Amended Report of the Cosmetic Ingredient Review Expert Panel

Amended Safety Assessment of p-Methylaminophenol Sulfate and p-Methylaminophenol

December 10, 2007

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on this Tentative Safety Assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings , will be available at the CIR office for review by any interested party, and may be cited in a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

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INTRODUCTION

The following report is an Amended Tentative Report on the chemistry, use, and toxicology of the oxidative hair dye ingredients p-Methylaminophenol Sulfate and p-Methylaminophenol (p-MAP). The ingredient p-Methylaminophenol Sulfate was previously reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel and was found to be "...safe as a cosmetic ingredient in the present practices of use and concentration". The original safety assessment considered data on the safety of p-MAP but did not include the ingredient in the conclusion (Elder 1991). Upon re-review, the Expert Panel felt that there was enough data to include p-MAP in the safety assessment. Therefore, this Tentative Amended Report adds the ingredient p-MAP.

In further support of the addition of p-MAP, the data in the original safety assessment of p-Aminophenol, m-Aminophenol, and o-Aminophenol are relevant (Elder 1988); this safety assessment has been re-reviewed by the Expert Panel and that data is also relevant. Both of these documents are summarized in this report.

CHEMISTRY

DEFINITION AND STRUCTURE

p-Methylaminophenol Sulfate (CAS Nos. 55-55-0 and 1936-57-8) and p-MAP (CAS No. 150-75-4) are substituted phenols. The are chemically classified as amines, color additives - hair, and phenols (Gottschalck and McEwen 2006).

p-Methylaminophenol Sulfate is also known as 4-(Methylamino)Phenol Sulfate (Estrin et al. 1982; Gottschalck and McEwen 2006); N-Methyl-para-Aminophenol Sulfate (Hawley 1971); Monomethyl-p-Aminophenol Sulfate; p-Hydroxymethylaniline Sulfate (Windholz 1983); Metol; Paramethylaminophenol Sulfate; and Phenol, 4-(Methylamino)-Sulfate Salt (2:1) (Gottschalck and McEwen 2006). It is also known as: 1-Hydroxy-4-Methylamino-Benzine Hemisulphate, 4-(Methylammonio)-Phenol Sulphate, N-(Methyl-4-Ammoniophenol) Sulphate, 4-Hydroxy-N-Methylanilinium Sulphate, p-Hydroxy-N-Methylaniline Sulphate, N-Methyl-4-Hydroxyanilinium Sulphate, N-Methyl-p-Hydroxyaniline Sulphate, and N-Methyl-N-(4-Hydroxy)Phenylammonium Sulphate (Scientific Committee on Consumer Products [SCCP] 2006). It is known commercially as Metol, Pictol, Rhodol,

and various other names (Windholz 1983) as well as Colorex PM and Rodol PM (Gottschalck and McEwen 2006). It conforms to the structure in Figure 1A.

p-MAP is also known as the following technical names: 4-Hydroxy-N-Methylaniline; 4-(Methylamino)Phenol; N–Methyl-p-Hydroxyaniline; Paramethylaminophenol; and Phenol, 4-(Methylamino)- (Gottschalck and McEwen 2006). It conforms to the structure in Figure 1B.

In many instances in the literature, the common name Metol, used for photographic developing, refers to both p-MAP and p-Methylaminophenol Sulfate interchangeably. In several publications on Metol, it is not clear which ingredient is being tested. In this paper, where the identification of the ingredient is clear it is identified; where the identification is not clear, the term Metol is used.

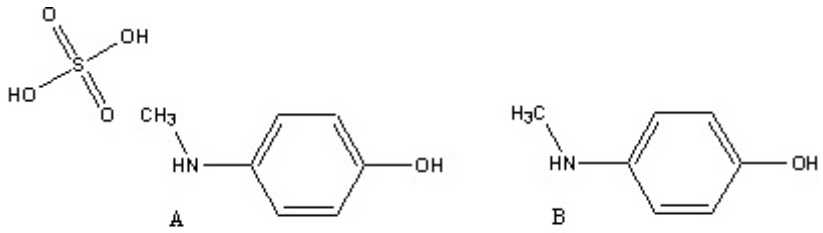

Figure 1. The structures of A) p-Methylaminophenol Sulfate and B) p-Methylaminophenol.

PROPERTIES

p-METHYLAMINOPHENOL SULFATE

p-Methylaminophenol Sulfate occurs as colorless needles (Hawley 1971) or other crystalline products (Windholz 1983). On exposure to air, p-Methylaminophenol Sulfate becomes discolored (Hawley 1971; Windholz 1983). It has a molecular weight of 344.39 and a melting range between 250°C and 260°C (Weast 1983). Decomposition of p-Methylaminophenol Sulfate occurs upon melting (Windholz 1983). It is soluble in water (Hawley 1971; Windholz 1983; Weast 1983), slightly soluble (Windholz 1983) to soluble (Hawley 1971; Weast 1983) in alcohol, and insoluble in ether (Hawley 1971; Windholz 1983).

p-MAP at 5 x 10^{-3} M is stable in the dark, at room temperature and pH values lower than ~7 for at least 1 week. The concentration decreases slowly over time at basic pH values (pH 9 decreases the concentration to ~86% after 24 h). Stability can be maintained by storage in nitrogen saturated solutions; oxidation with dissolved oxygen causes instability (Aceituno et al. 2002).

METHOD OF MANUFACTURE

p-Methylaminophenol Sulfate is manufactured by the methylation of p-aminophenol and the subsequent neutralization with sulfuric acid (Hawley 1971).

ANALYTICAL METHODS

Infrared, ultraviolet (UV), and nuclear magnetic resonance spectra have been published for p-Methylaminophenol Sulfate. The UV spectrum had peaks at 271 and 220 nm, with water as the solvent (Grasselli 1975). A UV spectrum also has been performed on p-Methylaminophenol at a concentration of 0.02 g/l in distilled water. The chemical absorbed at 219, 270, and 277 nm (L'Oreal 1989). The compound may be determined by thin layer chromatography (TLC), using a method that depends on color rather than R_F values as a more reliable method for distinguishing among o-, m-, and p-isomers (Mitchell and Waring 1978). In addition, it may be analyzed by either visual or potentiometric titration with N-bromosuccinamide using the following indicators: butaperazine dimaleate, trifluoperazine dihydrochloride, or promethazine hydrochloride (Gowda and Ahmed 1978).

IMPURITIES

The SCCP (2006) reported on the test of 3 batches of p-Methylaminophenol Sulfate and report the purity to be ≥97.0% (w/w) by titre and >97.5% by high-performance liquid chromatography (HPLC). The sulphate ion content was 30.0% to 30.5%. Water and ash content were < 0.1%. Other impurities include p-Aminophenol (~2.5g/100g) and N,N'-dimethylparaphenylenediamine (<0.4 g/100 g). Heavy metal impurities included: arsenic, antimony, and mercury (< 5 mg/kg); cadmium(< 10 mg/kg); and lead (< 20 mg/kg). There were no residual solvents detected.

CHEMICAL REACTIONS

p-Methylaminophenol Sulfate is used as a primary intermediate in oxidative or permanent hair dyes (Balsam and Sagarin 1972). The primary intermediate undergoes a reaction with hydrogen peroxide (the oxidant) to produce the corresponding imine, which then reacts with a coupler to form an indophenol

dye (Frost and Horowitz 1982). As an intermediate in combination with other intermediates, p-Methylaminophenol Sulfate is capable of producing browns, reds, gold blonds, blues, and grays (Balsam and Sagarin 1972).

NITROSATION

The SCCP (2006) stated that p-Methylaminophenol Sulfate is a secondary amine, thus prone to nitrosation. They have no information on the nitrosamine content of this ingredient.

USE

COSMETIC USE

The ingredients p-Methylaminophenol Sulfate and p-MAP are used as an intermediate in hair dyes/colors, which usually bear warning labels. According to information voluntarily supplied to the Food and Drug Administration (FDA 1989), p-Methylaminophenol Sulfate was used in a total of 49 hair dyes at the time of the first safety assessment (Table 1). Its concentration of use ranged from < 0.1% (31 products) to 10% (17 products). One product is listed at X-1 0%; this is a powder concentrate that was to be diluted before use. p-Methylaminophenol Sulfate is currently used in 112 hair coloring products (FDA 2006) with a concentration range of 0.1% to 0.7% (Cosmetic, Toiletry, and Fragrance Association [CTFA] 2007).

FDA (2006) has no reported uses for p-MAP. CTFA (2007) reports that p-MAP is used at the concentration of 0.7% in hair coloring products (Table 1).

Table 1. Historical and current cosmetic product uses and concentrations for p-Methylaminophenol Sulfate and p-MAP.

Product Category	1989 uses (Elder 1991)	2006 uses (FDA 2006)	1981 concentrations (Elder 1991) (%)	2007 concentrations (CTFA 2007) (%)
		p-Methylaminophenol Sulfate		
Hair coloring products				
Dyes and colors	49	112	<0.1-10	0.1-0.7
Total uses/ranges for p-Methylaminophenol Sulfate	**49**	**112**	**<0.1-10**	**0.1-0.7**
		p-Methylaminophenol		
Hair coloring products				
Dyes and colors	n/a	-	n/a	0.7
Total uses/ranges for p-Methylaminophenol	**n/a**	**-**	**n/a**	**0.7**

Both p-Methylaminophenol Sulfate and p-MAP are considered coal tar hair dyes for which regulations require caution statements and instructions regarding patch tests in order to be exempt from the principal adulteration provision and from the color additive provision in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act of 1938 (FDA 1979).

