fifty female Swiss mice were topically treated with 150 μg benzo[a]pyrene (B[a]P) as an initiator and 14 days later with 0.1 ml of a Resorcinol solution in acetone (10 mg Resorcinol) as a promoter; the Resorcinol solution was applied three times a week until the mice had been on test for 449 days. The initiator and the Resorcinol solution were applied to the dorsal skin. Fifty mice were treated with acetone alone, 100 were untreated, and two groups of mice were treated with B[a]P and with phorbol myristate acetate (PMA) and anthralin as positive controls. Resorcinol had no tumor-promoting activity.[121]

The cocarcinogenic potential of Resorcinol has also been investigated. Resorcinol inhibited B[a]P-induced tumor formation in mouse skin. Resorcinol, in a dose of 10 mg, was applied with and without 5 μg B[a]P in a single solution in acetone three times a week for 368 days to the clipped backs of groups of 50 female Swiss mice. The experiment included mice treated with PMA and anthraline with B[a]P as positive controls for cocarcinogenicity and mice treated with B[a]P alone. The first papilloma was observed at 249 days in mice treated with Resorcinol and B[a]P; 5 mice had papillomas and a total of 6 papillomas were observed. Two mice had squamous carcinomas. No papillomas or squamous carcinomas were seen in mice treated with Resorcinol alone. The first papilloma was observed at 251 days in mice treated with B[a]P alone; 14 mice had papillomas and a total of 16 papillomas were observed. Ten mice had squamous carcinomas. Resorcinol reduced the tumorigenicity of B[a]P by more than 50%.[121]

The carcinogenic potential of hair dye formulations containing Resorcinol has been investigated. A carboxymethylcellulose suspension with ammonia and sodium sulfite containing 0.75% Resorcinol and other hair dye ingredients was mixed with 6% hydrogen peroxide and topically applied at a dose of 0.5 g for 30 minutes two times a week for 2 years to the shaved dorsal skin of a group of 50 male and 50 female Sprague-Dawley rats; the animals were washed and dried after each application. The experiment also included a group of untreated controls and two groups treated with similar hair dye formulations that did not contain Resorcinol. The rats were observed for an additional 6 months after the 2-year treatment period. The lifespan and mortality rate of the rats treated with the hair dye formulation that contained Resorcinol were similar to those of the untreated controls. The incidence of tumors, proportion of males and females affected, and tumor types were comparable in the treated and untreated groups. No skin tumors were found in the area of application of the hair dye formulation.[81]

Three oxidation hair dye formulations containing 0.4% Resorcinol (and up to 10 other hair dye intermediates and ingredients) were topically applied weekly and every 2 weeks for 18 months to groups of 100 mice. The formulation was mixed with 6% hydrogen peroxide before use, and 0.05 ml was applied to a shaved midscapular area. Two groups of 100 mice received the hair dye base without intermediates or Resorcinol weekly or every 2 weeks. The experiment

also included 250 untreated mice and a positive control group that received topical applications of DMBA in acetone weekly (50 μg/week for 6 months, then 10 μg/week for 4 months, then 50 μg/week for the remainder of the study). The survival of the mice that received topical applications of the hair dye formulations containing Resorcinol was similar to that of the untreated controls. The incidence and type of tumors were not different from the untreated controls. There was no evidence of carcinogenicity produced by the three hair dye formulations containing Resorcinol.[84]

Two hair dye formulations containing 0.4% Resorcinol (and eight other ingredients) were mixed with 6% hydrogen peroxide and applied weekly for 2 years at a dose of 0.05 ml to the clipped intrascapular region of groups of 28 male and 28 female Swiss-Webster mice; the mice were dried with a hair dryer. The experiment included 76 male and 17 female untreated controls, 14 male and 14 female mice treated with acetone, and two groups of 28 male and 28 female mice as positive controls; the positive control groups received 0.02% and 0.005% DMBA. The survival rates of all the groups varied. There was no difference between the sexes or between the untreated controls and the hair dye formulation-treated mice in number of neoplasms (including skin neoplasms) or incidence of a particular type of neoplasm.[80]

CLINICAL ASSESSMENT OF SAFETY

Small volumes of a 10% (wt/vol) aqueous solution (pH 8–10) of 2-Methylresorcinol were repeatedly applied to the same forearm area of 5 female volunteers at 30-second intervals for 30 minutes.[77] No indication of skin irritation was observed during the application period or 24 h after treatment.

Patches containing 10% (wt/vol) aqueous solution of 2-methylresorcinol were applied to the forearm of 5 female volunteers for 2 h.[77] No indication of skin irritation was observed after the patches were removed or when sites were rescored 24 h later.

