EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Public Health and Risk Assessment
C7 - Risk assessment

SCIENTIFIC COMMITTEE ON CONSUMER PRODUCTS

SCCP

Opinion on

p-METHYLAMINOPHENOL sulphate

COLIPA N° A22

Adopted by the SCCP
during the 7th plenary meeting of 28 March 2006

TABLE OF CONTENTS

1. BACKGROUND

Submission I for *p*-Methylaminophenol sulphate was submitted in May 1991 by COLIPA[1, 2].

The Scientific Committee on Cosmetology (SCC), at its 46th plenary meeting of 19 February 1991, expressed its opinion with the conclusion:

"*The SCC requires an in vitro mouse lymphoma gene mutation study and a dermal absorption study on rats. Data on contamination of this compound are also required (with nitrosamine?).* "

Submission II for this substance was submitted in December 1993 by COLIPA.

Submission III for this substance was submitted in March 1997 by COLIPA.

The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) adopted at its plenary meeting on 23 June 1999 the opinion (SCCNFP/0179/99) with the conclusion:

"*The SCCNFP is of the opinion that 1-Hydroxy-4-methylamino-benzene can be used safely in permanent hair dye formulations at a maximum concentration of 3.0%. Since permanent hair dyes are mixed with hydrogen peroxide before application, the in-use concentration is 1.5%. The sensitisation data in the dossier was generated with a method not conforming to OECD n° 406. However, no further sensitisation data are requested provided that cosmetic products containing this substance carry a label warning of a risk of sensitisation."*

The substance is currently regulated by the Cosmetics Directive (76/768/EC), Annex III, Part 2 under entry 12 on the List of substances provisionally allowed, which cosmetic products must not contain except subject to restrictions and conditions laid down.

Submission IV for this substance was submitted by COLIPA in July 2005. According to this submission *p*-Methylaminophenol sulphate is used in oxidative hair dye formulations at a maximum concentration of 1.35%, which after mixing typically in 1:1 ratio with hydrogen peroxide prior to use, corresponds to a concentration of 0.68 % upon application.

Submission IV presents updated scientific data on the above mentioned substance in line with the second step of the strategy for the evaluation of hair dyes (http://europa.eu.int/comm/enterprise/cosmetics/doc/hairdyestrategyinternet.pdf) within the framework of the Cosmetics Directive 76/768/EEC.

[1] COLIPA - European Cosmetics Toiletry and Perfumery Association
[2] According to records of COLIPA.

2. TERMS OF REFERENCE

1. *Does the Scientific Committee on Consumer Products (SCCP) consider p-Methylaminophenol sulphate safe for use as an oxidative hair dyes with an on-head concentration of maximum 0.68% taken into account the scientific data provided?*

2. *Does the SCCP recommend any restrictions with regard to the use of p-Methylaminophenol sulphate in oxidative hair dye formulations?*

3. OPINION

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

3.1.1.1. Primary name and/or INCI name

p-Methylaminophenol sulphate (INCI name)

3.1.1.2. Chemical names

1-Hydroxy-4-methylamino-benzene hemisulphate
Phenol, 4-(methylamino)-sulphate (2:1) salt (CAS name)
4-(methylammonio)-phenol sulphate
p-methylaminophenol sulphate
N-(methyl-4-ammoniophenol) sulphate
N-methyl-p-aminophenol sulphate
4-hydroxy-N-methylanilinium sulphate
p-hydroxy-N-methylaniline sulphate
N-methyl-4-hydroxyanilinium sulphate
N-methyl-p-hydroxyaniline sulphate
N-methyl-N-(4-hydroxy)phenylammonium sulphate

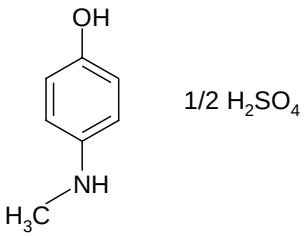
3.1.1.3. Trade names and abbreviations

Trade names: N-methyl para aminophenol sulphate, IFG 62/78
COLIPA n°: A22

3.1.1.4. CAS / EINECS number

CAS: 150-75-4 (free base)
55-55-0 (hemisulfate)
1936-57-8 (sulfate)
EINECS: 205-768-2 (free base)
200-237-1 (hemisulfate)
217-706-1 (sulfate)

3.1.1.5.	Structural formula



3.1.1.6.	Empirical formula

Formula: C_7H_9NO ½ H_2SO_4

3.1.2.	Physical form

White to beige powder

3.1.3.	Molecular weight

Molecular weight: 172.23

3.1.4.	Purity, composition and substance codes

- Batches used: F1058599 (August 2004), 4C461 (December 2004), 2070092 (October 1996), 8050313 (June 1988). Also batch SEL/1399 of phenyl-[U-^{14}C]-p-methylaminophenol sulphate (radiochemical purity 99.8%), used for the *in vitro* percutaneous absorption study [14]

The test substance was characterised by elemental analysis, NMR and MS in two batches.

Purity (Titre)*: ≥ 97.0 %(w/w) (by alkalimetric potentiometry) **
* The purity of the four batches above was found in the range 98.5 – 100 % (w/w).
** Neutralization of amine function with perchloric acid in an acetic acid medium.

H.P.L.C. purity: > 97.5 % (area % without response factor)

Sulphate ions content: 30.0-30.5 % (w/w) (theory 28.5%)

Water content (Karl Fisher): < 0.1 %

Ash content: < 0.1 g/100g
Loss on drying: < 0.1 g/100g

Impurities
- p-Aminophenol: ~ 2.5 g/100g
- N,N' dimethylparaphenylenediamine: < 0.4 g/100g

Heavy Metals
- As, Sb, Hg: each < 5 mg/kg
- Cd: < 10 mg/kg
- Pb: < 20 mg/kg

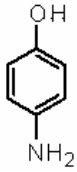
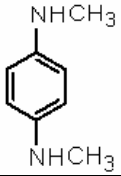
Residual solvents
No residual solvents such as methanol, ethanol, isopropanol, n-propanol, acetone, ethyl acetate, cyclohexane, methylethyl ketone or monochlorobenzene was detected (detection limit < 100 µg/g).

