Scientific Committee on Consumer Products

SCCP

OPINION ON

M-AMINOPHENOL

COLIPA N° A15

The SCCP adopted this opinion at its 10th plenary of 19 December 2006

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCP

Questions concerning the safety of consumer products (non-food products intended for the consumer).

In particular, the Committee addresses questions related to the safety and allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents and consumer services such as tattooing.

Scientific Committee members

Claire M. Chambers, Gisela Degen, Ruta Dubakiene, Ramon Grimalt, Bozena Jazwiec-Kanyion, Vassilios Kapoulas, Jean Krutmann, Carola Lidén, Jean-Paul Marty, Thomas Platzek, Suresh C. Rastogi, Jean Revuz, Vera Rogiers, Tore Sanner, Günter Speit, Jacqueline van Engelen, Ian R. White

Contact:
European Commission
Health & Consumer Protection DG
Directorate C: Public Health and Risk Assessment
Unit C7 - Risk Assessment
Office: B232 B-1049 Brussels

Sanco-Sc6-Secretariat@ec.europa.eu

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

External experts

Dr. M.-L. Binderup	National Food Institute, Denmark
Dr. H. Norppa	Finnish Institute of Occupational Health, Finland
Dr. K. Peltonen	EVIRA, Finland
Dr. J. van Benthem	RIVM, the Netherlands

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Opinion to be cited as:
Scientific Committee on Consumer Products (SCCP), 19 December 2006, Opinion on m-aminophenol COLIPA N° A15

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1. BACKGROUND

Submission I for *m*-Aminophenol was submitted in August 1981 by COLIPA[1, 2]

Submission II for *m*-Aminophenol was submitted in June 1985 by COLIPA.

Submission III for *m*-Aminophenol was submitted in March 1987 by COLIPA.

The Scientific Committee on Cosmetics (SCC) has at its 54th plenary meeting on 10 December 1993 expressed its opinion with the conclusion:

"However, the committee points out that the subchronic toxicity test by the oral route carried out with a single dose, was but of little significance and that it would have been preferable to have an adequate study and to know the no-effect dose. Approved by the SCC on 12 April 1988. The committee was aware that CTFA[3] has additional data on a 90 days study and this has been requested and should be assessed in due course: a modification to SCC opinion would be made if necessary."

Submission IV for *m*-Aminophenol was submitted in January 1995 by COLIPA[2].

The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) has at its 11th meeting on 17 February 2000 expressed its opinion (SCCNFP/0231/99) with the conclusion:

"*The SCCNFP is of the opinion that m-Aminophenol can be used safely in permanent hair dye formulations at a maximum concentration of 2.0%. However, as permanent hair dyes are mixed with hydrogen peroxide before application, the maximum in-use concentration should not exceed 1.0 %. The animal sensitisation data in the dossier was generated with a method not conforming to OECD[4] n° 406. Cosmetic products containing this substance shall 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 5 on the List of substances, provisionally allowed, which cosmetic products must not contain except subject to restrictions and conditions laid down.

Submission V for this substance was submitted in July 2005 by COLIPA. According to this submission *m*-Aminophenol is used in oxidative hair colouring products at a maximum of 2.4%, which after mixing typically in a 1:1 ratio with hydrogen peroxide just prior to use, corresponds to a concentration of 1.2% upon application.

Submission V 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
[3] CTFA The Cosmetic, Toiletry, and Fragrance Association
[4] OECD Organisation for Economic Co-operation and Development

2. TERMS OF REFERENCE

1. *Does the Scientific Committee on Consumer Products (SCCP) consider m-Aminophenol safe for use as an oxidative hair dye with an on-head concentration of maximum 1.2 % taken into account the scientific data provided?*

2. *Does the SCCP recommend any further restrictions with regard to the use of m-Aminophenol 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

m-Aminophenol

3.1.1.2. Chemical names

1-Hydroxy-3-amino-benzene
m-Aminophenol (INCI)
Phenol, 3-amino (CAS)
3-Aminophenol
m-Hydroxy-aniline
3-Hydroxy-aniline

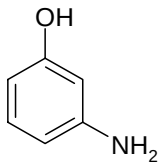
3.1.1.3. Trade names and abbreviations

Trade name: Fouramine EG (PCUK)
COLIPA n°: A15
Colour index n°: CI 76545 (oxidation base 7)

3.1.1.4. CAS / EINECS number

		Hydrochloride	Sulfate 2:1	Sodium salt
CAS:	591-27-5	51-81-0	68239-81-6	38171-54-9
EINECS:	209-711-2	200-125-2	269-475-1	/

3.1.1.5. Structural formula



3.1.1.6. Empirical formula

Formula: C_6H_7NO

3.1.2. Physical form

White to beige flakes

3.1.3. Molecular weight

Molecular weight: 109.16

3.1.4. Purity, composition and substance codes

The analytical study of m-aminophenol was carried out on four batches:

- Batch 220117 (in August 2004) – Analytical study
- Batch 4090202 (in February 1995) – Analytical certificate
- Batch 1997120128971 (in February 1999) – Analytical certificate
- Batch CFQ11141 (in December 1998) – Analytical certificate updated in February 2005

Batch 220117 was characterised by conventional analytical techniques:

- infra-red and UV spectrophotometry,
- mass and N.M.R. spectrometry,
- titre by potentiometry,
- H.P.L.C profile,
- determination of impurities content by H.P.L.C,
- determination of water content by Karl Fischer method,
- determination of residual solvents by GC,

Description	**Batch number**			
	220117 August 2004	**4090202** February 1995	**1997120128971** February 1999	**CFQ11141** December 1998 updated 2005
Structure Characterization	IR,NMR,MS,UV	IR,NMR,UV	IR	MS
Content by potentiometric titration (% w/w)	100.5 (99.0) [(1)]	100.0	99.9	–
HPLC purity, area % [(2)]	99.3	–	–	98.0
Impurities HPLC [(3)] (% w/w)				–
Impurity A	0.51	ND [(4)]	D < 0.01 [(4)]	–
Impurity B	D < 0.1	–	–	–
Impurities C,D	ND < 0.1	ND [(4)]	–	–
Water content (% w/w)	0.39	–	–	–
Melting point (°C)	120	–	–	120-124

D: detected
ND: Not detected
[(1)] *(Titre) – (Impurities content + Water content)*

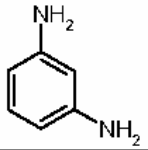
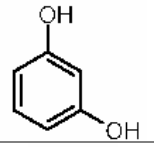
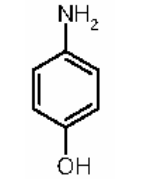
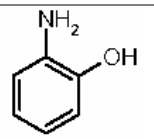
(2) *Relative purity – Area % without response factor – UV Detection Irrespective of residual solvents , salts etc.*
(3) *A: m-phenylenediamine - B: Resorcinol - C, D: p and o aminophenol*
(4) *Evaluation by H.P.T.L.C.*

3.1.5.	Impurities / accompanying contaminants

Water content: 0.39 g/100g (determined in one batch only – see table above)
Loss on drying: /
Ash content: < 0.1 g/100g
As, Sb, Hg: < 5 mg/kg each
Cd: < 10 mg/kg
Pb: < 20 mg/kg

Residual solvents such as methanol, ethanol, isopropanol, n-propanol, acetone, ethyl acetate, cyclohexane, methylethyl ketone or monochlorobenzene were not detected (detection limit 100 ppm) (batch 220117 only).

Residual reagents, intermediates or by-products from the synthetic process

	m-Phenylenediamine (impurity A); EU Mutagen cat. 3
	Resorcinol - 1,3 dihydroxybenzene (impurity B)
	p-Aminophenol (impurity C); EU Mutagen cat. 3
	o-Aminophenol (impurity D); EU Mutagen cat. 3
(see table above for contents)	

3.1.6.	Solubility

Water: 20.1 ± 2.9 g/l at 20.0 °C ± 0.5 °C (according to EEC method A6)
Ethanol: < 20 % (w/v) (at 22°C after 24 h)
DMSO: ≥ 20 % (w/v) (at 22°C after 24 h)

3.1.7.	Partition coefficient (Log P_{ow})

Log P_{ow}: 0.18 at 20°C (EEC method A8 - Shake-flask method)

3.1.8.	Additional physical and chemical specifications

- melting point: 120°C -124°C
- flash point: /
- vapour pressure: /

- boiling point: /
- density at 20 °C: /
- viscosity: /
- pKa: /
- UV absorption spectrum: λmax 234 nm, 284 nm
- Refractive index at 20 °C: /

3.1.9. Stability

- 1.0 mg ml solution in 0.5% methyl cellulose was stable (maximum deviation from initial concentration ± 8%) up to 6 hours, when stored at room temperature under inert atmosphere and protected from light.
- 200 mg/ml solution in 0.5% methyl cellulose was stable up to 9 days (maximum deviation from initial concentration ± 5%) when stored at 4 °C, under inert atmosphere and protected from light.
- 0.1 mg/ml and 500 mg/ml solutions in DMSO were stable up to 4 hour study period (maximum deviation from initial concentration ± 9%) at room temperature, when stored protected from light and under inert atmosphere.
- 0.5 mg/ml -250 mg/ml solutions in dimethylformamide were stable up to 4 hour study period (maximum deviation from initial concentration ±8%) at room temperature, when stored protected from light and under inert atmosphere.

General Comments on Physico-chemical characterisation

- Adequate analytical data are reported for one batch only;
- Stability of the test material in marketed products is not provided.