The sensitization potential of a 3% solution of 2-Methylresorcinol was investigated in two repeated insult patch test studies.[122,123] One hundred nineteen volunteers were enrolled in each study and were used to assess irritation; 102 subjects completed each study. Nine 24-h semiocclusive patches containing 0.1 ml of the 2-Methylresorcinol in a water-based vehicle with 24–48-h rests in between were applied to the right or left of the midline of the intrascapular area of the back. The vehicle contained the following additives: isopropanol (12%), polysorbate-80 (2.0%), hydroxyethylcellulose (2.0%), and sodium bisulfite (0.05%). Other products also were tested on the same volunteers. These induction patches were evaluated 48–72 h after application. A 14-day nontreatment period was followed by a 24-h semiocclusive patch applied to a previously unexposed site. This challenge was scored 48–72 h after application. Reactions were scored on a scale of 0–3.0 (gradations of 0.5). There were several reactions of 0.5 (doubtful response, barely perceptible erythema, only slightly different from surrounding skin) during induction, and two 0.5 reactions were observed at challenge sites. No clinically significant evidence of irritation or sensitization was

found. A summary of the clinical test data on 2-Methylresorcinol is shown in Table 10.

During one 12-month period, Howell[127] examined subjects with contact dermatitis, and 5 of 250 were positive in patch tests with Resorcinol. In another study, 179,800 patients from private practices or university dermatology clinics were examined by 11 dermatologists, and 487 cases of cosmetic-related contact dermatitis were found. Of these, 149 subjects were patch tested on the upper back with various cosmetic ingredients for 48 h; readings were done at 48 and/or 72 h. One subject had a cutaneous reaction to Resorcinol.[128]

The maximization test was performed on 22 volunteers with Resorcinol. Each subject received five 48-h occlusive induction patches of 15% Resorcinol in petrolatum on the forearm or calf. The induction patches were placed daily. The challenge patch of 5% Resorcinol in petrolatum remained in place for 48 h, and then the sites were scored after removal and 2 days later. None of the volunteers were sensitized to Resorcinol.[124]

A cosmetic product conditioning preparation containing 1.4% Resorcinol was used in a Schwartz-Peck Prophetic Patch Test on 102 subjects.[125] Both semiocclusive and open patches were applied for 48 h, followed by a 2-week

TABLE 10. Clinical Assessment of Safety

Ingredient	*Concentration (%)*	*Procedure*	*Vehicle*	*No. of subjects*	*Results*	*Reference*
2-Methyl-resorcinol	3	RIPT	Mixture	102	No clinical evidence of irritation or sensitization	122
2-Methyl-resorcinol	3	RIPT	Mixture	102	No clinical evidence of irritation or sensitization	123
2-Methyl-resorcinol	10	30-min exposure	Water	5	No signs of irritation at 0 and 24 h	77
2-Methyl-resorcinol	10	2-h exposure	Water	5	No signs of irritation at 0 and 24 h	77
Resorcinol	15 induction 5 challenge	Maximization	Petrolatum	22	No sensitization	124
Resorcinol	1.4	Prophetic patch	Formulation	102	No irritation, sensitization, or photosensitization	125
Resorcinol	1.4	Draize-Shelanski	Formulation	49	No irritation, sensitization, or photosensitization	126

nontreatment period, then challenged with semiocclusive and open patches. The skin under the semiocclusive patches was irradiated with a Hanovia Tannette Mark I Lamp at 12 inches for 1 minute after reading the second patch. No reactions were observed at any of the application sites.

A Draize-Shelanski repeat insult patch test using the same 1.4% formulation previously discussed was conducted on 49 subjects.[126] The test product was applied under semiocclusive and open patches at 48-h intervals for 3½ weeks for 10 insults. The skin under the closed patches was exposed to a Hanovia Tanette Mark I Lamp at a distance of 12 inches for 1 minute after the first, fourth, seventh, tenth, and eleventh challenge patch insults. The results were negative for all subjects.

Resorcinol has been reported to be an infrequent sensitizer. A summary of the test data is shown in Table 10. Cross-sensitivity reactions to Resorcinol have been observed; the most significant clinically are those to Resorcinol monoacetate and to hexylresorcinol. Milder cross reactions are sometimes seen between Resorcinol, hydroquinone, pyrocatechol, phenol, pyrogallol, and hydroxyhydroquinone, and orcinol.[35]

The threshold limit value (TLV) for Resorcinol set by the American Conference of Governmental Industrial Hygienists (ACGIH)[129,130] is 10 ppm. For a normal 8-h workday and 40-h work week, this is the time-weighted average concentration in the air to which most workers can be repeatedly exposed, day after day without adverse effect. The short-term exposure limit (STEL) set by the ACGIH is 20 ppm. This is the maximal concentration in the air to which workers can be exposed for 15 minutes without suffering irritation, tissue changes, or narcosis. Workers should have no more than four exposures per day, and the exposures should be at least 60 minutes apart.

SUMMARY

2-Methylresorcinol and Resorcinol are most frequently used in cosmetic hair dye formulations. Resorcinol has also been reported to be used in other cosmetic skin preparations, such as cleansing creams and fresheners at concentrations between 1 and 5%. Resorcinol has been classified as Generally Recognized As Safe (GRAS) up to 15 ppm in foods.