Comparative table

Batch	F1058599	4C461	2070092	8050313
Titre by potentiometry	99.8 %	98.7 %	99.6 %	99.5 %
Water Content (K.F. method)	0.04 %	0.01 %		
Melting point (°C) (1)	246	256		
H.P.L.C. Profile (2)	> 99.5 %	> 99.5 %		
Sulphate ions (H.P.I.C)	30.0 %	30.4 %		
Impurity A	0.22 %	0.17 %	1.5 %	
Impurity B	0.32 %	ND < 0.1 %		
^{1}H and ^{13}HC N.M.R. spectra	in accordance with structure			
Mass Spectrometry	in accordance with structure			

3.1.5. Impurities / accompanying contaminants

Detected impurities from reagents or intermediate reaction products:

Impurity A	Impurity B
	
p-Aminophenol	N,N' dimethylparaphenylenediamine

A difference of impurities content between batches was noticed:

- Batch F1058599: *0.22 g/100g (A) and 0.32g/100g (B) **
- Batch 4C461: *0.17 g/100g (A) and impurity B is not detected * (< 0.1 %)*
- Batch 2070092: *1.5 g/100g (A)** - Impurity B not done on this batch.*

** Directly carried out or calculated, against a reference standard*
*** Quantitative evaluation by HPTLC.*

3.1.6. Solubility

Solubility in water at 20°C ± 0.5 : 4.92 ± 0.6 % (w/v) - according to EEC method A6

Solubility measured at 23°C after 24 hours:

- Ethanol: Less than 1% (w/v)
- DMSO: More than 20% (w/v)

3.1.7. Partition coefficient (Log P_{ow})

Log $P_{o/w}$: 0.04 at 24°C at pH 7.2 - according to EEC method A8 – H.P.L.C. method

3.1.8. Additional physical and chemical specifications

organoleptic properties:	odourless
- melting point:	Decomposes between 245°C and 256°C* * (depending on batch, probably on sulphate content)
- flash point:	/
- vapour pressure:	/
- boiling point:	/
- density at 20 °C:	/
- viscosity:	/
- pKa:	/
- UV absorption spectrum:	λ_{max} 220.5 nm (ε=0.864), 271.5 nm (ε=0.154).
- Refractive index at 20 °C:	/

3.1.9. Stability

A 0.5 mg ml solution in 5% CMC was stable (maximum deviation from initial concentration ± 11 %) up to 4 days, when stored at room temperature or at 4°C, under inert atmosphere and protected from light.
A 200 mg/ml solution in 5% CMC was stable up to 9 days (maximum deviation from initial concentration ± 7%) when stored at room temperature, under inert atmosphere and protected from light.
0.1 - 50 mg/ml solutions in DMSO were stable up to 4 hour study period (maximum deviation from initial concentration ±11%) at room temperature, when stored protected from light and under inert atmosphere.

General Comments on Physico-chemical characterisation

- p-Methylaminophenol sulphate is a secondary amine, and thus is prone to nitrosation. Nitrosamine content in p-methylaminophenol sulphate is not reported, despite being requested in 1991 by the former Scientific Committee on Cosmetic Products.
- Stability of the test material in marketed products is not reported.

3.2. Function and uses

p-Methylaminophenol sulphate is used in oxidative hair dye formulations at a maximum concentration of 1.35 %, which after mixing typically in a 1:1 ratio with hydrogen peroxide prior to use, corresponds to a concentration of 0.68% upon application.

3.3. Toxicological Evaluation

3.3.1. Acute toxicity

3.3.1.1. Acute oral toxicity

Guideline:	OECD 420
Species/strain:	Rat, Sprague Dawley Rj:SD (IOPS Han)
Group size:	Sighting test: 3 females Main experiment: One group of 4 females
Test substance:	p-methylaminophenol sulphate (in a 0.5% suspension of carboxymethylcellulose)
Batch:	4C461
Purity:	98.7%
Doses:	500, 200 and 100 mg/kg bw (sighting experiment) 100 mg/kg bw in main experiment
Observation:	14 days
GLP:	in compliance

The acute oral toxicity of p-Methylaminophenol sulphate was evaluated in rats according to the "fixed dose method".
A preliminary test (sighting test) preceded the definitive test (main experiment) to allow selection of the appropriate dose for the main experiment.
In the sighting test, the test item was administered to single animals in a sequential manner. According to the results of the sighting test, the test item was administered by oral route (gavage) at the dose-level of 100 mg/kg, to one group of fasted Sprague-Dawley female rats. Clinical signs and mortality were checked for a period of 14 days following the single administration of the test item. The animals were checked for body weight gain and were subjected to necropsy.

Results
Sighting test
At 500 mg/kg, the animal was found dead on day 4; hypoactivity or sedation, piloerection, dyspnea and tremors were observed prior to death.
At 200 mg/kg, the animal was found dead on day 3; hypoactivity, piloerection and dyspnea were observed prior to death.
At 100 mg/kg, no clinical signs and no mortality were observed.

Main experiment
At the 100 mg/kg dose-level, no death occurred. Hypoactivity, piloerection and dyspnea were observed in the four treated animals within the 3 hours following the treatment. The body weight

gain of the animals given 100 mg/kg was not affected by treatment with the test item. At necropsy, no apparent abnormalities were observed.

Conclusion
Under the experimental conditions, the maximal non lethal dose of the test item p-Methylaminophenol sulphate was 100 mg/kg and the minimal lethal dose was 200 mg/kg by oral route in rats.

Ref.: 1

3.3.1.2. Acute dermal toxicity

No data submitted

3.3.1.3. Acute inhalation toxicity

No data submitted

3.3.2. Irritation and corrosivity

3.3.2.1. Skin irritation

Guideline:	OECD 404
Species:	New Zealand White rabbits
Group:	3 male
Substance:	N-methyl-p-aminophenol sulphate
Batch:	F1058599
Purity:	99.8%
Dose:	0.5 ml of 3% N-methyl p-aminophenol sulphate in 0.5% aqueous carboxymethylcellulose
GLP:	in compliance

Doses of 0.5 ml of N-methyl-p-aminophenol sulphate at a concentration of 3% were placed on gauze pads and successively applied to a clipped area on the left flank (3 minutes), the anterior right flank (1 hour) and the posterior right flank (4 hours) of one animal. The gauze pads were held in place under a semi-occlusive dressing and a restraining bandage. Untreated skin served as a control.
Because the dosage form was not irritating in the first animal, it was applied for 4 hours to the two additional animals.
No residual test compound was observed upon removal of the dressing. The skin was examined 1, 24, 48 and 72 hours after removal of the dressing.

Results
No cutaneous reactions were observed during the study.

Conclusion
Under the conditions of this study, a 3% concentration of N-methyl-p-aminophenol sulphate was non-irritating when applied to rabbit skin.