Product labels shall bear a caution statement and patch test instructions for determining whether the product causes skin irritation. In order to be exempt, the following caution statement must be displayed on all coal tar hair dye products:

> Caution - this product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

At its February 11, 1992 meeting, the Cosmetic Ingredient Review (CIR) Expert Panel issued the following policy statement on coal tar hair dye product labeling:

> The Cosmetic Ingredient Review (CIR) Expert Panel has reviewed the cosmetic industry's current coal tar hair dye product labeling, which recommends that an open patch test be applied and evaluated by the beautician and/or consumer for sensitization 24 hours after application of the test material and prior to the use of a hair dye formulation.
>
> Since the recommendation on the industry's adopted labeling establishes a procedure for individual user safety testing, it is most important that the recommended procedure be consistent with current medical practice.
>
> There is a general consensus among dermatologists that screening of patients for sensitization (allergic contact dermatitis) should be conducted by the procedures used by the North American Contact Dermatitis Group and the International Contact Dermatitis Group (North American Contact Dermatitis Group, 1980; Eiermann et al., 1982; Adams et al., 1985). Basically, these procedures state that the test material should be applied at an acceptable concentration to the patient, covered with an appropriate occlusive patch, and evaluated for sensitization at 48 and 72 hours after application. The CIR Expert Panel has cited the results of studies conducted by both the North American Contact Dermatitis Group and the International Contact Dermatitis Group in its safety evaluation reports on cosmetic ingredients (Elder, 1985).
>
> During the August 26-27, 1991 public meeting of the CIR Expert Panel, all members agreed that the cosmetics industry should change its recommendation for the evaluation of the open patch test from 24 hours to 48 hours after application of the test material.
>
> The industry was advised of this recommendation and asked to provide any compelling reasons why this recommendation should not be made by the Expert Panel and adopted by the cosmetics industry. No opposition to this recommendation was received. At the February 11, 1992 public meeting of the CIR Expert Panel, this policy statement was adopted.

NON-COSMETIC USE

The ingredient p-Methylaminophenol Sulfate is used in spectrophotometric analyses of such compounds as dapsone (Siraj et al. 1981), isoniazid (Siraj et al. 1982), riboflavin (Sastry et al. 1986a), and antibiotics (Sastry et al 1986b) and in the calorimetric analyses of thiamine hydrochloride (Sane et al. 1985) and penicillins G and V (Siraj et al. 1982). It also is listed in various patents for pharmaceuticals as

a treatment for neoplastic disease (Danila 1984; Leontopol and Andronescu 1984). p-Methylaminophenol Sulfate also is used in film developing (Liden 1984a,b).

Both p-Methylaminophenol Sulfate and p-MAP are used to in the film developing process (Brancaccio et al. 1993; Aceituno et al. 2002).

The ingredient p-Methylaminophenol Sulfate is used to react with Nicorandil ((*N*-92-nitroxy)ethyl]3-pyridine carboxamide), a potassium channel activator, for its detection in drug formulation and biological fluids by color recognition (Rahman et al. 2004).

INTERNATIONAL

The European Commission (2002) restricts the concentration of p-Methylaminophenol and its salts to 1.5% in combination with hydrogen peroxide.

p-Methylaminophenol and its sulfates are listed as quasi-drugs by the Minister of Health and Welfare of Japan (Ministry of Health, Labor and Welfare [MHLW] 2001).

GENERAL BIOLOGY

ABSORPTION

p-METHYLAMINOPHENOL SULFATE

The SCCP (2006) reported on an in vitro absorption study using 8 female human skin donors (5 breast and 3 abdomen donors; n = 12 samples). The skin was frozen until use. Skin samples were dermatomed and mounted in flow-through diffusion cells with calcium and magnesium-free phosphate buffered saline in the receptors. [^{14}C]p-Methylaminophenol Sulfate was applied under oxidative (use) and non-oxidative conditions. In the former, the test substance was incorporated into a hair coloring formulation at 1.35% (w/w) associated to the coupler m-Aminophenol at 0.86% (w/w) before mixing with oxidative developer (1:1, w/w) giving a final concentration of 0.68% p-Methylaminophenol Sulfate. In the latter, the test substance was incorporated into the same formulation (without a coupler) at 1.35% (w/w) before mixing with water (1:1, w/w), also at a concentration of 0.68%. The test preparations (~20 mg/cm^2) were applied to the skin surface for 30 min. The skin surfaces were then washed. Twenty-four h after application, the percutaneous absorptions of [^{14}C]p-Methylaminophenol Sulfate was measured.

One oxidative cell did not yield usable results. Most of the p-Methylaminophenol Sulfate, oxidative and non-oxidative, was removed at washing (91.34% and 90.70%, respectively). At 24 h, an

additional 1.37% and 0.73% was recovered, for total recoveries of 96.42% and 97.74%, respectively. The receptors held 0.49 ± 0.24 (0.36%) and 3.04 ± 1.10 µg equiv/cm^2 (2.21%), respectively (Table 2).

Table 2. Recovery of p-Methylaminophenol Sulfate after application to human skin (SCCP 2006).

	Oxidative conditions in hair dye formulation		Non-oxidative conditions	
Cutaneous distribution	µg equiv/cm^2	% applied dose	µg equiv/cm^2	% applied dose
Extractable dose	125.60 ± 3.80	92.72 ± 3.17	126.03 ± 6.14	91.44 ± 4.73
Receptor fluid	0.49 ± 0.24	0.36 ± 0.18	3.04 ± 1.10	2.21 ± 0.80
Dermal delivery (receptor fluid + epidermis/dermis)	1.35 ± 0.78	1.00 ± 0.59	6.19 ± 2.24	4.49 ± 1.62

DISTRIBUTION

The SCCP (2006) reported on the oral administration of p-Methylaminophenol Sulfate to Sprague Dawley (Crl CD(SD) IGS BR) rats (n = 10 of each sex). The test substance (0, 3, 10, or 30 mg/kg/d) was administered daily for 13 weeks (additional details are in the SUBCHRONIC TOXICITY section). Blood was sampled on day 1 and in week 13 at 0.5, 1, 2, 4, 8, and 24 h after dosing. Plasma levels of p-Methylaminophenol Sulfate were below detectable limits at all time points in the 3 mg/kg/d group and only detectable at 0.5 h in week 13 in the 10 mg/kg/d group. In the high dose group, the maximum plasma level was at 0.5 h at both day 1 and week 13. The levels quickly decreased and p-Methylaminophenol was below detectable limits at 2 h on day 1 and 4 h at week 13. No definitive gender or time effects to the plasma levels were observed.

NEPHROTOXIC EFFECTS

p-METHYLAMINOPHENOL SULFATE

Groups of 5 female hooded rats were used in a comparative study of the nephrotoxicity of aspirin and its derivatives and of phenacetin derivatives (which are structurally similar to p-MAP) (Calder et al. 1971). p-Methylaminophenol Sulfate was administered intravenously to 2 groups of rats at doses of 0.1 mM/kg and 0.6 mM/kg. Renal proximal tubular necrosis was observed and was graded 1 to 4 to indicate the degree of severity. Grade 1 was defined as necrosis of individual cells or groups of cells but not of all of the cells in adjoining tubules, and grade 4 was defined as necrosis of the entire proximal convoluted tubule. Those rats with grade 4 renal damage died in anuria, but the other test rats remained

in good condition throughout the study.

Those rats receiving the lower dose of p-Methylaminophenol Sulfate had grade 3 lesions of the tubules (necrosis of the distal third of all tubules as indicated by a band of necrosis in the inner cortex), whereas those rats receiving the higher dose had grade 4 lesions. The phenacetin derivatives were more nephrotoxic than aspirin and its derivatives, and the renal damage induced by the phenacetin derivatives was more clearly dose dependent than that caused by the aspirin derivatives. The authors concluded that a *para* arrangement of the amino and hydroxyl groups on the benzene ring was the basis for the nephrotoxicity of the phenacetin derivatives. In addition, substitutions on the amino group could also affect the nephrotoxicity of a particular compound, as in the case of p-Methylaminophenol Sulfate. The dose of p-aminophenol required to cause renal toxicity of grade 3 was approximately 20 times greater than that of p-Methylaminophenol Sulfate (2.1 mM/kg and 0.1 mM/kg, respectively).

BIOCHEMICAL EFFECTS

p-METHYLAMINOPHENOL SULFATE

In a study of the effects of various chemicals on the depolarizing or hyperpolarizing effects of acetylcholine on the giant neurons of *Lymnea stagnalis*, p-Methylaminophenol Sulfate was inhibitory to the depolarizing action of acetylcholine in 92% of the giant neuron D cells tested. p-Methylaminophenol Sulfate did not enhance the action of acetylcholine in any test (Puppi and Kiss 1973).

The effects of aminophenols on hemoglobin and methemoglobin in the blood of various species were studied in vivo and in vitro (Kiese and Rachor 1964). In ox erythrocytes in Krebs-Ringer phosphate solution, p-Methylaminophenol Sulfate reacted with hemoglobin to form methemoglobin at a much faster rate (40 x 10-5 equiv/l/min) than did p-aminophenol. The reaction in dog erythrocytes was considerably faster than that in ox erythrocytes, with all of the p-Methylaminophenol Sulfate having disappeared from the solution within 10 min and with the methemoglobin concentration reaching its peak at 5 min. In the erythrocytes of both humans and rabbits, the rate of methemoglobin formation was a little faster than that of ox erythrocytes. When the p-Methylaminophenol Sulfate was added to a cell suspension already containing a high concentration of methemoglobin, the methemoglobin concentration decreased initially and then remained unchanged, whereas the aminophenol concentration remained high. Repeated additions of the p-Methylaminophenol Sulfate to the same erythrocyte solution had no greater effect on

the methemoglobin concentration.