3.2. Function and uses

m-Aminophenol is used in oxidative hair dye formulations at a maximum concentration of 2.4%, which after mixing typically in a 1:1 ratio with hydrogen peroxide just prior to use, corresponds to a concentration of 1.2% 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
Group size:	4 females
Test substance:	m-Aminophenol suspended in 0.5 % methylcellulose
Batch:	220117
Purity:	99 %
Dose:	500 mg/kg bw by gavage
Observation:	14 days
GLP:	in compliance

The acute oral toxicity of m-aminophenol was investigated using the "fixed dose method". Four females were treated with 500 mg/kg bw of the test substance by oral gavage. Clinical signs and mortality were checked for 2 weeks.
No mortality occurred. On day 1 hypoactivity or sedation, pilorection and dyspnea were observed in all animals. Recovery was complete on day 2. Body weight gain and macroscopic examination revealed no abnormalities.

The maximum non-lethal dose is > 500 mg/kg bw.

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/strain:	male New Zealand White rabbit
Group size:	3
Test substance:	m-aminophenol
Batch:	220117
Purity:	99%
Concentration:	2%
Vehicle:	0.5 g of m-aminophenol in suspension of methylcellulose with purified water
GLP:	in compliance

A single dose of 0.5 ml of 2% m-aminophenol was applied under a semi-occlusive dressing for 4 hours in male New Zealand White rabbits. In 1/3 animals a very slight erythema was noted 1 hour after application. No skin reactions were observed from 24 hours onwards. Accordingly, m-aminophenol at 2% was non-irritating to rabbit skin.

Ref.: 2

Conclusion
m-Aminophenol at 2% was non-irritating to rabbit skin.

3.3.2.2. Mucous membrane irritation

Guideline:	OECD 405
Species/strain:	male New Zealand White rabbit
Group size:	3
Test substance:	m-aminophenol
Batch:	220117
Purity:	99%
Concentration:	2%
Vehicle:	0.5% suspension of m-aminophenol in methylcellulose with purified water
GLP:	in compliance

Instillation of 0.1 ml of 2% m-aminophenol into the conjunctival sac of 3 New Zealand White rabbits resulted in very slight chemosis and very slight conjunctival redness in 2/3 animals on the day of dosing only. No ocular reactions were observed during the remainder of the study. Accordingly, 2% m-aminophenol produced minimal conjunctival reactions which were rapidly reversible and was thus considered to be non-irritating

Ref.: 3

Conclusion
m-Aminophenol at 2% was considered non-irritating to rabbit eyes.

3.3.3. Skin sensitisation

Local Lymph Node Assay (LLNA)

Guideline:	OECD 429
Species/strain:	mouse – CBA/J
Group size:	28 females allocated to 7 groups of 4 animals
Test substance:	m-aminophenol
Batch:	220117
Purity:	99 %
Doses:	first experiment 1, 2.5, 5, 10 and 25 %, second experimentation for the calculation of the EC_3: 0.05, 0.1, 0.5, 1.0 and 2.5% (w/v)
Positive control	alpha-hexylcinnamaldehyde in DMF (5, 10 and 25%)
Vehicle:	DMF
GLP:	in compliance

A Local Lymph Node Assay was conducted in female CBA/J mice to investigate the sensitisation potential of m-aminophenol. Concentrations up to 25% (the maximum soluble concentration) in dimethylformamide were tested in two successive experiments. A positive control group received 25% alpha-hexylcinnamaldehyde in dimethylformamide. No mortality, clinical signs or body weight changes could be attributed to compound administration. An increase in stimulation index was observed with increasing dose and the threshold positive value of 3 was exceeded at concentrations of 0.5% and higher.

Treatment	Concentration (%)	Signs of local irritation	Stimulation Index (SI)
m-Aminophenol (A015)	1	no	7.62
m-Aminophenol (A015)	2.5	no	12.57
m-Aminophenol (A015)	5	no	10.38
m-Aminophenol (A015)	10	no	7.19
m-Aminophenol (A015)	25	no	6.00
HCA	25	no	4.11

Treatment	Concentration (%)	Signs of local irritation	Stimulation Index (SI)
m-Aminophenol (A015)	0.05	no	1.04
m-Aminophenol (A015)	0.1	no	1.41
m-Aminophenol (A015)	0.5	no	5.88
m-Aminophenol (A015)	1	no	9.00
m-Aminophenol (A015)	2.5	no	11.01
HCA	25	no	5.77

The EC_3 value (0.24%) indicated a strong sensitisation potential for m-aminophenol.

Ref.: 4

Comment
m-Aminophenol induced contact sensitisation in a murine Local Lymph Node Assay and was rated to have a strong sensitisation potential.