Ref.: 3

3.3.2.2. Mucous membrane irritation

Guideline: OECD 405
Species: New Zealand White rabbits
Group: 3 male
Substance: N-methyl-p-aminophenol sulphate
Batch: F1058599
Purity: 99.8%
Dose: 0.1ml of 3% N-methyl-p-aminophenol sulphate in 0.5% aqueous carboxymethylcellulose
GLP: in compliance

A single dose of 0.1 ml of a preparation of N-methyl-p-aminophenol sulphate diluted to a concentration of 3% in 0.5% aqueous carboxymethylcellulose was placed into the conjunctival sac of the left eye of the animals. The upper and lower lids were held closed for about 1 second to avoid any loss of test substance. The eyes were not rinsed after administration of the test substance. The untreated right eye of each animal served as a control. Evaluations of the conjunctiva, cornea and iris were made 1 hour after compound administration, and 24, 48 and 72 hours thereafter.

Results
Very slight chemosis and redness of the conjunctiva were noted in 1/3 animals 1 hour after ocular instillation only. No other signs of ocular irritation were observed during the study.

Conclusion
Under the conditions of this study, a 3% concentration of N-methyl-p-aminophenol sulphate was slightly and transiently irritating to rabbit eyes.

Ref.: 2

3.3.3. Skin sensitisation

Local Lymph Node Assay (LLNA)

Guideline: OECD 429
Species: CBA/J mice
Group: 7 groups of 4 females
Substance: N-methyl-p-aminophenol sulphate
Batch: F1058599
Purity: 99.8%
Dose: 25µl of 0.25, 0.5, 1, 2.5, 5% N-methyl p-aminophenol sulphate in DMSO
Control: α-hexylcinnamaldehyde
GLP: in compliance

The sensitisation potential of N-methyl-p-aminophenol sulphate in dimethysulfoxide (DMSO) was assessed. This vehicle was selected on the basis of the results from a previous solubility study showing that N-methyl p-aminophenol sulphate was non-soluble in other recommended vehicles, and that 5% N-methyl-p-aminophenol in DMSO was the maximal practicable concentration [15]. This concentration was non-irritating in a preliminary test performed in 4 female mice.

The principal study was performed in 7 groups of 4 mice. The dose volume of 25 µl was applied to the dorsal surface of both ears at concentrations of 0.25%, 0.5%, 1%, 2.5% and 5% once daily for 3 days designated as days 1, 2 and 3. Vehicle control animals received DMSO, while positive control animals received 25% (v/v) α-hexylcinnamaldehyde (HCA) in DMSO.
Animals were observed at least once daily for mortality/morbidity and clinical signs. Body weights were recorded on day 1 and on the day of sacrifice (day 6). On days 1, 2, 3 and 6, the thickness of the left ear was measured and any irritation reactions recorded to assess any possible irritant effect of the test item. Ear thickness was not measured in the positive control group.
On day 6, all animals were administered 250 µl of 0.9% NaCl containing 20 µCi of tritiated thymidine (^{3}H-TdR). After approximately 5 hours, they were killed and the auricular lymph nodes excised. The nodes from each group were pooled, a suspension of auricular lymph node cells prepared, and proliferation of these cells measured using β-scintillation counting. The results were used to calculate the Stimulation Index (SI) for proliferation. The EC3 value (the theoretical concentration resulting in an SI value of 3) was subsequently determined.

Results
No compound-related cutaneous reactions were observed at any tested concentration. A dose-related increase in SI was observed in animals treated with N-methyl-p-aminophenol sulphate and the threshold positive value of 3 was exceeded at concentrations of 2.5% and 5%. The calculated EC3 value was 2.2%.

Conclusion
N-methyl p-aminophenol sulphate induced delayed contact hypersensitivity under the conditions of this study. The EC3 value calculated (2.2%) indicates that it should be considered a moderate sensitiser.

Ref.: 4

3.3.4.	Dermal / percutaneous absorption

***In Vitro* Percutaneous Absorption Study using Human dermatomed Skin**

Guideline:	Draft OECD 428
Species:	Human
Group:	8 female donors (5 breast, 3 abdomen)
Substance:	p-methylaminophenol sulphate in a hair dye formulation
Batch:	4C461
Purity:	98.7%
Radiolabel:	[Phenyl-U-^{14}C]-p-methylaminophenol sulphate
Radiolabel batch/purity:	SEL/1399 (99.8% radiochemical pure)
GLP:	in compliance

Human skin samples (5 breast, 3 abdomen) were obtained from eight female donors (27 to 58 years old) subjected to plastic surgery. They were kept frozen at about -20°C until their use in the present study. Skin samples were dermatomed (350-390 µm in thickness) and mounted in flow-through diffusion cells (12 cells per study condition), using calcium and magnesium-free phosphate-buffered saline as the receptor fluid (flow rate 1.5 ml/h). Their integrity was checked before application of the test preparation by determination of the permeability coefficient for tritiated water (<2.5 x 10^{-3} cm/h for all selected membranes). The skin was maintained at 32°C.

p-methylaminophenol sulphate was tested under oxidative (use conditions) and non-oxidative conditions. In oxidative conditions, it was incorporated into a typical hair colouring formulation at 1.35% (w/w) associated to the coupler m-aminophenol at 0.86% (w/w) before mixing with the oxidative developer (1:1, w/w) to give a final concentration of 0.68% p-methylaminophenol sulphate (w/w). In non-oxidative conditions, it was incorporated into the same formulation (without a coupler) at 1.35% (w/w) before mixing with water (1:1, w/w) to give a similar final concentration of 0.68% p-methylaminophenol sulphate (w/w).
About twenty (20) mg/cm² of oxidative and non-oxidative test preparations were applied to the skin surface for 30 minutes. After this time period, the remaining formulation on the skin surface was removed using a standardized washing procedure. Twenty-four (24) hours after application, the percutaneous absorption of [^{14}C]-p-methylaminophenol sulphate was estimated by measuring its concentration by Liquid Scintillation Counting in the following compartments: extractable dose, stratum corneum (isolated by tape strippings), skin (epidermis + dermis) and receptor fluid.