In a second part of the same study, p-Methylaminophenol Sulfate was injected intravenously into dogs and cats. The p-Methylaminophenol Sulfate was administered at a dose of 15 mg/kg, and after 2 min, the concentration in the blood was 3 pg/ml. The methemoglobin reached its maximum concentration (approximately 7 g/100 ml blood) in both species in 5 to 10 min. In cats, the effect of the dose of p-Methylaminophenol Sulfate "...increased in proportion to the logarithm of the dose over a wide range of doses." The slopes of the lines characterizing the increase of effect of a particular aminophenol with the log dose were similar for all of the aminophenols tested, but it was noted that the activities of the individual aminophenols varied independently of these slopes.

The authors concluded that the differences between species with regard to the rates of reaction of the aminophenols with hemoglobin were due to the differences in structure of the various hemoglobins. Because both p-Methylaminophenol Sulfate (and similar p-alkylaminophenols) and o-aminophenol cause a rapid increase in methemoglobin concentration and because there is a dose-response relationship, the authors suggested that these aminophenols may be useful for rapid alleviation of the effects of cyanide poisoning (Kiese and Rachor 1964).

ANTIOXIDATIVE ACTIVITY

p-METHYLAMINOPHENOL

Takahashi et al. (2002) used an α,α-diphenyl-β-picrylhydrazyl (DPPH) radical analysis to test the antioxidant activities of p-MAP. Ethanol (2 ml) and DPPH (500μM) were added to an acetic acid buffer (pH 5.5, 2 ml). To 5 ml of this mixture 100 μl of 1mM solution of p-MAP dissolved in dimethylsulfoxide (DMSO) and cysteine in acetic acid buffer were added. The final concentrations were 10, 20, and 40 μM. The mixture was incubated for 30 min at room temperature and absorbance measured at 517 nm. Acetic acid buffer or DMSO in place of p-MAP served as the blank.

The control absorbance was ~0.99; the absorbance of 20 μM p-MAP was 0.60, a 40% decrease from DPPH radicals relative to the control. p-MAP exhibited a dose-dependent antioxidant activity in the range of 0 to 40 μM to the same extent as vitamin E. One molecule of p-MAP scavenged 2 DPPH

radical molecules.

These authors also used microsomes (0.5 mg protein/ml) from Sprague-Dawley rats (Slc. SD) to measure microsomal lipid peroxidation by measurement of malondialdehyde using adenosine 5'-diphosphate (ADP)-chelating ions and ascorbate. p-MAP dissolved in DMSO in 100 mM Tris-HCl (pH 7.5) containing 15 µM $FeCl_3$ and 4 mM ADP were preincubated at 37°C for 1 min. Reaction mixtures with ascorbic acid (1 mM) were incubated at 37°C for 20 min. An equal volume of tert-butyl alcohol (TBA) reagent was added, the mixtures heated in boiling water for 15 min, and centrifuged. Absorbance was measured at 535 nm.

Malondialdehyde formation, resulting from the breakdown of polyunsaturated fatty acids, was inhibited in a dose-dependent manner by p-MAP in the range of 1 to 10 µM. The approximate median inhibition concentration (IC_{50}) was 4.5 µM (Takahashi et al. 2002).

Takahashi et al. (2003) used a DPPH radical assay, as above, to measure the antioxidant properties of p-MAP and to compare them to similar compounds. p-MAP exhibited the same level of antioxidant activity relative to vitamin E as *p*-hexylaminophenol, *p*-octylaminophenol, and *p*-methoxybezylaminophenol in a dose-dependent manner in the range of 0 to 20 µM.

These authors used a lipid-derived malondialdehyde production test, as above, to measure lipid peroxidation in vitro. p-MAP inhibited lipid peroxidation in a dose-dependent manner in the range of 1 to 5 µM with an IC_{50} of ~4.6 µM (Takahashi et al. 2003).

CYTOTOXICITY

p-METHYLAMINOPHENOL

Richard et al. (1991), after growing the cells in a medium including [^{14}C]thymidine (TdR) (0.01 µCi/ml) for 24 h, exposed V79 Chinese hamster cells to p-MAP at various concentrations (up to 0.5% for 30 min; n = 2). [^{3}H]TdR (4 µCi/ml) was then incorporated into the medium for a 10-min pulse-labeling period. The incorporation of [^{14}C]TdR and [^{3}H]TdR into the DNA was determined by liquid scintillation counting. The IC_{50} for p-MAP was 0.022 mM and it was classified as having a high inhibition of DNA synthesis.

Takahashi et al. (2002) used cultured human myeloid leukemia cells (HL-60) in medium containing p-MAP (1 or 10 µM) for 94 h to measure growth inhibition. At 1 µM p-MAP inhibited

approximately 33% of HL-60 cell growth and ~99.7% at 10 µM.

DNA isolated from HL-60 cells exposed to 1 or 10 µM p-MAP for 24 h was extracted and dried under vacuum then dissolved in sample solution for analysis by agarose gel electrophoresis. Ethidium bromide was used to visualize the presence of DNA in the gels. There was no DNA fragmentation due to exposure to the lower concentration (1 µM) of p-MAP; the higher concentration (10 µM) contained fragmented ladder DNA demonstrating that p-MAP may potentially induce apoptosis of HL-60 cells.

These authors exposed HL-60R cells (resistant to retinoic acid; 1 and 2 x 10^5/ml, respectively) to various concentrations of p-MAP. Cell count was determined by electric particle counter and viability by trypan blue dye exclusion. This experiment was repeated with MCF-7 and MCF-7/AdrR cells (having and not having estradiol receptors, respectively).

HL-60R cell growth was completely inhibited by p-MAP (>99%) at 10 µM while retinoic acid was inactive (no other results were provided). p-MAP inhibited MCF-7 cell growth in a dose-dependent manner; at 10 µM cell growth was inhibited ~20% for MCF-7 cells. At 10 µM cell growth was inhibited ~60% for MCF-7/AdrR cells. The proliferation of HepG2 and DU-145 cells was also suppressed by exposure to p-MAP at 40 µM by >80% (Takahashi et al. 2002).

ANIMAL TOXICOLOGY

ACUTE TOXICITY

ORAL

P-METHYLAMINOPHENOL SULFATE

The SCCP (2006) reported a study where 3 female Sprague Dawley Rj:SD rats were orally administered a single dose of 100, 200, or 500 mg/kg p-Methylaminophenol Sulfate (in 0.5% suspension of carboxymethylcellulose) after fasting. At 500 mg/kg, hypoactivity, sedation, piloerection, dyspnea, and tremors were observed before death on day 4. At 200 mg/kg, hypoactivity, piloerection, and dyspnea were observed before death on day 3. There were no clinical signs and the rat lived until the end of the 14-d observation period at 100 mg/kg.

A single dose of p-Methylaminophenol Sulfate (100 mg/kg) was administered orally to 4 more rats. No deaths occurred. Hypoactivity, piloerection, and dyspnea were observed in all 4 animals within

3 h. Body weight was not affected during the observation period. There were no abnormalities observed at necropsy. The authors conclude that the maximum non-lethal dose of p-Methylaminophenol Sulfate was 100 mg/kg and the minimal lethal dose was 200 mg/kg (SCCP 2006).

INTRAVENOUS

P-METHYLAMINOPHENOL SULFATE

The i.v. LD_{50} for p-Methylaminophenol Sulfate in NMRI mice was estimated as 85 mg/kg (Kiese and Rachor 1964).

SUBCHRONIC TOXICITY

DERMAL

p-METHYLAMINOPHENOL SULFATE

Two hair dye formulations containing 0.05% and 1.0% p-Methylaminophenol Sulfate were tested for dermal toxicity in groups of 12 adult New Zealand white rabbits (Burnett et al. 1976). These dye formulations contained other active ingredients in an aqueous solution and were mixed with an equal volume of 6% hydrogen peroxide (H_2O_2) prior to application. The formulations were applied twice weekly for 13 weeks to the clipped skin, with the skin of 3 rabbits of each group having been abraded at the beginning of each week. No significant differences were found between control and test animals with respect to body weight gain and urinalyses, and no discoloration of the urine was produced by the dyes. Statistically significant differences were found in some organ weights and in certain clinical chemistry and hematological values, but these were not considered toxicologically significant.

ORAL

p-METHYLAMINOPHENOL SULFATE

The SCCP (2006) reported on the daily oral administration of p-Methylaminophenol Sulfate to Sprague Dawley (Crl CD (SD) IGS BR) rats for 92 d. Six additional rats were followed for a 4-week recovery period in the control and high-dose groups. The rats (n = 10 of each sex) were administered 0 (vehicle only), 3, 10 or 30 mg/kg/d in a 0.5% suspension of carboxymethylcellulose. The rats were weighed and observed for clinical signs. The rats were killed and necropsied.

No deaths occurred. No clinical signs were observed nor any changes were seen in function observation battery parameters or motor activity. Body weights and food consumption rates were

unaffected. There were no ophthalmological findings. There were no effects on the hematology or blood biochemistry parameters. The males in the high-dose group had a higher urinary output with a lower specific gravity. There were no notable observations at necropsy. Microscopic examination found tubular epithelial degeneration/single cell necrosis in the kidneys of most males and half the females in the high-dose group but not the rats who had the 4-week recovery period. The authors conclude that the no observed adverse effect level (NOAEL) was 10 mg/kg/d.