3.3.4. Dermal / percutaneous absorption

***In Vitro* Percutaneous Absorption**

Guideline:	OECD 428 (2004)
Tissue:	Dermatomed human skin (4 samples kept frozen at -20°), spilt thickness skin 390 µm
Tissue integrity:	TEWL measurement and skin percutaneous absorption of 14C-caffeine
Method:	Flow through glass diffusion cells, exposed membrane area 2 cm^2, flux: 1.1 ml/h at 32 °C ± 1°C
Test substance:	3 amino [U-14C]-phenol labelled compound, Batch: CFQ 11141Unlabelled 3-aminophenol sample number 1997120128978
Purity:	98% for the labelled compound
Purity of the formulation:	Due to the reactive nature of hair dyes, the radiolabelled test item will exist in many different forms once the oxidative reactions are under way
Formulations/dose applied:	m-aminophenol was included at 2.4% in both dye bases. • Aminophenol plus water, reference: 175315, • Aminophenol plus hydrogen peroxide and toluene-2, 5-diamine sulfate, reference: 175316, • 20 µg/cm^2
Receptor fluid:	Phosphate buffered saline containing Ca++, Mg++, Instamed 9.55 g/l
Contact:	30 minutes, then washing of the skin surface, and monitoring of the diffusion during 24 hours.
No. of replicates:	formulation reference: 175315, 11 samples tested, formulation reference: 175316, 8 samples tested 19 cells (formulations 175315 and 175316) from 4 subjects
Assay:	Liquid scintillation counting, dpm
GLP:	in compliance

The *in vitro* percutaneous absorption of m-aminophenol was determined in human dermatomed skin mounted in flow-through diffusion cells, using PBS Buffer without Ca^{++}, Mg^{++} as the receptor fluid. To mimic actual use conditions, m-aminophenol was incorporated into a typical hair colouring formulation at 2.4% (w/w) associated with the primary intermediate toluene-2,5-diamine sulphate before mixing with an equal amount (w/w) of hydrogen peroxide for a final concentration of 1.20% (w/w). Twenty (20) mg/cm^2 of the test preparation were applied on the skin surface for 30 minutes. At the end of the exposure period, any of the test preparation remaining on the skin surface was removed by washing. Twenty-four hours after application, skin samples were removed and analysed by liquid scintillation counting to assess the cutaneous distribution of m-aminophenol.

Hair Dye	**175315 + H_2O** (n = 11)	**175316 + H_2O_2** (n = 8)
Skin excess µg_{eq}/cm^2 % of the applied dose	224.40 (189.43 – 249.93) **96.51 (88.92 – 101.34)**	207.55 (157.84 – 237.96) **93.39 (88.25 – 102.59)**
Stratum corneum (SC) µg_{eq}/cm^2 % of the applied dose	0.22 (0.04 – 0.44 **0.09 (0.01 – 0.19)**	0.73 (0.19 – 2.34) **0.31 (0.06 – 0.35)**
Epidermis + dermis µg_{eq}/cm^2 % of the applied dose	0.41 (0.17 – 0.68) **0.17 (0.09 – 0.29)**	1.10 (0.46 – 1.96) **0.49 (0.21 – 0.75)**
Receptor fluid (RF) µg_{eq}/cm^2 % of the applied dose	3.42 (1.42 – 6.41) **1.49 (0.63 – 2.61)**	3.28 (1.06 – 5.48) **1.48 (0.47 – 2.19)**

Hair Dye	175315 + H_2O (n = 11)	175316 + H_2O_2 (n = 8)
Total recovery % of the applied dose	**98.26 (90.05 – 104.09)**	**95.68 (90.77 – 103.55)**

The dermal delivery (sum of the amounts measured in the living epidermis, dermis and receptor fluid) of m-aminophenol represented 4.37 ± 1.79 µgeq/cm² (1.97 ± 0.68%) in use conditions.

Conclusion
The dermal absorption of m-aminophenol coupled with toluene-2,5-diamine sulphate into a typical hair colouring formulation mixed with hydrogen peroxide at 1.2% (final concentration) was estimated to be at most 7.14 µg/cm² in use conditions, this value can be used for calculating the Margin of Safety.

Ref.: 15

Comment
The percutaneous absorption of m-aminophenol was also evaluated in the absence of primary intermediate and in non-oxidative conditions. As this ingredient is only used in oxidative conditions in the presence of primary intermediate, the results obtained were considered not to be relevant for the safety evaluation of m-aminophenol.

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

Sub-chronic (90 days) oral toxicity study in rats

Guideline:	OECD 408
Species/strain:	Sprague-Dawley rat, Crl:CD (SD) BR strain
Group size:	10 male + 10 female
Test substance:	m-Aminophenol suspended in 0.5 % aqueous methylcellulose solution + d-iso-ascorbic acid at 1 %
Batch:	4090202
Purity:	100 %
Dose levels:	0, 20, 70, 200 or 600 mg/kg bw/d by gavage
Exposure:	13 weeks
GLP:	in compliance

The dose levels were selected based on the results of a 2-week oral toxicity study in rats. Purity, homogeneity and stability of the test substance in the vehicle were checked.

The animals received the test substance at 0, 20, 70, 200 or 600 mg/kg bw/d by daily gavage for 13 weeks in the vehicle 0.5 % aqueous methylcellulose solution + d-iso-ascorbic acid at 1 %. No recovery group was included. The animals were checked daily for clinical signs and mortality. Food consumption and body weight were recorded once a week. Ophthalmological examinations were performed before the treatment period in animals of the control and the high dose group, on week 13 in animals of the control, 200 and 600 mg/kg bw/d group. Haematology, biochemistry and urinalysis of all animals were performed in week 13.