Results
Eleven and twelve diffusion cells yielded data that could be analysed in oxidative and non-oxidative conditions, respectively. Most of the p-methylaminophenol sulphate applied on the skin surface was removed at 30 minutes post dose (91.34% and 90.70% of the applied dose in oxidative and non-oxidative conditions, respectively). At 24 hours post dose, a further 1.37% and 0.73% was removed, yielding a total extractable dose of 92.72% and 91.44% for a total recovery rate of 96.42% and 97.74% in oxidative and non-oxidative conditions, respectively. The penetrated dose (amount measured in the receptor fluid) was 0.49 ± 0.24 µg equiv/cm² (0.36%) and 3.04 ± 1.10 µg equiv/cm² (2.21%) in oxidative and non-oxidative conditions, respectively. Similarly, the amounts considered to be absorbed (dermal delivery, sum of the amounts measured in the living epidermis, dermis and receptor fluid) represented 1.35 ± 0.78 µg equiv/cm² (0.33 – 4.01 µg equiv/cm²) and 6.19 ± 2.24 µg equiv/cm² (2.75 – 9.38 µg equiv/cm²) in oxidative and non-oxidative conditions, respectively.

	Oxidative conditions in typical hair dye formulations		**Non-Oxidative conditions**	
Cutaneous distribution	**µg equiv/cm²**	**% applied dose**	**µg equiv/cm²**	**% 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*	1.35 ± 0.78	1.00 ± 0.59	6.19 ± 2.24	4.49 ± 1.62

* Receptor fluid + epidermis/dermis

Conclusion
The dermal absorption (sum of the amounts measured in the epidermis, dermis and receptor fluid) of p-methylaminophenol sulphate incorporated at 0.68% (final concentration) in a typical oxidative hair dye formulation was estimated to be 1.35 ± 0.78 µg/cm² (1.00% ± 0.59% of the applied dose) under use conditions. Under non-oxidative conditions, the dermal delivery was 6.19 ± 2.24 µg/cm².
The maximum dermal absorption of 4.01 µg equiv/cm², observed under oxidative conditions in typical hair dye formulations, will be used for the calculation of the Margin of Safety.

Ref.: 14

3.3.5. Repeated dose toxicity

3.3.5.1. Repeated Dose (28 days) oral / dermal / inhalation toxicity

No data submitted

3.3.5.2. Sub-chronic (90 days) oral / dermal / inhalation toxicity

Guideline:	OECD 408
Species/strain:	Rat, Sprague Dawley, Crl CD (SD) IGS BR
Group size:	10 animals per sex and dose; 6 additional animals per sex for the high dose + control group (which were kept for a 4-week treatment free period) and 6 animals per sex in the satellite groups (low, mid and high dose)
Observation:	92 days (+4 weeks recovery period)
Test substance:	p-methylaminophenol sulphate (in a 0.5% suspension of carboxymethyl-cellulose)
Batch:	4C461
Purity:	98.7 %
Dose:	0, 3, 10, 30 mg/kg bw/day
GLP:	in compliance

A total of 140 Sprague-Dawley rats (70 males and 70 females) were allocated to three treated groups and one control group. Each group was composed of 10 animals/sex. Recovery animals (six animals/sex) were added to the control and high-dose groups for a 4-week treatment-free period. Satellite animals (six animals/sex) were allocated to each treated group for toxicokinetic investigations. The test item, p-Methylaminophenol sulphate, was administered daily for 13 weeks, by gavage, as a suspension in the vehicle (0.5% carboxymethylcellulose), at the dose-level of 3, 10 or 30 mg/kg/day. Control animals received the vehicle only under the same experimental conditions (5 ml/kg).

The animals were checked daily for mortality and clinical signs. Detailed clinical observations were carried out weekly and a functional observation battery (including motor activity) was conducted at the end of the treatment period. Body weight and food consumption were recorded once a week during the study.

Ophthalmological examinations were performed before the beginning and at the end of the treatment period. Haematological and blood biochemical investigations as well as urinalysis were performed at the end of the treatment period.

Blood samples for the determination of plasma levels of the test item were taken on day 1 and in week 13 from satellite animals at the following time-points: 0.5, 1, 2, 4, 8 and 24 hours post-dosing.

On completion of the treatment or treatment-free period, the animals were sacrificed and submitted to a full macroscopic examination. Designated organs were weighed and specified tissues preserved. A microscopic examination was performed on selected tissues from animals in the control and high-dose groups and on macroscopic lesions from all animals killed on completion of the treatment period. In addition, the kidneys and spleen from animals of the low and mid-dose groups and from those killed on completion of the treatment-free period were microscopically examined.

Results
No premature deaths occurred during the study.
No clinical signs related to treatment with the test item were observed during the study period. There were no changes in functional observation battery parameters or motor activity in any treated group. Body weight and food consumption were considered to be unaffected by treatment with the test item. No ophthalmological findings were noted at the end of the treatment period.
There were no treatment-related effects on the haematological or blood biochemical parameters.
A higher urinary volume and a lower specific gravity were noted in some males given 30 mg/kg/day. A slight decrease in thymus weight was seen in a few females from the high dose group. No other treatment-related effects on organ weights were noted at the end of the treatment or treatment-free period and no treatment-related necropsy findings were observed.
Microscopic examination showed tubular epithelial degeneration/single cell necrosis in the kidneys of most males and half females given 30 mg/kg/day. These lesions were not present at the end of the treatment-free period.
Plasma levels of p-Methylaminophenol sulfate were below quantifiable limits at all time points in animals given 3 mg/kg/day and were only detectable at 0.5 hours post-dosing in animals given 10 mg/kg/day, in week 13.
In contrast, for the high-dose group, the maximum mean plasma level was measurable at 0.5 hours after dosing on day 1 and in week 13 in both sexes. Thereafter, the levels quickly decreased and the test item was not quantifiable 2 hours after dosing on day 1 and 4 hours after dosing in week 13.
The systemic exposure (as measured by C_{max} and $AUC_{(0-t)}$), was difficult to analyse due to the low number of available results but the systemic exposure seemed to increase with the dose-level.
The plasma levels showed no definitive gender or time effects.

Conclusion
The test item, p-Methylaminophenol sulphate was administered daily by gavage to Sprague-Dawley rats at the dose-level of 3, 10 or 30 mg/kg/day for 13 weeks followed by a 4-week treatment-free period.
The test item was clinically well tolerated at all dose-levels and did not cause any change in haematological and blood biochemical parameters. Only a higher urinary volume and a lower specific gravity were noted in some males given 30 mg/kg/day.
No effects on organ weights and no macroscopic findings were noted.
Microscopic examination revealed tubular epithelial degeneration/single cell necrosis in the kidneys of animals given 30 mg/kg/day, and complete reversibility of these changes was noted at the end of the treatment-free period.
Consequently, under the experimental conditions of the study, the No Observed Adverse Effect Level (NOAEL) is 10 mg/kg/day.