CHRONIC TOXICITY

DERMAL

p-METHYLAMINOPHENOL SULFATE

Two hair dye formulations containing 0.05% and 1.0% p-Methylaminophenol Sulfate were administered topically to groups of male and female Eppley Swiss Colony mice (n = 50) weekly for periods of 23 and 21 months, respectively (Burnett et al. 1980). The dye formulations were mixed with an equal volume of 6% H_2O_2, and a dose of 0.05 ml was applied to the clipped skin within 15 min. At the conclusion of the study, the survival rates and organ/body weight ratios of the test animals did not differ significantly from those of the controls, although there was considerable variation among the individual values.

OCULAR IRRITATION

p-METHYLAMINOPHENOL SULFATE

The SCCP (2006) reported on the administration of p-Methylaminophenol Sulfate (0.1 ml at 3% in 0.5% aqueous carboxymethylcellulose) into the conjunctival sac of the left eyes of New Zealand White rabbits (n = 3). The eyes were examined at 1, 24, 48, and 72 h after application. One rabbit had chemosis and redness of the conjunctiva at 1 h. No other signs of ocular irritation were noted.

p-METHYLAMINOPHENOL

A 2% solution of p-MAP in distilled water, 0.10 ml, was instilled into the conjunctival sac of the right eye of 6 albino rabbits, the eyes were not rinsed, and the untreated left eye served as a control (L'Oreal 1977a). The eyes were examined 1, 2, 3, 4, and 7 d after instillation of the test substance. The eyes were also examined under UV light with fluorescein dye. Three of the rabbits had no reaction to the p-MAP. Of the remaining 3 rabbits, 1 rabbit had slight redness of the conjunctiva on days 1 and 2,

clearing by day 3; 1 rabbit had slight redness of the conjunctiva on day 1 that had cleared by day 2; and the third rabbit had severe redness of the conjunctiva that moderated through days 2 and 3 and cleared by day 4. This rabbit also had a slight discharge on day 1 that did not continue through day 2. The test group average irritation score on day 1 was 2 out of a total possible score of 110; on day 2, the group average was 1/110; on day 3, the group average was 0.33/110. The score was 0 for the rest of the study. p-MAP was considered practically nonirritating to the rabbit eye.

DERMAL IRRITATION

p-METHYLAMINOPHENOL SULFATE

The SCCP (2006) reported a dermal irritation test of p-Methylaminophenol Sulfate (0.5 ml at 3% in 0.5% aqueous carboxymethylcellulose) on New Zealand White rabbits (n = 3). The test substance was placed on gauze pads and applied to a clipped area of the left flank for 3 min, anterior right flank for 1 h, and the posterior right flank for 4 h. The gauze was held in place under a semi-occlusive dressing. The skin was examined 1, 24, 48, and 72 h after removal of the dressing. No reactions were observed.

p-METHYLAMINOPHENOL

The primary irritation potential of p-Methylaminophenol was assessed using 6 albino Bouscat rabbits, equally divided by sex (L'Oreal 1977b). p-MAP, 0.5 ml of a 2% solution in distilled water, was applied under a patch to abraded and intact skin on the flanks of each rabbit. The patches remained in place for 24 h. The test sites were evaluated 0.5 h after patch removal and again 48 h later. Two rabbits had slight erythema at both the intact and the abraded sites at both readings. One rabbit had slight erythema at both sites at the first reading, and 1 rabbit had slight erythema at the abraded site at the first reading. These reactions had subsided by the 48-h reading. The remaining 2 rabbits had no reactions. The primary irritation index (PII) for p-MAP was 0.74 out of a maximum of 8, and the ingredient was considered slightly irritating to rabbit skin.

DERMAL SENSITIZATION

p-METHYLAMINOPHENOL SULFATE

Lidén and Boman (1988) performed the guinea pig maximization test (GPMT) to test for cross-reactivity between 4-N,N-diethyl-2-methyl-1,4-phenylenediamine · HCl (CD-2) or 4-(N-ethyl-N-2-methansulphonamido- ethyl)-2-methyl-1,4-phenylenediamine · H_2SO_4 · H_2O (CD-3) and p-

Methylaminophenol Sulfate. Induction was carried out at 0.25% (11.64 mmo/l for CD-2 and 5.73% for CD-3 in saline) intradermally. The challenge with p-Methylaminophenol Sulfate was carried out at 0.5% in saline and read 48 h after application. Neither the control (n = 19) nor treated (n = 20) animals had a positive reaction for CD-2. Both the treated (n = 21) and the control (n = 21) groups had a single reaction to p-Methylaminophenol Sulfate for CD-3.

Basketter and Lidén (1992) performed the GPMT using p-Methylaminophenol Sulfate (5.0%) administered intradermally in 0.9% sodium chloride (NaCl) solution and applied topically in 0.9% NaCl (n = 10). Cross-challenges were carried out 1 and 2 weeks after the primary challenge using: paraphenylenediamine (PPDA; 0.5%) in 0.9% NaCl, p-aminophenol and m-aminophenol (5.0%) in acetone/0.9% NaCl (50/50 v/v), and p-benzoquinone (2.5%) in acetone/polyethylene glycol 400 (70/30 v/v). Four naive guinea pigs were controls. There was sensitization to all test chemicals due to exposure to p-Methylaminophenol Sulfate (Table 3).

Table 3. Results of cross-challenges in a GPMT of p-Methylaminophenol Sulfate (Basketter and Lidén 1992).

Challenge Material (concentration)	Number of positive reactions	Mean erythema score, scale 0 - 3
p-Methylaminophenol Sulfate (5.0%)	9 + ?1/10	1.5
p-Phenylenediamine (0.5%)	3 + ?3/10	0.9
p-Benzoquinone (2.5%)	9/10	1.6
p-Aminophenol	8/10	1.3
m-Aminophenol	3/10	0.9
Control	0/4	0

The SCCP (2006) reported a local lymph node assay (LLNA) of p-Methylaminophenol Sulfate (25 µl at 0.25%, 0.5%, 1%, 2.5%, and 5% in DMSO) on female CBA/J mice (n = 4). The test substance was administered to the dorsal surface of both ears daily for 3 d. The negative control received the vehicle; the positive control received 25% (v/v) α-hexylcinnamaldehyde in DMSO. The animals were observed daily. Ear thickness was measured on days 1, 2, 3, and 6. On day 6, all mice were administered 250 µl 0.9% sodium chloride containing 20 µCi tritiated thymidine. The mice were killed 5 h later and the auricular lymph nodes excised, pooled, suspended, and proliferation of these cells measured by scintillation counting. No cutaneous reactions were observed at any concentration. There was a dose-related increase in the stimulation index; the threshold positive value of 3 (EC_3) was

exceeded at concentrations of 2.5% and 5%. The calculated EC_3 value was 2.23%. The authors conclude that p-Methylaminophenol Sulfate induced delayed contact hypersensitivity and should be considered a moderate sensitizer.

p-METHYLAMINOPHENOL

The skin sensitization potential of p-MAP was evaluated using 20 albino Hartley guinea pigs, 10 of each sex (Institut de Formation en Région Bretagne [IFREB] 1978). A preliminary study to determine the dose of p-MAP to be used in the challenge phase of the definitive study had been previously done using 4 Hartley guinea pigs and doses of 0.25 g and 0.5 g of undiluted p-MAP per animal. Patch sites were evaluated 1, 6, 24, and 48 h after patch removal. Because the test substance caused a slight discoloration of the skin, erythema scores made at 1 h were not accurate.

In the preliminary study, none of the guinea pigs had any sign of erythema or edema at any of the scorings. No evidence of sensitization was noted during the study. The dose of p-MAP to be used during the challenge phase of the definitive sensitization study was determined to be 0.5 g. At the start of the definitive study, 6 h after the area behind the left shoulder blade of each guinea pig had been shaved, 0.5 g of p-MAP was applied under an occlusive patch to the shaved area, where it remained for 48 h. Evaluations of the site were made 1, 6, 24, and 48 h after patch removal. Any of the animals that had signs of orthoergic reactions were eliminated from the study. During the induction phase of the study, 0.5 g of p-MAP was applied under an occlusive patch to the shaved area behind the right shoulder blade every Monday, Wednesday, and Friday for 3 weeks and on the Monday of week 4. Patches remained in place for 48 h. Twice during the induction phase, at the first and fifth patch applications, the test site was injected with 0.1 ml of Freund's complete adjuvant at a concentration of 50% in sterile isotonic saline. After removal of the final (tenth) patch, there was a 12-day non-treatment period. At the end of this period (day 36 of the study), an area on the left flank of each guinea pig was shaved, and 0.5 g of the test substance was applied under an occlusive patch, remaining in place for 48 h. Evaluations of the challenge site were made 1, 6, 24, and 48 h after patch removal, and erythema and edema were scored on a scale of 1 to 4. Histological examinations were performed on any animal that had lesions or in which a doubtful reaction was noted.

Two of the guinea pigs died during the study; death was not related to treatment with p-MAP. Of

the 18 remaining guinea pigs, 3 had doubtful signs of erythema, 2 at the 6 h evaluation, and 1 at the 24 h evaluation. No reactions were noted in the other 15 guinea pigs. Biopsies were performed on the 3 animals that had doubtful reactions. The stratum corneum, cuticle, dermis, and appendages were examined, and no signs of sensitization were noted. p-MAP was not considered a dermal sensitizer under the conditions of the study (IFREB 1978).