Results

No treatment-related mortalities were observed. While in the 20 mg/kg group no clinical signs were observed, ptyalism was seen at 70 mg/kg (some animals) and in all animals at 200 and 600 mg/kg. At the latter dose, lacrimation and reddish or orange coloured urine (all animals) and tail (all females) was seen indicating distribution of the test substance. Food consumption was decreased at 600 mg/kg in males accompanied by a lower body weight gain. No substance-related effects were observed during ophthalmoscopy.
Haematology revealed anaemia at 600 mg/kg (changes in erythrocytes count, cell volume and. haemoglobin values). This was associated with higher reticulocytes count. Thromboplastin time and fibrinogen concentration were lowered. With males a decrease in erythrocytes count was also seen at 200 mg/kg as well as changes in neutrophils and leukocytes. In blood biochemistry treatment-related changes were observed in total protein, potassium, calcium, total bilirubin, inorganic phosphorus, glucose and cholesterol at 200 and/or 600 mg/kg. Urinalysis revealed changes in pH and volume at 200 and/or 600 mg/kg. Relevant absolute and/or relative organ weight changes were observed at 200 and/or 600 mg/kg with kidneys, liver, spleen and thyroids. Macroscopic examination showed yellowish deposits on the stomach mucosa (1/10 males at 600 mg/kg) and orange coloured tails (8/10 females at 600 mg/kg). Blackish spleen discolouration (related to haemosiderosis) was noted in one animal at 70 mg/kg, some animals at 200 mg/kg and all animals at 600 mg/kg. Liver and thyroid gland enlargement was noted in 1 animal of the highest dose group. Treatment-related changes in thyroid activity were noted in both sexes at 70 mg/kg and higher doses. Brownish pigment was found in the cortical tubular epithelium of the kidneys in 2 males at 70 mg/kg, in 8 males at 200 mg/kg and in all males and 3 females at 600 mg/kg.
The NOAEL is considered to be 20 mg/kg bw/d, based on effects on thyroid activity and kidney.

Ref.: 5

13-Week oral (dietary) toxicity study in rats (part of a combined 90 day feeding, teratology and dominant lethal study in rats)

Guideline:	/
Species/strain:	Sprague-Dawley rat, TAC:N (SD) fBR strain
Group size:	30 male + 35 female
Test substance:	m-Aminophenol in the diet
Batch:	49
Purity:	> 101%
Dose levels:	0, 0.1%, 0.25% and 1%
Exposure period:	12 weeks
GLP:	not in compliance

Three groups of 30 males and 35 females received m-aminophenol in control diet at a concentration of 0.1%, 0.25% or 1.0% for 90 days (*i.e.* approximately 50-100, 125-250 and 500-1000 mg/kg/day, respectively). An additional group of 30 males and 35 females received the control diet alone, and served as the control. Animals were observed daily for mortality/morbidity and once weekly for clinical signs. Body weights were recorded weekly; food consumption was recorded twice weekly. Following 6 weeks of feeding, blood was collected from 5 males and 5 females to determine methaemoglobin levels. Following 12 weeks of study 10 males and 10 females were randomly selected from each group and killed over a two-week period. Blood was collected for haematology and clinical chemistry evaluations prior to killing.

Results
Significant changes in body weight gain were observed in the 0.1%, 0.25% and 1% group. Feed consumption was significantly lower in the 1% group and sporadically at 0.25%. No changes in methaemoglobin levels were observed. Bilirubin levels were increased in the high dose group. Significant lower blood triglyceride levels were observed in 1% males.

Statistically significant lower red blood cell count, haemoglobin and mean corpuscular haemoglobin in 1% females were noted.
No compound-related gross lesions were observed. Reduction of body weight was observed in 1% males and in 0.25% and 1% females. Significantly higher relative liver and kidney weights were observed in both sexes at 1%; no microscopic correlates for these changes were noted. Relative liver weight was increased in males and females at 1%. Significant decrease in absolute and relative thyroid weight was observed in 0.1% and 0.25% dose groups with males and females, but not at 1%. In the thyroid, a generalized higher epithelial cell height and lower follicular size of animals of all dose groups was reported. Compound-related histopathological findings consisted of deposition of iron-positive pigment in spleen, liver and kidney in males and females given 1% m-aminophenol and the above-mentioned changes in the thyroid gland in all dose groups.

Ref.: 6

Comment
No NOAEL can be derived from this study.