Ref.: 5

3.3.5.3. Chronic (> 12 months) toxicity

See 3.3.7. Carcinogenicity

3.3.6. Mutagenicity / Genotoxicity

3.3.6.1. Mutagenicity / Genotoxicity *in vitro*

Bacterial gene mutation assay

Guideline:	OECD 471
Species/strain:	*Salmonella typhimurium*, TA98, TA100, TA1535, TA1537, TA102
Replicates:	Two independent tests
Test substance:	p-Methylaminophenol sulphate
Batch:	4C461
Purity:	98.7%
Concentrations:	0.064 - 1000 µg/plate without S9 mix (depending on the strain) 0.064 - 2000 µg/plate with S9 mix (depending on the strain)
GLP:	in compliance

p-Methylaminophenol sulphate has been investigated for the induction of gene mutations in *Salmonella typhimurium*. Liver S9 fraction from rats induced with Aroclor 1254 was used as the exogenous metabolic activation system. Concentrations were defined by a preliminary toxicity study. Negative and positive controls were in accordance with the OECD guideline.

Results
p-Methylaminophenol sulphate induced gene mutations in *S. typhimurium* in some of the five strains (TA 100 in the presence and absence of metabolic activation; TA 98 and TA 1537 in the presence of metabolic activation only).
p-Methylaminophenol sulphate is mutagenic in the bacterial gene mutation assay.

Ref.: 6

***In vitro* chromosome aberration test**

Guideline:	OECD 473
Cells:	human lymphocytes
Replicates:	one test with and without S9 mix
Test substance:	p-Methylaminophenol sulphate
Batch:	4C461
Purity:	98.7%
Concentrations:	11.26 – 27.49 µg/ml with and without metabolic activation; treatment for 3h
GLP:	in compliance

p-Methylaminophenol sulphate has been investigated for induction of chromosomal aberrations in cultured human lymphocytes after treatment for 3 hours (in the absence and presence of metabolic activation) and a harvest time of 20 hours. Liver S9 fraction from Aroclor1254-induced rats was used as the exogenous metabolic activation system. Test concentrations for scoring of experiments without metabolic activation were based upon the reduction in the mitotic index. Negative and positive controls were in accordance with the OECD guideline.

Results

The test substance induced a significant increase in the frequency of chromosome aberrations in experiments with and without S9 mix. Under the experimental conditions used, p-Methylaminophenol sulphate was clastogenic in mammalian cells (human lymphocytes) *in vitro*.

Ref.: 9

In vitro mammalian cell gene mutation test (TK+/-)

Guideline:	OECD 476
Cells:	L5178Y mouse lymphoma cells (TK+/-)
Replicates:	3 independent tests with and without S9 mix
Test substance:	p-Methylaminophenol sulphate
Batch:	2070092
Purity:	99.6%
Concentrations:	0.1 –3.0 µg/ml without metabolic activation
	1.0 – 38 µg/ml with metabolic activation
GLP:	in compliance

p-Methylaminophenol sulphate has been investigated for induction of gene mutations at the TK-locus in L5178Y mouse lymphoma cells after exposure for 3 hours without and with metabolic activation. Liver S9 fraction from Aroclor1254-induced rats was used as the exogenous metabolic activation system. Test concentrations were based on the level of toxicity. Negative and positive controls were in accordance with the OECD guideline.

Results
The test substance induced significant increases in the mutant frequencies after the 3-hour treatment in the presence of S9 mix. Under the experimental conditions used, p-Methylaminophenol sulphate was mutagenic in mammalian cells (L5178Y mouse lymphoma cells) *in vitro*. Colony sizing was not performed for the induced mutant colonies and, therefore, no information is available on the mechanism of mutation induction (i. e. induction of point mutations or chromosomal effects).

Ref.: 7

In vitro mammalian cell gene mutation test (HPRT)

Guideline:	OECD 476
Cells:	L5178Y mouse lymphoma cells (HPRT)
Replicates:	2 independent tests with and without S9 mix
Test substance:	p-Methylaminophenol sulphate
Batch:	4C461
Purity:	98.7%
Concentrations:	0.5 – 2.0 µg/ml without metabolic activation
	2.5 – 60 µg/ml with metabolic activation
GLP:	in compliance

p-Methylaminophenol sulphate has been investigated for induction of gene mutations at the HPRT-locus in L5178Y mouse lymphoma cells after exposure for 3 hours without and with metabolic activation. Liver S9 fraction from Aroclor1254-induced rats was used as the

exogenous metabolic activation system. Test concentrations were based on the level of toxicity. Negative and positive controls were in accordance with the OECD guideline.

Results
The test substance did not induce significant and / or reproducible increases in the mutant frequencies after the 3-hour treatment in the presence or absence of S9 mix. Under the experimental conditions used, p-Methylaminophenol sulphate was not mutagenic in the *in vitro* HPRT gene mutation test with L5178Y mouse lymphoma cells.

Ref.: 8

3.3.6.2 Mutagenicity/Genotoxicity *in vivo*

Rat bone marrow micronucleus test

Guideline:	OECD 474
Species/strain:	Rat, Sprague-Dawley
Group size:	5 males + 5 females
Test substance:	p-Methylaminophenol sulphate
Batch:	4C461
Purity:	98.7%
Dose:	100, 200 and 400 mg/kg bw (once by gavage)
Sacrifice time:	24 and 48 (highest dose group only) hours after the treatment
GLP:	in compliance

p-Methylaminophenol sulphate has been investigated for induction of micronuclei in the bone marrow cells of rats. Since in the preliminary range-finding study mortality was observed at 500 mg/kg, 400 mg/kg was tested as the top dose-level. Negative and positive controls were in accordance with the OECD guideline.

Results
There was no indication of bone marrow toxicity in the micronucleus test because the PCE/NCE ratio was not lower in all treated groups than in the negative control group. However, oral bioavailability can be assumed by the systemic clinical signs and the death of one animal treated with 400 mg/kg. The mean MNPCE frequencies were not significantly increased in any of the groups treated with the test substance. The positive control substance gave the expected result.
p-Methylaminophenol sulphate did not induce chromosome aberrations or damage to the mitotic apparatus in bone marrow cells of rats after oral treatment under the appropriate test conditions used.