METOL

Basketter and Scholes (1992) tested Metol using both the GPMT and the LLNA. In the GPMT, induction was 6 injections (0.5%) in the shoulder region followed 6 to 8 d later by an occluded induction patch (25%) applied for 48 h. The challenge patch was 5.0%. After 24 and/or 48 h, 90% of the animals were judged to be positive for a reaction to Metol giving a rating of extreme for sensitization. In the LLNA, Metol was tested at 0.5%, 1.0%, and 2.5% with an exposure of 5 d with dimethyl formamide as the vehicle. The ratios of test to control lymphocyte proliferation were 2.5, 3.4, and 6.7, respectively. The authors classified the 90% reaction as extreme. The authors gave Metol a positive rating for sensitization.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

p-METHYLAMINOPHENOL SULFATE

Two hair dye formulations containing p-Methylaminophenol Sulfate at concentrations of 0.05% and 1% were tested by topical application at a dose of 2 ml/kg every 3 days for a total of 7 doses during gestation to the shaved dorsoscapular region of groups of 20 mated Charles River CD female rats (Burnett et al. 1976). The hair dye ingredients were in aqueous solution, and there were other active ingredients, such as phenylenediamines and aminophenols, present in the solutions. The hair dyes also were mixed with 6% H_2O_2 before application. No significant embryotoxic or teratogenic effects were observed.

The SCCP (2006) reported a teratogenicity study on Sprague Dawley (Crl CD (SD) IGS BR) rats. The rats (n = 24) were orally administered p-Methylaminophenol Sulfate (0, 5, 25, or 125 mg/kg/d) on days 6 to 19 post coitum. The rats were observed for clinical signs; food consumption and body weight were monitored. On day 20, the rats were killed and necropsied. The uterus was weighed and

fetuses weighed and examined. There were no deaths during the study and no treatment related signs were observed. Net body weight gain was slightly reduced in the 25 and 125 mg/kg/d groups. No treatment-related findings were reported at necropsy. There were no effects observed in the litters. There were no treatment-related malformations or variations in any of the fetuses.

METOL

Balaji and Kannan (1988) exposed the egg masses of the nematode *Meliodogyne incognita* to various concentration of Metol. The eggs were withdrawn at 24 h intervals and counted (n = 5). Controls were exposed to distilled water. At 1000 ppm, the hatchability of the egg masses was 644 ± 2.35, 48.48% of the control at 1250 ± 0.71 (Table 4).

Table 4. The hatchability of *M. incognita* eggs exposed to Metol (Balaji and Kannan 1988).

Concentration (ppm)				
Control	1000	500	250	125
1250 ± 0.71	644 ± 2.35 (48.48%)	700 ± 2.45 (44.00%)	758 ± 1.41 (39.36%)	813 ± 3.08 (34.96%)

GENOTOXICITY

p-METHYLAMINOPHENOL SULFATE

The SCCP (2006) reported a mutagenicity test of p-Methylaminophenol Sulfate (0.064 to 1000 µg/ plate without S9 mix and 0.064 to 2000 µg/plate with S9 mix) using *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and TA102. The test was run in duplicate. p-Methylaminophenol Sulfate induced gene mutations in TA100 (with and without S9), and TA1537 (with S9). The authors concluded that the test substance is mutagenic in the bacterial gene mutation assay.

The SCCP (2006) reported on an in vitro chromosome aberration test using human lymphocytes with and without S9 at 11.26 to 27.49 µg/ml p-Methylaminophenol Sulfate. The lymphocytes were exposed for 3 h and harvested at 20 h. There was an increase in frequency of chromosome aberration with and without S9. The authors conclude that p-Methylaminophenol Sulfate was clastogenic in mammalian cells in vitro.

The SCCP (2006) reported on a mammalian cell gene mutation test on p-Methylaminophenol Sulfate using L5178Y mouse lymphoma cells (TK+/-). The test was run in triplicate with (1.0 to 38 µg/ml) and without S9 (0.1 to 3.0 µg/ml) for 3 h. p-Methylaminophenol Sulfate induced increases in the mutant

frequencies in the presence of S9.

The SCCP (2006) reported on a mammalian cell gene mutation test on p-Methylaminophenol Sulfate using L5178Y mouse lymphoma cells (HPRT). The test was run in duplicate with (2.5 to 60 µg/ml) and without S9 (0.5 to 2.0 µg/ml) for 3 h. p-Methylaminophenol Sulfate did not induce increases in the mutant frequencies in the presence or absence of S9.

The SCCP (2006) reported a rat bone marrow micronucleus test using Sprague-Dawley rats (5 male, 5 female) to evaluate the mutagenicity of p-Methylaminophenol Sulfate (100, 200, and 400 mg/kg by gavage). One rat died in the 400 mg/kg group. There was no observed bone marrow toxicity. There were no increase in chromosome aberrations or damage to the mitotic apparatus in the bone marrow cells of the rats.

The SCCP (2006) reported on an unscheduled DNA synthesis (UDS) assay on p-Methylaminophenol Sulfate using Wistar Han rats (n = 3). The test substance was administered by gavage at 50 and 500 mg/kg; the rats were killed 16 h later. An additional high-dose group was killed at 2 h. One rat in the high-dose group died. There was no induction of UDS in any group; there was no difference in viability of hepatocytes in any group.

p-METHYLAMINOPHENOL

Yoshikawa et al. (1976) performed an Ames test of p-MAP (15 to 150 µg/plate) using *S. typhimurium* TA98 with and without S9. It was found to be non-mutagenic (Table 5).

The mutagenic potential of p-MAP was tested in the Ames assay using *S. typhimurium* strains TA98, TA100,T A1535, TA1537, and TA1538 (Inveresk Research International 1979). The positive control was 2-aminoanthracene. The concentrations of p-MAP tested ranged from 30 pg to 2.0 mg. Though p-MAP did not appear to be mutagenic, it was toxic to the bacterial cells, especially to strains TA98 and TA1538, in the absence of S-9 mix. At concentrations ranging from 8 to 500 pg/plate, p-MAP was retested in strains TA98 and TA1538 with metabolic activation to determine whether possible mutagenic activity was masked by the toxicity of the compound when not detoxified by the S-9 mix. No mutagenic activity was noted in the repeat test, and p-MAP was considered nonmutagenic in the Ames assay.

The micronucleus test also was used to determine the mutagenic potential of p-MAP (L'Oreal

1982). Groups of 10 male Swiss mice were administered 2 intraperitoneal (i.p.) injections 24 h apart of 50, 75, or 100 mg/kg p-MAP. A vehicle control (Baker water) group also was included. Under the conditions of the study, p-MAP was considered nonmutagenic in the mouse micronucleus assay.

The uterotrophic potential of p-MAP was evaluated in the chromosome aberration test using Chinese hamster ovary (CHO) cells (L'Oreal 1983). CHO cells were treated for 1 h, with and without metabolic activation, with 0.125, 0.25, 0.5, or 1 mg/ml p-MAP. Usually, the cells that are exposed to the test chemical without metabolic activation remain in contact with the test chemical until fixation at 6, 12, or 16 h, but because of the toxicity of the p-MAP, treatments were administered for 1 h only for assays with or without metabolic activation, and fixation times remained at 6, 12, and 16 h. Methyl methanesulfonate (MMS) and cyclophosphamide were the positive controls. Chromosomal aberrations were scored per 100 metaphasic cells. A positive response was indicated when the frequency of aberrations increased in a dose-dependent manner. The 1 mg/ml dose resulted in few, if any, metaphases, and only doses of 0.5 mg/ml and below were scored. Though p-MAP was quite toxic to CHO cells, no evidence of mutagenic potential was observed under the conditions of the study.

CARCINOGENICITY

p-METHYLAMINOPHENOL SULFATE

In the chronic dermal toxicity study previously described (Burnett et al. 1980) of two hair dye formulations, one with 1.0% and the other with 0.05% p-Methylaminophenol Sulfate. The mice (8 to 10 weeks old; n = 50; 12 treatment groups; 3 negative control groups) also were evaluated for neoplasms at the end of the 21- and 23-month treatment periods. Of special interest were neoplasms of the skin, which were of low incidence. Several other types of neoplasms were found at necropsy and microscopic evaluation, but none of the incidences were statistically significant. There was no differences in liver or kidney weights. The authors concluded that the hair dye formulations tested did not have any carcinogenic effects.

The SCCP (2006) reported on a carcinogenicity test of topically applied p-Methylaminophenol Sulfate on male and female Sprague Dawley rats (n = 60). The same hair dyes (0.5 ml) as in the previous study were applied to the shaved neck and back area of the rats twice weekly for 114 weeks.

There were 3 control groups containing 60 males and 60 females. The rats were observed for signs of toxicity and mortality daily. Hematological, biochemical, and urinalysis studies were conducted on 5 males and 5 females/group at 3, 12, 18, and 24 months. At 12 months, 5 males and 5 females/group were killed and necropsied. All the rats were killed when survival of a group reached 20% or at 114 weeks.

Survival to 114 weeks was 16 to 24 males and 14 to 17 females/treatment group and 15 males and 9 to 18 females in the control groups. Body weights in the treatment groups for males was 713 to 719 g and 443 to 513 g for females; in the control groups the body weights were 682 to 759 g for males and 477 to 513 g for females. The dyes containing p-Methylaminophenol Sulfate did not affect survival nor produced any adverse effects. There were no differences observed in the biochemical analyses. Females treated with the hair dye containing 0.5% p-Methylaminophenol Sulfate had an increase in incidence of mammary adenomas when compared to a single control group, but not the other 2 control groups. Life-table analyses found no treatment-related variations (SCCP 2006).

CLINICAL ASSESSMENT OF SAFETY

P-METHYLAMINOPHENOL SULFATE

Basketter and Lidén (1992) patch tested p-Methylaminophenol Sulfate on patients (n = 10, 9 women, 1 man) with a history of a positive patch test reaction to p-phenylenediamine (scored ++ or +++). Finn Chambers and Scanpor tape were used to apply the patches to the upper back. The patches were left in place for 2 d and the readings were performed 3 d after application. The minimum criteria for a positive reaction was erythema and infiltration. Four of the 10 patients had positive reactions to the p-Methylaminophenol Sulfate (2 +, 1 ++, and 1 +++).