3.3.5.3. Chronic (> 12 months) toxicity

No data submitted

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, TA102, TA1535, and TA1537.
Replicates:	3 replicates in 2 individual experiments both in the presence and absence of S9.
Test substance:	m-Aminophenol
Solvent:	DMSO
Batch:	220117
Purity:	99 %
Concentrations:	Experiment 1: 156.3 - 2500 µg/plate for TA98 and TA1537 (without S9) 625 - 5000 µg/plate for TA100, TA102, TA1535 (without S9) 625 - 5000 µg/plate for TA100, TA102, TA1535 (with S9) Experiment 2: 625 - 5000 µg/plate for TA100, TA102, TA1535 (without S9) 625 - 5000 µg/plate for TA100, TA102, TA1535 (with S9)
Treatment:	Direct plate incorporation (49 to 72 h treatment) method except for the second experiment with S9 metabolic activation, where the pre-incubation method was used (60 minutes treatment)
GLP:	in compliance

m-Aminophenol was investigated for the induction of gene mutations in *Salmonella typhimurium* (Ames test) using the direct plate incorporation method with exposure of 49 to 72 h. However, in the second experiment with S9 metabolic activation the pre-incubation method with a pre-incubation of 60 minutes was applied. Liver S9 fraction from Aroclor 1254-induced rats was used as exogenous metabolic activation system. Test concentrations were based on the level of toxicity in a toxicity range finding experiment.
Toxicity was evaluated on the basis of a reduction in the number of revertant colonies and/or a thinning of the bacterial lawn. Negative and positive controls were in accordance with the OECD guideline.

Results
Precipitation of m-aminophenol and toxicity was not observed. In the absence of S9 metabolic activation m-aminophenol did not induce an increase in the number of revertant colonies as compared to concurrent vehicle controls in any of the five *Salmonella* strains in both experiments. A reproducible, dose dependent increase in the number of revertants was found for TA98 in the presence of S9 metabolic activation.

Conclusion
Under the experimental conditions used m-aminophenol is (weakly) genotoxic (mutagenic) in the gene mutation tests in bacteria.

Ref.: 7

In vitro hprt Mutation Assay

Guideline:	OECD 476	
Cells:	L5178Y Mouse lymphoma cells	
Replicates:	2 replicates in 3 (-S9) or 2 (+S9) independent experiments	
Test substance:	m-Aminophenol	
Solvent:	DMSO	
Batch:	220117	
Purity:	99 %	
Concentrations:	Experiment 1:	25 - 250 µg/ml (without S9)
		100 - 1090 µg/ml (with S9)
	Experiment 2:	100 - 500 µg/ml (without S9)
		100 - 600 µg/ml (with S9)
	Experiment 3:	150 - 1090 µg/ml (without S9)
Treatment	3 h both in absence and presence of S9; expression period 7 days	
GLP:	in compliance	

m-Aminophenol was assayed for gene mutations at the *hprt* locus in mouse lymphoma cells using a fluctuation protocol both in the absence and presence of S9 metabolic activation. Cells were treated for 3 h followed by an expression period of 7 days to fix the DNA damage into a stable *hprt* mutation. Liver S9 fraction from Aroclor 1254-induced rats was used as exogenous metabolic activation system. Toxicity was determined by measuring the reduction in percentage relative survival. Test concentrations were based on the level of toxicity in a cytotoxicity range finding experiment. Since m-aminophenol was only moderately toxic, in experiment 1 (with S9) and 3 (without S9) the prescribed maximum concentration of 10 mM (equivalent to 1090 µg/ml) was used. Negative and positive controls were in accordance with the OECD guideline.

Results
Measurements on post-treatment media in the absence or presence of S9 indicated that m-aminophenol had no effect on osmolarity or pH as compared to concurrent vehicle controls.
Since in the absence of S9 the appropriate level of toxicity (10-20% survival in the highest concentration tested) was not reached, the prescribed maximal concentration of 10 mM was used resulting in a relative survival of 27.70 %. In the presence of S9 the appropriate level of toxicity was reached pointing to sufficient exposure of the cells.
When tested up to 10 mM, a statistically significant increase in the mutant frequency at the *hprt* locus was not observed following treatment with m-aminophenol at any dose level tested in the absence or presence of S9 in all three experiments.

Conclusion
Under the experimental conditions used m-aminophenol is not genotoxic (mutagenic) at the *hprt* locus of mouse lymphoma cells.

Ref.: 8

In vitro chromosome aberration test

Guideline:	OECD 473
Cells:	human lymphocytes from a healthy male and female donor per experiment
Replicates:	2 replicates in 2 independent experiments
Test substance:	m-Aminophenol
Solvent:	DMSO
Batch:	220117
Purity:	99 %
Concentrations:	Experiment 1: 0.078 – 10 mM (both with and without S9) Experiment 2: 0.63 – 10 mM (both with and without S9)
Treatment:	3 h both in absence and presence of S9; harvest time 20 h after start of treatment.
GLP:	in compliance

m-Aminophenol has been investigated in 2 independent experiments in the absence and presence of metabolic activation for the induction of chromosomal aberrations in cultured human lymphocytes. Mitogenesis was stimulated by 48 h incubation with PHA. Cells were treated for 3 h in the absence or presence of S9 metabolic activation. Harvest time was 20 hours after the beginning of treatment. One and a half hours before harvest, each culture was treated with colcemid solution (final concentration of 10 µg/ml) to block cells at metaphase of mitosis. Liver S9 fraction from Aroclor 1254-induced rats was used as exogenous metabolic activation system. Toxicity was determined by measuring the reduction in mitotic index (MI). Chromosome (metaphase) preparations were stained with Giemsa and examined microscopically for MI and chromosomal aberrations. Negative and positive controls were in accordance with the OECD draft guideline.