Ref.: 10

Rat liver *in vivo/in vitro* UDS assay

Guideline:	draft OECD guideline 486 (1991)
Species/strain:	Wistar Han rat
Group size:	3 males
Test substance:	p-Methylaminophenol sulphate
Batch:	2070092
Purity:	99.6%

Dose levels: 50 and 500 mg/kg bw, by gavage
Sacrifice times: 16 hours: both dose groups; 2h: high dose group
GLP: in compliance

p-Methylaminophenol sulphate has been investigated for induction of unscheduled DNA synthesis (UDS) in rat hepatocytes *in vitro* following *in vivo* dosing. The top dose level was selected on the basis of a preliminary toxicity study. Negative and positive controls were in accordance with the OECD guideline. Animals were sacrificed after 16 hours and for an additional high dose group after 2 hours.

Results
One animal treated with 500 mg/kg died. In none of the groups treated with the test substance there was a significant induction of UDS compared to the control group. There were no differences in the viability of hepatocytes isolated from rats of different dose groups. The results met all the pre-defined criteria for a negative response. The positive control substance agent gave the expected results. The negative test result indicates that p-Methylaminophenol sulphate does not induce DNA damage that is detectable with the UDS test.

Ref.: 11

3.3.7. Carcinogenicity

Topical application, mice

Guideline: /
Species/strain: Swiss Webster mice
Group size: 50 animals per sex and dose
Test substance: Two hair dye formulations, one (7404) containing 1.0 % p-methylaminophenol sulfate and another (P26) containing 0.05% p-methylaminophenol sulfate (The latter formulation used was not given in reference to the study, but was found in: E. Goldenthal. Formulae P-25 and P-26: Lifetime Chronic Toxicity/Carcinogenesis Study in Rats. IRDC Study No. 355-003 (c), 1979) prior to mixing with equal volume 6% hydrogen peroxide. The mixture was used within 15 minutes after mixing
Batch: /
Purity: not stated
Dose: 0.05 ml of a solution containing p-methylaminophenol and hydrogen peroxide
Route: Topical, 1 application weekly
Exposure: 21 months: 7404; 23 months: P-26
GLP: not in compliance

The experiment involved 12 treatment groups and 3 negative control groups.

Dye applied topically to a 1 cm^2 area on a clipped (24 hours prior to application) site in the interscapular region. Mice received a dose of 0.05 ml topically without occlusion once weekly from 8 – 10 weeks of age for 21 – 23 months. The animals were observed daily for mortality and signs of toxicity, and were weighed monthly. A continuous weekly record was maintained for any skin lesions noted. After 9 months of treatment, 10 males and 10 females per group were

necropsied and the study was terminated after 21 – 23 months. Skin and internal organs were evaluated histologically.
9 – 11 males and 10 –13 females survived to 21 months in the group receiving the oxidative formulations containing p-methylaminophenol. At 21 months, there were 9-12 males and 11-14 females surviving in the control groups. There were no significant differences in absolute or relative liver or kidney weights in groups of 10 male and 10 female mice necropsied after 7 and 9 months. There were no statistically significant differences in the distribution of tumours among treated and control groups.

Ref.: AD 1

Topical application, Rats

Guideline:	/
Species/strain:	Male and female weanling Sprague Dawley rats
Group size:	60 animals per sex and dose
Test substance:	Two hair dye formulations, one (7404) containing 1.0 % p-methylaminophenol sulfate and another (P26) containing 0.05% p-methylaminophenol sulfate (The latter formulation used was not given in reference to the study, but was found in: E. Goldenthal. Formulae P-25 and P-26: Lifetime Chronic Toxicity/Carcinogenesis Study in Rats. IRDC Study No. 355-003 (c), 1979) prior to mixing with equal volume 6% (?) hydrogen peroxide (concentration of hydrogen peroxide unclear. According to: Burnett C, Jacobs MM, Seppala A and Shubik P. Evaluation of the Toxicity and Carcinogenicity of Hair Dyes. J. Toxicol. Environ. Health 6: 247-257, 1980; 6% and according to: E. Goldenthal. Formulae P-25 and P-26: Lifetime Chronic Toxicity/Carcinogenesis Study in Rats. IRDC Study No. 355-003 (c), 1979, 20 volume hydrogen peroxide). The mixture was used within 15 minutes after mixing
Batch:	/
Purity:	not stated
Dose:	0.5 ml of the test substance
Route:	Topical. 1 application twice weekly
Exposure:	114 weeks
GLP:	not in compliance

The experiment involved altogether ten different dye formulations and six control groups.
Groups of 60 male and 60 female were obtained from the first mating (F_{1a}) of a multigeneration reproduction study in rats treated with two different hair dye formulations containing up to 0.5% p-methylaminophenol. The F_0 parents had received topical application of the hair dye formulation from the time of their weaning to the weaning of their offspring. The dye formulations were administered topically to the shaved (24 hours prior to application) neck and back area twice weekly. An initial dosage level of 0.2 ml/rat was increased incrementally by 0.1 ml per week until 0.5 ml was achieved. There were three independent control groups each containing 60 males and 60 females, which received no treatment.

The rats were observed daily for overt signs of toxicity and for mortality. Detailed observations were recorded weekly. Individual body weights were recorded weekly for the first 14 weeks and monthly thereafter. Group food consumption was recorded weekly. Haematological, biochemical and urinalysis studies were done on 5 males and 5 females per group at 3, 12, 18, and 24 months

of study. After 12 months of treatment, 5 males and 5 females from each group were sacrificed and necropsied and all rats of a sex group were sacrificed and necropsied when survival reached 20%. Histopathological evaluations were performed on 18 tissues (plus tumour masses) including treated skin.

Survival just prior to terminal sacrifice (at week 114) the survival was 16 – 24 males and 14 – 17 females for the exposed groups. Survival was 15 males and 9 – 18 females for the control groups. After 114 weeks, group mean body weights in the treated groups were 713 – 719 g in males and 443 – 513 g in females. Control group values ranged from 682 to 759 g in males and 477 to 513 g in females.

The p-methylaminophenol containing formulations produced no local adverse effects and had no effect on survival rate. It did not produce any clinical signs or any changes in body weight, food consumption or clinical pathology parameters. No significant differences considered to be treatment related were observed in the biochemical studies or in the urinalysis. Non-neoplastic lesions were those commonly found in ageing rats and were considered to be spontaneous. Females treated with formulation 7404 (0.5% p-methylaminophenol) had a significant increase in the incidence of mammary adenomas when compared to a single control group. Since this increase was confined to one of the three control groups and this treatment group showed a decrease in the number of mammary carcinomas compared to the same control group, this finding was not considered to be biologically significant. Moreover, life-table analyses showed no compound-related variations for the treated groups as compared to the three control groups by sex.