The results of cutaneous and oral feeding studies have indicated that both 2-Methylresorcinol and Resorcinol are readily absorbed by rodents. Both compounds are rapidly eliminated in the urine and feces, principally as metabolites.

The results of acute oral toxicity studies indicate that 2-Methylresorcinol is moderately toxic and Resorcinol is slightly to moderately toxic. Subchronic feeding studies of both ingredients produced no deaths or other significant effects. A subchronic dermal study of 2-Methylresorcinol was negative for toxic effects. In a 2-year chronic dermal study, Resorcinol in hair dye formulations up to 0.75% produced no toxic effects.

Significant skin effects were observed in mice, but not in rabbits, following dermal application of Resorcinol (pure ingredient) at 5% concentration. A 10% Resorcinol solution was not irritating to guinea pigs. A 0.5 g application of Resorcinol to intact rabbit skin was not a primary irritant to intact skin but did produce

tissue necrosis when applied to abraded skin. A 2.5% 2-Methylresorcinol solution was classified as a primary irritant in rabbits. A 10% 2-Methylresorcinol solution was not irritating to guinea pigs. Neither 2-Methylresorcinol at 5% nor Resorcinol at 3% produced sensitization in guinea pigs. 2-Methylresorcinol was not photoallergenic to guinea pigs but was a sensitizer when a 10% solution was used during the induction and challenge exposure. Resorcinol was not photoallergenic to guinea pigs but was a sensitizer when a 10% solution was used during the induction and 10% and/or 2% was used in the challenge exposures.

2-Methylresorcinol at 2.5% was not an ocular irritant to rinsed or unrinsed rabbit eyes, but irritation was produced at 5% concentration in unrinsed rabbit eyes. The addition of 2% 2-Methylresorcinol to a cream that was already classified as "slightly irritating" to rabbit eyes did not produce a more "unfavorable" reaction. Resorcinol at 100% concentration was a severe eye irritant to rabbits. A cosmetic formulation containing 1.4% produced corneal effects and conjunctivitis in rinsed and unrinsed eyes of 9 rabbits within 24 h and persisted throughout the 7-day observation period.

A series of hair dye formulations containing 2-Methylresorcinol and Resorcinol has been studied for reproductive and/or teratogenic effects following dermal application. Topical applications of these hair dye formulations to pregnant rats at 3-day intervals during the gestation period produced no significant teratogenic effects. Male and female weanlings (F_0) from this study were treated with the same hair dye formulations before mating. This procedure was repeated until F_{3C} litters were produced. No treatment-related effects on reproductive performance or teratogenic effect on the offspring was attributed to the topical applications of hair dyes containing 2-Methylresorcinol or Resorcinol. Other studies of these hair dyes topically applied to either mice or rabbits did not reveal a teratogenic effect. Resorcinol (pure ingredient) did not produce embryotoxicity or teratogenesis following gastric intubation of 25–100 mg/kg in pregnant rats or 40–250 mg/kg in rabbits.

Resorcinol and 2-Methylresorcinol were nonmutagenic, both with and without metabolic activation, in the Ames *Salmonella* test. Other microbial and tissue culture assays for mutagenicity of both ingredients were also negative.

Extensive testing of topically applied hair dyes containing 2-Methylresorcinol and Resorcinol for carcinogenicity in rats and mice has been reported. There were no statistically significant increases or decreases of adenoma of the pituitary, the most common neoplasm, reported in both the treated and control groups. All five hair dye formulations were considered noncarcinogenic under the test conditions used. Other carcinogenicity studies of topically applied hair dyes containing 2-Methylresorcinol and Resorcinol in mice supported this conclusion. Topically applied Resorcinol (pure ingredient) has also been tested in mice and rabbits. Both studies were negative for carcinogenicity.

The cocarcinogenic potential of topically applied Resorcinol has been investigated in mice and rats. No cocarcinogenic effect was reported in either. In similar studies in mice, oxidative hair dyes containing 0.4% Resorcinol did not produce a cocarcinogenic effect.

2-Methylresorcinol at 3% concentration produced no evidence of irritation or sensitization in 119 human subjects. A concentration of 10% 2-Methylresorcinol was not irritating to two groups of 5 subjects.

Resorcinol has been reported to be a skin irritant and rarely a sensitizer. In clinical testing, 5 of 250 and 1 of 149 patients reacted positively to Resorcinol. No sensitization to 15% Resorcinol was reported in a study of 22 nonclinical subjects. No application site irritation or sensitization was reported in the testing of two groups of 102 human volunteers to a formulation containing 1.4% Resorcinol. Phototoxicity testing of 49 subjects in this latter study was also negative.

DISCUSSION

There are data indicating that Resorcinol is a mild skin irritant and a rare sensitizer in clinical testing. However, at the concentrations used in cosmetic products there was no application site irritation, sensitization, or photosensitization when tested on human volunteers.

CONCLUSION

On the basis of the available animal and clinical data presented in this report, the CIR Expert Panel concludes that 2-Methylresorcinol and Resorcinol are safe as cosmetic ingredients in the present practices of use and concentrations.

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