Results
The highest dose level of 10 mM did not show precipitation whereas osmolarity and pH values were equivalent to those of the concurrent vehicle controls. m-Aminophenol induced sufficient toxicity, as shown by around 50 % decrease in MI at the highest concentration tested, indicating to sufficient exposure of the cells.
Without S9 metabolic activation, in the first experiment a statistical significant increase in the frequency of cells with chromosomal aberrations was only found at 10 mM whereas in the second experiment a statistical significant and dose-related increase in the number of cells with chromosomal aberrations was observed. With S9 metabolic activation in both experiments a statistical significant and dose-related increase in the number of cells with chromosomal aberrations was noted.

Conclusion
Under the experimental conditions used m-aminophenol induced an increase in chromosomal aberrations and, consequently, is genotoxic (clastogenic) in human lymphocytes *in vitro*.

Ref.: 9

In vitro micronucleus test

Guideline:	OECD draft guideline 487 (2004)
Cells:	human lymphocytes of 4 healthy, non-smoking, male volunteers
Replicates:	2 replicates in 3 (-S9) or 4 (+S9) independent experiments
Test substance:	m-Aminophenol
Solvent:	DMSO
Batch:	220117
Purity:	99 %

Concentrations:	Experiment 1:	704 - 1100 µg/ml (without S9) 564.7 - 1100 µg/ml (with S9)
	Experiment 2:	794.8 - 1100 µg/ml (without S9) 794.8 - 1100 µg/ml (with S9)
	Experiment 3:	794.8 - 1100 µg/ml (without S9) 488.1 - 1100 µg/ml (with S9)
	Experiment 4:	794.8 - 1100 µg/ml (with S9)
Treatment	experiment 1:	24h PHA stimulation, 20h treatment and 28h recovery without S9 24h PHA stimulation, 3h treatment and 45h recovery with S9
	experiment 2, 3 and 4:	48h PHA stimulation, 20h treatment and 28h recovery without S9 48h PHA stimulation, 3h treatment and 45h recovery with S9
GLP:	in compliance	

m-Aminophenol has been investigated in 4 independent experiments in the absence and presence of metabolic activation for the induction of micronuclei in cultured human lymphocytes. Treatment periods were 20 h without S9 and 3 h with S9. Harvest times were 72 hours (experiment 1) or 96 hours (experiments 2 – 4) after the beginning of culture. The final 24 h of incubation was in the presence of cytochalasin B (at a final concentration of 6 µg/ml). Liver S9 fraction from Aroclor 1254-induced rats was used as exogenous metabolic activation system. Toxicity was determined by measuring the reduction in replication index (RI). Micronucleus preparations were stained and examined microscopically for RI and micronuclei. Negative and positive controls were in accordance with the OECD draft guideline.

Results
Measurements on post-treatment media in the absence or presence of S9 indicated that m-aminophenol had no effect on osmolarity or pH as compared to concurrent vehicle controls.
Cytotoxicity levels, measured as RI, never reached the (in the draft guideline) suggested reduction of 60% after treatment with the highest dose. However, the highest dose tested is higher then the prescribed maximum concentration of 10 mM (equivalent to 1090 µg/ml) from the draft and related OECD guidelines.
In experiment 1 without S9 metabolic stimulation m-aminophenol did not induce an increase in the frequency of micronuclei compared to concurrent vehicle controls. Statistical significant increases in the MN-frequency were found in the presence of S9. However there was no clear dose response relationship. In experiment 2 and 3 in the absence of S9 but with an extended PHA stimulation, statistical significant increases in micronucleus induction were observed. Again a dose response relationship was not apparent. Since data observed in experiment 2 were confirmed in experiment 3 these results were considered as biological relevant. In the presence of S9 and an extended PHA treatment only in experiment 3 a statistical significant increase in micronucleus induction (without dose response relationship) was observed. In both other experiments (experiment 3 and 4) micronucleus frequencies similar to those of concurrent control cultures were found. The biological relevance of the positive results in the presence of S9 are considered questionable.

Conclusion
Under the experimental conditions used m-aminophenol induced micronuclei and, consequently, is genotoxic (clastogenic and/or aneugenic) in human lymphocytes *in vitro*.