METOL

Lisi and Hansel (1998) employed patch tests to the upper back with Van der Bend square chambers to test 22 patients (9 male, 13 female; 19 to 72 years old) sensitized to p-phenylenediamine for sensitivity to Metol (4 of these patients also had benzoquinone-positive tests). Patches were read on days 2 and 4 after 2 d of exposure. Five patients had positive reactions to Metol, 2 of them were among the 4 sensitive to benzoquinone.

OCCUPATIONAL STUDIES

p-METHYLAMINOPHENOL SULFATE

Because certain chemicals used in photographic developing were known to cause skin diseases, an evaluation of the skin diseases reported by employees at a film developing plant was undertaken (Lidén 1984a). The study was an attempt to determine the frequency and types of occupational and nonoccupational dermatoses among the plant employees. The study consisted of multiple parts. In the first part, the employees responded to a questionnaire detailing their previous and current tasks at the plant and any previous or current skin diseases. In the second part of the study, all of the questionnaire respondents who had indicated previous or current skin diseases were invited to be examined by a doctor. At the examination, the patients were questioned about any skin problems (past or present) and about their tasks at the plant. If any skin lesions were present, these were examined, noted, and treated. A preliminary assessment of any correlation between skin disease and job was made at this time.

In the third stage of the study, those patients who were thought to have occupationally-related dermatoses were offered the chance to be patch tested with 11 standard series substances and with 20 film laboratory chemicals. The patches remained in place for 48 h and were scored 24 h and 2 to 3 weeks after patch removal. At this stage in the study, 23 patients were tested with p-Methylaminophenol Sulfate. Of the 23 test subjects, 6 had positive reactions to p-Methylaminophenol Sulfate at concentrations of 5% and 1%. Of these 6 subjects, 3 were also positive for either 2 or 3 of the following chemicals: CD-2, CD-3, PPDA, and persulfate bleach accelerator-1 (PBA-1; found to be a potent sensitizer). p-Methylaminophenol Sulfate, at a concentration of 1%, was then tested on a group of 200 control subjects (eczema patients without known previous contact with the chemical); 1 subject had a positive reaction.

Forty-nine percent of the film laboratory employees had been afflicted with occupational dermatoses directly related to their work with film laboratory chemicals. Contact allergies to the chemicals p-Methylaminophenol Sulfate, CD-2, CD-3, and PBA-1 were found in 28% of the employees working with the chemicals. In many of these contact allergy cases, the reactions had been so severe that the employees had either seen a doctor, changed jobs, or taken sick leave (Lidén 1984a).

Lidén (1988) patch tested 23 volunteers with dermatoses who worked in film developing plants for sensitization to p-Methylaminophenol Sulfate (1% and 5% in water). Induction was for 48 h and read at 72 h after application. Minimum criteria for a positive reading was erythema and infiltration. Six of 23 patients who work with p-Methylaminophenol Sulfate and other film developing chemicals had positive patch test for this ingredient at 1% or 5%.

In testing for the occurrence of occupational dermatoses at a film laboratory following plant-wide modernization to minimize exposure to chemicals, Lidén (1989) patch tested the employees for sensitivity to p-Methylaminophenol Sulfate at 0.1%, 0.5%, and 1% in both water and petrolatum. The induction patches were in place for 48 h, read 72 h after exposure, and read again after 2 weeks (when possible). Six of 14 employees tested positive. No new reactions were noted after 2 weeks. Of 39 subjects, one had recurring hand eczema who patch tested positive for colophone, Venice turpentine, hydroquinone, and p-Methylaminophenol Sulfate.

In control patch tests on unexposed subjects, 2 of 11 tested positive to aqueous solutions of p-Methylaminophenol Sulfate (1%) using the Finn Chamber and 4 of 11 tested positive to the same solution using the A1-test. There were no positive results for p-Methylaminophenol Sulfate in petrolatum (1%) (Lidén 1989).

p-Methylaminophenol Sulfate is listed as an allergen in Kodak photographic developing systems material safety data sheets (Scheman and Katta 1997).

METOL

Lidén (1984b) patch tested 23 employees of a film processing plant with contact dermatitis after exposure to Metol, CD-2, CD-3, and PBA-1 for sensitivity to Metol (5% and 1% aqueous). Patches were left on for 48 h and read 72 h after application and 2 to 3 weeks later. Two hundred non-exposed volunteers were also patch tested. Six of the 23 Metol exposed employees tested positive. One in 200 non-exposed volunteers tested positive.

Lidén and Brehmer-Andersson (1988) patch tested 24 people (23 men, 1 woman) who had developed dermatoses caused by color developing agents (including CD-2 and CD-3) for an allergic reaction to Metol at 1% in petrolatum. Induction patches were removed after 48 h and read 72 h after application. A second reading was taken at 2 to 3 weeks for 18 cases. Four of the volunteers had a

positive result at 72 h. There were no positive reactions at 2 to 3 weeks.

HAIR DYE EPIDEMIOLOGY

Hair dyes may be broadly grouped into oxidative (permanent) and direct (semipermanent) hair dyes. The oxidative dyes consist of precursors mixed with developers to produce color, while direct hair dyes are a preformed color.

While the safety of individual hair dye ingredients are not addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information and have been considered by the CIR Expert Panel.

In 1993, an International Agency for Research on Cancer (IARC) working group evaluated 78 epidemiology literature citations and concluded that "...personal use of hair colourants cannot be evaluated as to its carcinogenicity..." and that "...occupation as a hairdresser or barber entails exposures that are probably carcinogenic" (IARC 1993). The IARC report did not distinguish between personal use of oxidative/permanent versus direct hair dyes, or distinguish among the multiple chemical exposures in addition to hair dyes to which a hairdresser or barber might be exposed.

Rollison et al. (2006) reviewed the available epidemiology literature published since 1992. The authors found that hair dye exposure assessment ranged from ever/never use to information on type, color, duration and frequency of use. The authors found insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers. The review highlighted well-designed studies with an exposure assessment that included hair dye type, color, and frequency or duration of use, which found associations between personal hair dye use and development of acute leukemia, bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma. These findings, however, were not consistently observed across studies.

The CIR Expert Panel did specifically note reports from a case-control study (Gago-Dominguez et al. 2001, 2003), which did suggest a possible genetically susceptible subgroup, which detoxify arylamines to a lower degree than the general population. The study authors hypothesized that this subgroup may be at greater risk of bladder cancer from hair dye exposure. Rollison et al. (2006) noted that these results were based on small sample sizes.

Several studies published since 2003 also have been considered. Discussion of the available hair dye epidemiology data is also available at http://www.cir-safety.org/findings.shtml.

Bladder Cancer - Andrew et al. (2004) reported a case-control study of New Hampshire residents whose bladder cancers were entered into a state registry from 1994 to 1998. A follow-up study by Kelsey et al. (2005) examined the links between those bladder cancer cases with an inactivated tumor suppressor gene (TP53) and various exposures. Huncharek and Kupelnick (2005) performed a meta-analysis of 6 case-control and 1 cohort study. Takkouche et al. (2005) performed a meta-analysis of the Andrew et al. (2004) study and 9 other personal use case-control or cohort studies. Ji et al. (2005) reported a cohort occupational study not included in the above meta-analyses. Kogevinas et al. (2006) presented evidence from a case-control study in Spain. Lin et al. (2006) presented a case-control study of personal permanent hair dye use. Serretta et al. (2006) reported preliminary results from a multicentric study.

Lymphoma and Leukemia - Rauscher et al. (2004) reported a U.S./Canadian case-control study of adult acute leukemia. Zhang et al. (2004) and Zheng et al. (2004) examined the relationship of hair dye use or diet with non-Hodgkin's lymphoma in a case-control study in Connecticut. Takkouche et al. (2005) reported a meta-analysis of reports of hematopoietic cancers, including that by Rauscher et al. (2004) and Zhang et al. (2004) and 17 other studies. Mester et al. (2005) reviewed 10 epidemiology studies regarding the relationship between occupational exposure in hairdressing and diseases of the malignant lymphoma group. A case-control study in Spain by Benavente et al. (2005) examined the association between lifetime hair dye exposure with various lymphomas, including chronic lymphocytic leukemia. de Sanjosé et al. (2006) reported on the association between personal use of hair dyes and lymphoid neoplasm using data from a European multicenter case-control study.

Other Cancers - Takkouche et al. (2005) included breast cancer and childhood cancers in their meta-analysis. Efird et al. (2005) studied the association between the use of hair-coloring agents the month before or during pregnancy with childhood brain tumors in 1218 cases between 1976 and 1994.

Heineman et al. (2005) studied 112 women in Nebraska newly diagnosed with brain cancer (glioma). McCall et al. (2005) reported on the relationship between childhood neuroblastomas and maternal hair dye use in 538 children born between 1992 and 1994 in the U.S. and Canada.

Other Diseases - Park et al. (2005) reported an occupational case-control study of neurodegenerative diseases, including Alzheimer's disease, presenile dementia and motor neuron disease.

In considering all these data, the CIR Expert Panel concluded that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other endpoints.

The Panel stated that use of direct hair dyes, while not the focus in all investigations, appears to have little evidence of an association with adverse events as reported in epidemiology studies. However, direct hair dyes are a diverse group of chemicals and the determination of safety may hinge on other safety test data.