Ref.: 12

The study with formulation P26 is not presented in the submission.
The reference to the study is: E. Goldenthal. Formulae P-25 and P-26: Lifetime Chronic Toxicity/Carcinogenesis Study in Rats. IRDC Study No. 355-003 (c), 1979.

Comment
2,4-Diaminoanisole (EU, carc. Cat. 2) was tested in the same experiments and no response was found.
No conclusion with regard to carcinogenicity can be made from the studies.

3.3.8. Reproductive toxicity

3.3.8.1. Two generation reproduction toxicity

No data submitted

3.3.8.2. Teratogenicity

Prenatal development toxicity study

Guideline:	OECD 414
Species/strain:	Rat, Sprague Dawley, Crl CD (SD) IGS BR
Group size:	24 females / dose level
Observation:	20 days

Test substance:	p-methylaminophenol sulphate (in a 0.5% suspension of carboxymethylcellulose)
Batch:	4C461
Purity:	98.7%
Dose:	0, 5, 25, 125 mg/kg bw/day
GLP:	in compliance

Four groups of 24 pregnant rats received p-methylaminophenol sulphate by oral gavage at doses of 0, 5, 25 or 125 mg/kg bw/day from day 6 through day 19 *post-coitum.* The day of positive proof for sperm in the vaginal smear or sperm plug was designated as day 0 *post coitum* (p.c.) or gestation day 0.
Animals were checked daily for clinical signs. Food consumption and body weight were recorded at designated intervals during pregnancy.
On day 20 post-coitum, the dams were sacrificed and subjected to a macroscopic examination. The gravid uterus was weighed and the foetuses were removed by hysterectomy. The following litter parameters were recorded: number of corpora lutea, implantation sites, early and late resorptions, dead and live foetuses. The foetuses were weighed, sexed and subjected to external, soft tissue or skeletal examinations.

Results
Maternal data
There were no premature deaths during the study. No treatment-related clinical signs were observed. Relevant maternal changes were only observed at 25 and 125 mg/kg/day where net body weight gain was slightly reduced when compared to controls. No relevant necropsy findings were recorded.
Litter data
None of the litter parameters evaluated were affected by treatment with the test item.
Foetal evaluation
There were no treatment-related malformations or variations in any groups at external, soft tissue or skeletal examinations.

Conclusion
When compared to controls, the maternal body weight gain was slightly decreased at 25 and 125 mg/kg/day. None of the litter data examined were affected. No foetal malformations or variations were considered to be related to treatment.
Consequently, under the experimental conditions of this study, a No Observed Adverse Effect Level (NOAEL) for maternal toxicity was set at 5 mg/kg/day, and the dose-level of 125 mg/kg/day was considered to be the NOAEL for embryo-foetal toxicity.

Ref: 13

3.3.9. Toxicokinetics

No data submitted

3.3.10. Photo-induced toxicity

3.3.10.1. Phototoxicity / photoirritation and photosensitisation

No data submitted

3.3.10.2. Phototoxicity / photomutagenicity / photoclastogenicity

No data submitted

3.3.11. Human data

No data submitted

3.3.12. Special investigations

No data submitted

3.3.13. Safety evaluation (including calculation of the MoS)

CALCULATION OF THE MARGIN OF SAFETY

(p-Methylaminophenol sulphate)
(Oxidative/permanent)

Maximum absorption through the skin	**A (µg/cm^2)**	**=**	**4.01 µg/cm^2**
Skin Area surface	**SAS (cm^2)**	**=**	**700 cm^2**
Dermal absorption per treatment	**SAS x A x 0.001**	**=**	**2.807 mg**
Typical body weight of human		**=**	**60 kg**
Systemic exposure dose (SED)	**SAS x A x 0.001/60**	**=**	**0.047 mg/kg**
No observed adverse effect level (mg/kg) (oral, rat, prenatal developmental)	**NOAEL**	**=**	**5 mg/kg**
Margin of Safety	**NOAEL / SED**	**=**	**106**

3.3.14. Discussion

Physico-chemical properties
p-Methylaminophenol sulphate is a secondary amine, and thus is prone to nitrosation. The nitrosamine content in p-methylaminophenol sulphate is not reported. The stability of the test material in marketed products is not reported.

Toxicity
The No Observed Adverse Effect Level (NOAEL) was set at 10 mg/kg bw/day (90 day, rat), at 5 mg/kg bw/day (maternal toxicity) and at 125 mg/kg bw/day (embryo-foetal toxicity).

Irritation, sensitisation
Under the conditions of the tests, N-methyl p-aminophenol sulphate was non-irritating when applied to the skin. It was slightly and transiently irritating to the eyes. It is considered as a moderate sensitiser.

Percutaneous absorption
A maximum dermal absorption of 4.01 µg equiv/cm² was observed under oxidative conditions in typical hair dye formulations.

Mutagenicity
p-Methylaminophenol sulphate is mutagenic *in vitro*. It induced gene mutations in bacteria and in cultured mammalian cells (TK locus). It also induced chromosome aberrations in mammalian cells *in vitro*. The test substance did not induce damage to chromosomes or the mitotic apparatus in the *in vivo* micronucleus test. It was also negative in the *in vivo* UDS test, i. e. it did not cause DNA damage in the liver that induces DNA excision repair. Thus, the mutagenic potential of p-Methylaminophenol sulphate seen *in vitro* does not lead to genotoxic or mutagenic effects *in vivo* under appropriate test conditions.

Carcinogenicity
2,4-Diaminoanisole (EU, Carcinogenic Category 2) was tested in the same experiments and no response was found. Therefore, no conclusion with regard to carcinogenicity can be made from the studies.

4. CONCLUSION

Based on the information provided, the SCCP is of the opinion that the use of p-methylaminophenol sulphate itself as an oxidative hair dye at a maximum concentration of 0.68% in the finished cosmetic product (after mixing with hydrogen peroxide) does not pose a risk to the health of the consumer, apart from its sensitising potential.

p-Methylaminophenol sulphate is a secondary amine, and thus is prone to nitrosation. It should not be used in combination with nitrosating substances. The nitrosamine content should be < 50 ppb.

Studies on genotoxicity/mutagenicity in finished hair dye formulations should be undertaken following the relevant SCCNFP opinions and in accordance with its Notes of Guidance.