The Panel recognizes that hair dye epidemiology studies do not address the safety of individual hair dyes, but is concerned that studies have demonstrated an association between use of oxidative/permanent hair dyes and some cancer endpoints. The Panel, therefore, strongly supports the need to continue these studies, along with further studies to examine the possibility of susceptible subpopulations.

OTHER EVALUATION

The SCCP (2006) reported their opinion that the use of p-Methylaminophenol Sulfate should be at a maximum of 0.68% in the finished cosmetic product. The nitrosamine content should be < 50 ppb.

CASE REPORTS

Lidén (1984b) reported on a man who had been mixing photographic chemicals for 16 years without skin problems. A few days after grazing his hand he developed eczema which quickly spread to his arms, neck, and face. He recovered after a few days off and topical treatment. The eczema

returned within hours of returning to work. He was patch tested for individual chemicals, including Metol, and chemical mixes to which he was exposed. He tested positive for Metol at 1% aqueous.

Brancaccio et al. (1993) reported on 2 men who work with photographic chemicals with contact dermatitis. The first man, 33 years old, with no history of dermatitis placed his right hand and arm into film developing solution. Two weeks later a pruritic dermatitis of the right forearm developed with patchy involvement of the face, upper chest, and left arm. He was diagnosed with acute allergic contact dermatitis and treated with topical corticosteroid ointment and an oral antihistamine. His second eruption had a distinct lichenoid appearance with violaceous flat-topped papules with polygonal borders. Biopsy showed focal vaculolar alteration and absence of hypergranulosis with patchy superficial infiltrate.

The second man was a 62-year-old man who managed a photographic laboratory with a 2-year history of hand dermatitis. Both palms were erythematous with diffuse scaling and fissuring; the fingers had confluent vesicles. Diffuse erythematous scaling plaques were present on both lower extremities and scaling was observed on the forearms. Biopsy showed superficial and mid perivascular infiltrate of lymphocytes, histiocytes, and eosinophils. He was also diagnosed with allergic contact dermatitis. Patch tests on both men resulted in positive results for CD-2, CD-3, and 4-amino-3-methyl-N-ethyl-N(betahydroxy-ethyl) aniline sulfate (CD-4). The former tested negative for p-Methylaminophenol Sulfate and the latter positive (Brancaccio et al. 1993).

Śpiewak et al. (1995) reports on 2 women working in the same photographic processing plant. The first woman's work required constant contact with photographic chemicals, including Metol. Two months after a new processing technology was introduced, the first skin lesions appeared on the wrist with itching and reddish macula. Subsequently, furfuraceous desquamation and exudating papules formed. The changes gradually extended over the upper half of the body (upper extremities, chest, and abdomen). Erythema and edema appeared on the face and neck. After hospitalization, allergic and seborrheic dermatitis was diagnosed. Skin prick tests were positive for paraaminoazobenzene, mercury chloride, N-isopropyl-N'-phenyl-paraphenylenediamine (IPPD), and 3 developing solutions but not for Metol. The second woman had the same job as the first woman, thus exposure was identical. She presented with reddish, dry macules on the hands. After contact with water, burning clusters of

exudating papules developed on the skin lesions, mostly in the palmar region. She had erythematosquamous reddish-brown lesions with tiny papules on the upper half of her body, except the back. Skin prick tests were positive for Metol, mercury chloride, and IPPD.

m-, o- and p-AMINOPHENOL SUMMARIES

SUMMARY OF SAFETY ASSESSMENT

Elder (1988) states that para-, meta-, and ortho-aminophenols are the 3 possible isomers of a disubstituted aminohydroxybenzene. The aminophenols are manufactured by nitrophenol reduction and occur as products and by-products of chemical and biological degradation or derivatization. Analytical methods for their determination include TLC and reversed-phase HPLC.

p-Aminophenol (PAP), m-Aminophenol (MAP), and o-Aminophenol (OAP) are used in permanent (oxidative) hair dyes. The FDA product formulation data lists PAP in 402, MAP in 278, and OAP in 75 hair coloring formulations in the "hair dye and colors" and "hair tints" product categories in 2002. Concentrations of the Aminophenols in these formulations range from 0.1 to 5%. The oxidative hair dyeing process involves combination of 3 types of colorless components to produce a permanent, colored, covalently bound product within the hair fiber. PAP and OAP are used as "primary intermediates," which are oxidized by an "oxidant," such as hydrogen peroxide. The oxidized primary intermediate then reacts with a "coupler," such as MAP, producing a conjugated polynuclear dye.

In vivo and in vitro studies of skin absorption have been performed using radioactive PAP, MAP, phenols, and other hair dye intermediates. As much as 11% of the radioactivity introduced as ^{14}C-PAP in a simple vehicle was detected in the excreta, viscera, and skin of rats after topical application. Hepatic metabolism of aminophenols includes such reactions as glucuronidation, sulfation, and acetylation to form aminophenol conjugates excreted in the urine.

Intravenous and subcutaneous administration of PAP were melanocytotoxic to neonatal mice and nephrotoxic to rats. Varying degrees of methemoglobinemia have been induced by i.v. and i.p. administration of the aminophenols in several species, although oral administration of PAP and MAP did not affect methemoglobin concentrations in rats. The oral toxicities of PAP and MAP were studied using rats. Oral LD_{50}s for PAP in rats were 671 and 1270 mg/kg. Those for MAP ranged from 812 to 1000

mg/kg. The oral LD_{50} for OAP in rats was 1300 mg/kg. Oral administration of up to 0.70% PAP in the diet to rats for a period of 3 to 6 months resulted in decreased body weights and feed consumption as well as increased relative liver and kidney weights at the high dose and nephrosis at all doses. Oral consumption of up to 1% MAP in the diet by rats for 90 days resulted in decreased body weights and feed consumption, deposition of iron-positive pigment in the spleen, liver, and kidneys, and increased thyroid gland activity.

Topical application of PAP at doses up to 8.0 g/kg in aqueous gum tragacanth to the skin of NZW rabbits produced no mortality and no irritation.

Subcutaneous administration to rats of PAP as the hydrochloride in doses as low as 100 mg/kg produced morphological and functional nephrotoxic effects. No nephrotoxic effects were observed in similar studies with OAP and MAP.

Concentrations of 2.5% to 50% PAP and approximately 3% MAP (in an aqueous vehicle) applied to the skin of NZW rabbits produced minimal or no skin irritation. The 50% PAP preparation stained the skin at treatment sites green-brown, obscuring observations. One-half gram OAP and 5% OAP in ethanol produced no skin irritation.

MAP, 0.1 ml or at 3% in an aqueous vehicle, was nonsensitizing in guinea pigs. PAP, in petrolatum, sensitized 9 of 10 guinea pigs challenged with a 2% preparation and 3 of 10 guinea pigs challenged with a 0.1% preparation after the animals had been treated with four 24-h occlusive patches containing 2% PAP. PAP did not sensitize guinea pigs that had been treated with 18 patches containing 3% PAP in an aqueous vehicle and challenged with the same dose of PAP. Staining of the skin was noted at the site of administration. Cross sensitization between OAP and p-phenylenediamine was noted in guinea pigs. No photosensitization was produced by topical administration of PAP or MAP to the guinea pigs, although some contact hypersensitivity was noted.

Oxidative hair dye formulations containing the Aminophenols at low concentrations (0.04-1%) were tested for chronic toxicity after topical administration twice weekly for 13 weeks to rabbits and weekly for 21 to 23 months to mice under conditions designed to mimic human use of hair dyes. No gross alterations were observed. A 4-generation chronic dermal toxicity and reproduction study of 3 oxidative hair dye formulations containing the Aminophenols were performed with rats. A few skin

reactions were observed. However, no treatment-related toxicity was found.

Neither 100 mg powdered PAP nor 2.5% PAP in aqueous gum tragacanth was irritating to eyes of NZW rabbits. OAP and a 2.5% solution of MAP in aqueous gum tragacanth caused minimal or no eye irritation.

A range of results were obtained from studies assessing the mutagenic activity of the Aminophenols. PAP tested positive in 6 of 8 mutagenicity tests (not including a dominant lethal study in which the investigators suggested the study should be repeated). MAP and OAP gave positive results in 2 of 8 and 5 of 7 mutagenicity tests, respectively.

Oxidative hair dye formulations containing PAP, MAP, and OAP did not produce gross or microscopic alterations or have carcinogenic effects after chronic topical application to mice under conditions designed to mimic hair dye use. Feeding of OAP-HCI and PAP to albino rats at a dose of 8.01 mmo/kg produced no hepatic cirrhosis and no neoplasms.

Oxidative hair dye formulations containing low concentrations of PAP, MAP, and OAP were tested for teratogenic activity after topical application to mice, rats, and rabbits under typical hair dyeing conditions. No embryotoxic or teratogenic effects were observed in mice and rats, although a retardation of ossification in mice was indicated. No teratogenic effects were noted in treated rabbits; however, embryotoxicity was indicated.

Oral administration by gavage of 250 mg PAP/kg produced maternal toxicity and teratogenicity in rats. Chronic feeding of PAP in the diet of rats at a concentration of 0.70% produced embryotoxicity mediated by maternal toxicity. Chronic feeding of MAP in the diet of rats at concentrations of up to 1% resulted in maternal toxicity during gestation but produced no teratogenic effects. Oral administration of 100 to 200 mg/kg PAP to pregnant hamsters was not teratogenic, but i.p. and i.v. administration of PAP within the same dose range induced fetal malformations. Intraperitoneal administration of OAP (in hamsters) resulted in teratogenic effects, whereas no conclusive evidence was found for MAP teratogenicity by this route.