5. MINORITY OPINION

Not applicable

6. REFERENCES

References in *italics* are not submitted as full reports in the present dossier [16-30]. They consist of reports for studies considered to be inadequate for submission and reports on preliminary toxicity studies; they can be provided upon request. Appropriate data bases were searched for relevant safety data on A022. No reports were identified in the literature that provided new information which is reasonably expected to substantially alter the human risk assessment performed in the present submission. In addition, the majority of published studies were performed with test articles of unknown purity and/or impurity profile, which does not permit to put the results into proper perspective. Therefore, the studies were not included in the present submission. However, results of the literature search can be provided upon request.

1. G. Sire. p-methylaminophenol sulphate (A022): Acute Oral Toxicity in Rats "Fixed Dose Method". CIT Study No. 28294 TAR, 2005
2. G. Sire. N-methyl para aminophenol sulphate (A022) at the concentration of 3%: Acute Eye Irritation in Rabbits. CIT Study No. 26957 TAL, 2005
3. G. Sire. N-methyl para aminophenol sulphate (A022) at the concentration of 3%: Acute Dermal Irritation in Rabbits. CIT Study No. 26958 TAL, 2005
4. G. Sire. p-methylaminophenol sulphate (A022): Evaluation of Skin Sensitization Potential in Mice using the Local Lymph Node Assay (LLNA). CIT Study No. 26959 TSS, 2005
5. V. Haag. p-methylaminophenol sulphate (A022): 13-Week Toxicity Study by Oral Route (Gavage) in Rats Followed by a 4-Week Treatment-Free Period. CIT Study No. 26899 TCR, 2005
6. L. Williams. p-methylaminophenol sulphate (A022): Reverse Mutation in five Histidine-requiring strains of *Salmonella typhimurium*. Covance Study No. 413/75, 2005
7. K. Adams. N-methyl para aminophenol sulphate: Mouse Lymphoma TK Locus Assay. Huntingdon Study No. LRL 171/930274, 1993
8. M. Lloyd. N-methyl para amino phenol sulphate (A022): Mutation at the *hprt* locus of L5178Y Mouse Lymphoma Cells using the Microtitre® Fluctuation Technique. Covance Study No. 413/77, 2005
9. T. Kumaravel. p-methylaminophenol sulphate (A022): Induction of chromosome aberrations in cultured human peripheral blood lymphocytes. Covance Study No. 413/76, 2005
10. G. Erexson. *In Vivo* Rat Micronucleus Assay in p-methylaminophenol sulfate (A022). Covance Study No. 6182-116, 2005
11. W. Völkner. *In Vivo / In Vitro* Unscheduled DNA Synthesis in Rat Hepatocytes with p-methylaminophenol sulfate. CCR Project No. 574800, 1997
12. E. L. Goldenthal. Formulations 7401, 7402, 7403, 7404, 7405, 7406: Lifetime Toxicity/Carcinogenesis Study in Rats. IRDC Study No. 355-003 (a), 1979
13. G. Chevalier. p-methylaminophenol sulphate (A022): Prenatal developmental toxicity study by oral route (gavage) in rats. CIT Study No. 27067 RSR, 2005
14. F. Toner. The *in vitro* percutaneous absorption of radiolabelled p-methylaminophenol sulphate through human skin. INVERESK Study No. 774300, 2005
15. R. Groult. p-methylaminophenol sulphate (A022): Validation of the Analytical Method and Determination of Homogeneity and Stability of Dosage Forms. CIT Study No. 26955 AHS, 2005
16. *Toxicité aiguë. Universita di Siena, 1977*
17. *K.G. Dossou. Détermination de l'indice d'irritation primaire. L'Oréal, 1977*

18. *K.G. Dossou. Détermination de l'indice d'irritation oculaire. L'Oréal, 1977*
19. *B. Coquet and J.P. Guillot. Evaluation of the sensitization potential of a test substance by topical applications in the guinea-pig. IFREB Study No. 807309, 1978*
20. *C. Boutemy. Evaluation de la toxicité du produit N-méthyl-para-aminophénol administré chez le rat pendant 1 mois par voie orale. LERS study No. 1493 TMR, 1989*
21. *R.M. Hastwell. Testing for mutagenic activity in Salmonella typhimurium with N-methyl-p-aminophenol. Inveresk Research International study No. 1384, 1979*
22. *W.G.H. Blijleven. Evaluation of compound N-methyl-para-aminophenol in the chromosome aberrations test: Chinese Hamster Cells (in vitro). University of Leiden, 1983*
23. *N. Loprieno. Forward mutation induction on yeast Schizosaccharomyces pombe (strain P1) in vitro. Universita di Pisa, 1984*
24. *W.G.H. Blijleven. Evaluation of compound N-methyl-para-aminophenol in the sex-linked recessive lethal test with Drosophila melanogaster. University of Leiden, 1983*
25. *K.G. Dossou. Micronucleus test. L'Oréal, 1982*
26. *C. Boutemy. Etude des effets embryotoxiques et/ou tératogènes éventuels chez le rat du produit N. Méthyl para-aminophénol administré par voie orale. LERS study No. 1500 RMR, 1989*
27. *F.X. Wazeter. Multigeneration reproduction study in rats. International Research and Development Corporation study 355-002, 1977*
28. *M. Bauer. Penetration in vitro du N-methyl-para-aminophenol. L'Oréal, 1986*
29. *J. Hadgraft. Penetration of the hair dye 1-hydroxy-4-methylamino-benzene sulphate in the presence of 1-hydroxy-3-aminobenzene across human epidermis mounted in horizontal diffusion cells. An-eX analytical services Ltd study No. SP/HD/PR/05/92B, 1992*
30. *G. Chevalier. N-methyl para aminophenol sulphate: Preliminary study of prenatal developmental toxicity by oral route (gavage) in rats. CIT study No. 27330 RSR, 2004*

Additional references

AD1. Burnett C, Jacobs MM, Seppala A and Shubik P. Evaluation of the Toxicity and Carcinogenicity of Hair Dyes. J. Toxicol. Environ. Health 6: 247-257, 1980

7. ACKNOWLEDGEMENTS

Members of the working group are acknowledged for their valuable contribution to this opinion. The members of the working group are:

Dr. C. Chambers
Prof. R. Dubakiene
Prof. V. Kapoulas (rapporteur)
Prof. C. Lidén
Prof. J.-P. Marty
Prof. T. Platzek (chairman)
Dr. S.C. Rastogi
Prof. T. Sanner
Prof. G. Speit
Dr. J. van Engelen
Dr. I.R. White