A 3% solution of MAP in an aqueous vehicle was tested for irritation and sensitization in 2 clinical studies using semiocclusive (open) repeated insult patch tests. Slight irritation during induction and no sensitization to the challenge patch were observed in one study. Some irritation and a low

degree of sensitization were observed in 2 of the 99 subjects in another study. No skin depigmentation in any subject and slight skin irritation and staining in a few subjects were observed after repeated topical applications of aqueous solutions of 1.0% MAP and 0.5% PAP. Dose-related responses to applications of PAP in petrolatum were observed on the skin of 10 of 31 workers from a chemical factory.

A variety of epidemiological studies have assessed whether and to what degree occupational exposure to and personal use of hair dyes (not chemically defined) increase the risk of cancer. Based on these studies, no definitive carcinogenic effect from hair dyes has been proven.

In a clinical study, 1 of 7 p-phenylenediamine-sensitized hairdressers cross reacted to challenge patches containing OAP and PAP.

On the basis of the available animal and clinical data presented in this report, the CIR Expert Panel concludes that p-, m-, and o-Aminophenols are safe as cosmetic ingredients in the present practices of use and concentrations (Elder 1988).

SUMMARY OF RE-REVIEW

The CIR Expert Panel (CIR 2005) reviewed the safety of m-, o- and p- aminophenol (MAP, OAP, PAP) in 1988. Based on that review, the Panel concluded that these Aminophenols "...are safe as cosmetic ingredients in the present practices of use and concentration". There have been additional studies since then including studies on irritation and sensitization that were not present in the first review. In addition, a large body of hair dye epidemiology data are now available. All studies, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. Based on its consideration of the data discussed below, the Panel did not reopen this safety assessment and confirmed the original conclusion.

MAP has increased in usage from 278 products in 1981 to 855 products in 2002. OAP has increased in usage from 75 products in 1981 to 89 products in 2002. PAP has increased in usage from 402 products in 1988 to 1024 products in 2002. The product categories are similar for all 3 ingredients for 1981 and 2002. The concentrations at which these ingredients are used are similar between 1981 and 2005.

The Panel noted that the discussion in the original review explained that there were likely

sufficient endogenous stores of glutathione to inactivate potentially genotoxic aminophenol metabolites. Among the additional studies reviewed by the Panel, however, were several in which glutathione conjugates produced by the reaction with aminophenols were nephrotoxic at high doses. Because of the short duration of contact with these oxidative hair dyes and the time needed for diffusion across the stratum corneum, the actual concentration of aminophenol in the skin is low relative to the amount in the hair dye product. Since the level in the hair dye product is already low, the Panel does not consider it likely that glutathione conjugates could reach nephrotoxic levels (CIR 2005).

SUMMARY

p-Methylaminophenol Sulfate and p-Methylaminophenol (p-MAP) are substituted phenols used as dyes and for photographic developing. p-Methylaminophenol Sulfate is manufactured by the methylation of p-aminophenol followed by neutralization with sulfuric acid. They may be determined analytically by infrared, UV, and nuclear magnetic resonance spectra, by TLC, and by visual or potentiometric titration. p-Methylaminophenol Sulfate absorbed in the UV range at 220 and 271 nm, whereas p-Methylaminophenol absorbed at 219, 270, and 277 nm. The term Metol may refer to either compound and is often used without distinguishing.

p-Methylaminophenol Sulfate is a secondary amine, thus prone to nitrosation.

In oxidative hair dyes, p-Methylaminophenol Sulfate and p-Methylaminophenol are used as primary intermediates. They react with an oxidant to produce the corresponding imine, which then reacts with a coupler to form an indophenol dye. p-Methylaminophenol Sulfate is listed as an ingredient in 112 hair dye formulations, its concentration ranging from 0.1% to 0. 7%. p-Methylaminophenol is not listed by FDA as an ingredient in any cosmetic products but is reported to be used by CTFA in hair dye formulations at 0.7%.

p-Methylaminophenol Sulfate was an inhibitor of the depolarizing action of acetylcholine on the giant neurons of *Lymnea stagnalis*. In the erythrocytes of oxen, dogs, rabbits, and humans, p-Methylaminophenol Sulfate caused the formation of methemoglobin at a much greater rate than did p-aminophenol.

p-Methylanimophenol Sulfate had low dermal penetration on human skin.

Oral administration of p-Methylaminophenol Sulfate to rats resulted in undetectable or very low levels of p-Methylaminophenol Sulfate over 13 weeks.

The intravenous LD_{50} of p-Methylaminophenol Sulfate in NMRI mice was 85 mg/kg. The maximum non-lethal oral dose of p-Methylaminophenol Sulfate for rats was 100 mg/kg and the minimal lethal dose was 200 mg/kg. The dose of p-Methylaminophenol Sulfate causing necrosis of the distal third of all tubules of the kidneys of hooded rats was 0.1 mM/kg, 20 times greater than the dose of p-aminophenol required to produce the same effect. In subchronic and chronic dermal toxicity studies of hair dyes containing p-Methylaminophenol Sulfate, among other active ingredients, no toxicologically significant differences were observed between the test and control animals (rabbits and mice, respectively). The subchronic oral NOAEL for rats for p-Methylaminophenol is 10 mg/kg/d.

In an ocular irritation study, p-Methylaminophenol was considered practically nonirritating to the rabbit eye. p-Methylaminophenol was slightly irritating to rabbit skin in a primary irritation study and was not considered a dermal sensitizer in a guinea pig skin sensitization study. p-Methylaminophenol Sulfate was a sensitizer in the GPMT and LLNA. In both the GPMT and LLNA, Metol received a positive rating for sensitization at 25% and 2.5%, respectively.

No significant embryotoxic or teratogenic effects were found when hair dyes containing p-Methylaminophenol Sulfate and other active ingredients were administered topically to Charles River CD rats once every 3 days for a total of 21 days during gestation or orally to Sprague Dawley rats at doses up to 125 mg/kg/d. Metol at 1,000 ppm reduced nematode hatchability by 48.48%).

p-Methylaminophenol Sulfate was mutagenic to *S. typhimurium* TA98 and TA 1537 with metabolic activation and TA100 without. It was clastogenic in mammalian cells (human lymphocytes) in an in vitro chromosome aberration test. Mixed results were reported for the mutagenicity of p-Methylaminophenol Sulfate to mouse lymphoma cells. There was no toxicity nor mutagenicity observed in the rat bone marrow micronucleus test or unscheduled DNA synthesis assay.

p-Methylaminophenol was not mutagenic in the Ames assay using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. The p-Methylaminophenol was toxic to the bacterial cells, especially to those of strains TA98 and TA1538, in the absence of metabolic activation. Additional testing in strains TA98 and TA1538 with metabolic activation indicated that the toxic effect of the p-

Methylaminophenol did not mask any possible mutagenic effect. p-Methylaminophenol was nonmutagenic in the mouse micronucleus assay and in the Chinese hamster ovary chromosome aberration test.

No statistically significant incidences of neoplasms, dermal and other, were found in mice and rats after 21 to 28 months of weekly dermal exposure to hair dyes containing p-Methylaminophenol Sulfate in addition to other active ingredients.

Of 23 panelists known to have occupationally related dermatoses who were patch tested with p-Methylaminophenol Sulfate, 6 had positive reactions to the ingredient at concentrations of 1% and 5%. Three of these panelists also had positive reactions to 2 or 3 of a group of 4 chemicals used in film laboratories. When p-Methylaminophenol Sulfate was tested in 200 eczema patients without known previous contact with the chemical, 1 patient had a positive reaction. Four of 10 patients who had positive reactions to p-phenylenediamine had positive reactions to the p-Methylaminophenol Sulfate.

Twenty-four people who had developed dermatoses caused by color developing agents (including CD-2 and CD-3) were patch tested for an allergic reaction to Metol at 1% in petrolatum. Four of the volunteers had a positive result at 72 h. There were no positive reactions at 2 to 3 weeks. Five of 22 patients sensitized to p-phenylenediamine had positive reactions to Metol.

A number of studies have been performed in order to determine the possibility of a correlation between the use of hair dyes and an increased risk for cancer. No positive correlation has been found.

DISCUSSION

In the earlier safety assessment, only p-Methylaminophenol Sulfate was considered, even though data for p-Methylaminophenol was included. The Panel notes that p-Methylaminophenol Sulfate is the salt of p-Methylaminophenol and believe that the safety data on each ingredient may be applied to the other.

Both ingredients have low dermal penetration and are used in rinse-off products. Therefore, there is no expectation of systemic toxicity from their use. This is confirmed with animal studies with dermal exposure. These ingredients are not irritants to eyes. They are not genotoxic, carcinogenic, nor reproductively/developmentally toxic. Data on m-, o-, and p-Aminophenol from a separate assessment,

which are chemically related, were also considered and found safe.

p-Methylaminophenol Sulfate and p-Methylaminophenol are known sensitizers. However, as coal tar hair dyes, they fall under the coal tar derivative exemption to the Federal Food, Drug, and Cosmetic Act which requires caution statements and instruction regarding patch tests. The Panel expects that individuals following these instructions will minimize sensitization.

The CIR Expert Panel expressed concern about toxic metal residues that may be present in p-Methylanimophenol Sulfate and p-Methylaminophenol and advised industry that this ingredient should not contain more than: 3 mg/kg of arsenic (as As), 1 ppm mercury (as Hg), and 0.1 mg/kg of lead (as Pb). Additionally, p-Methylaminophenol Sulfate and p-Methylaminophenol should not contain N-nitroso impurities, nor should they be used in products where N-nitroso compounds may be formed.

CONCLUSION

The CIR Expert Panel concluded that p-Methylaminophenol Sulfate and p-Methylaminophenol are safe as hair dye ingredients in the practices of use and concentration as described in this safety assessment.

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