Ref.: 10

3.3.6.2 Mutagenicity/Genotoxicity *in vivo*

Mouse bone marrow micronucleus test

Guideline:	OECD 474
Species/strain:	Crl:CD (SD)BR rats
Group size:	5 rats/sex
Test substance:	m-Aminophenol
Batch:	220117
Purity:	99 %
Dose level:	375, 750 and 1500 mg/kg bw
Route:	Oral gavage
Vehicle:	0.5 % aqueous carboxymethylcellulose
Sacrifice times:	24 h for all concentrations, 48 h for the vehicle control and the highest dose.
GLP:	in compliance

m-Aminophenol has been investigated for the induction of micronuclei in bone marrow cells of rats. Test concentrations were based on the level of mortality and toxicity in a dose range finding experiment. Rats were exposed to a single doses of 0, 375, 750 and 1500 mg/kg bw by oral gavage. 24 h or 48 h (highest dose and concurrent vehicle control only) after dosing bone marrow cells were collected. Toxicity and thus exposure of the target cells was determined by measuring the ratio between polychromatic and normochromatic erythrocytes (PCE/NCE). A satellite group of 3 rats/sex treated with 1500 mg/kg bw was included for possible determination of plasma concentrations of m-aminophenol. In a partial repeat micronucleus assay additional rats were exposed to 1000 mg/kg bw (24 and 48 h sacrifice groups as well as a plasma satellite group).
Bone marrow preparations were stained and examined microscopically for the PCE/NCE ratio and micronuclei. Negative and positive controls were in accordance with the OECD draft guideline.

Results
m-Aminophenol induced mortality in male (2/16) and female (9/16) rats treated with the highest dose of 1500 mg/kg bw and in one female (1/16) treated with 1000 mg/kg bw. Clinical signs indicating to systemic toxicity were observed in all animals treated. Decreases in the PCE/NCE ratio were not observed at doses up to 1000 mg/kg bw. However, plasma analysis confirmed systemic exposure of the target cells at 1000 mg m-aminophenol/kg bw. Significant increases in the number of micronucleated PCEs compared to the concurrent vehicle controls were not found following treatment with m-aminophenol at any dose level tested.

Conclusion
Under the experimental conditions used m-aminophenol did not induce micronuclei in bone marrow cells of treated rats and, consequently, m-aminophenol is not genotoxic (clastogenic and/or aneugenic) in bone marrow cells of rats.

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 (7403 and 7406) containing 0.7 % m-aminophenol prior to mixing with equal volume 6% hydrogen peroxide, and two dye formulations (P-25 and P-26) containing 0.09% and 0.02% m-aminophenol, respectively, 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:	0.05 ml of a solution containing m-aminophenol and hydrogen peroxide
Route:	Topical, 1 application weekly
Exposure:	21 months: 7403, 7406, P-24 male, and P-26 male; 23 months: P-24 female and P-26 female
GLP:	not in compliance

The experiment involved altogether 12 different dye formulations 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 – 13 males and 10 –15 females survived to 21 months in the group receiving the oxidative formulation containing m-aminophenol. 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.: AD1

Comment:
2,4-Diaminoanisole (EU, carcinogenic Category 2) was tested in the same experiment and no response was found.

No conclusion with regard to carcinogenicity can be made from the study.

Topical application, rats

Guideline:	/
Species/strain:	Male and female weanling Sprague Dawley rats, 60 per sex per group
Group size:	60 animals per sex and dose
Test substance:	Two hair dye formulations (7403 and 7406) containing 0.7 % m-aminophenol prior to mixing with equal volume 6% hydrogen peroxide, and two dye formulations (P-25 and P-26) containing 0.09% and 0.02% m-aminophenol, respectively 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 level:	0.5 ml of the test substance

Route: Topical. 1 application twice weekly
Exposure period: 114 weeks
GLP: not in compliance

The experiment involved altogether ten different dye formulations and three negative control groups.

Groups of 60 male and 60 female animals were obtained from the first mating (F_{1a}) of a multi-generation reproduction study in rats treated with four different hair dye formulations containing up to 0.35% m-aminophenol. 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 formulation was 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.

Just prior to terminal sacrifice (at week 117, 118 or 119) the survival was 12 – 20 males and 12 – 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 656 – 713 g in males and 452 – 527 g in females. Control group values ranged from 682 to 759 g in males and 477 to 513 g in females.

There were no significant changes in haematological values in the treated groups at 18 and 24 months. 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. The incidence of pituitary adenomas in the females of group 7406 was significantly higher than in all three control groups, but the high background incidence of this lesion casts doubt on the biological significance of this finding. It was concluded that no increased tumour incidence were found in any of the tissues examined.

Ref.: 13, 14

Comment
2,4-Diaminoanisole (EU, Carcinogenicity Category 2) was tested in the same experiment and no response was found.

No conclusion with regard to carcinogenicity can be made from the study.

3.3.8. Reproductive toxicity

3.3.8.1. Two generation reproduction toxicity

No data submitted

3.3.8.2. Teratogenicity

Prenatal developmental toxicity study in rats

Guideline:	OECD 414 (2001)
Species/strain:	Sprague-Dawley rat, Crl CD (SD) BR strain
Group size:	24 mated females
Test substance:	m-Aminophenol suspended in 0.5 % aqueous methylcellulose
Batch:	220117
Purity:	99%
Dose levels:	0, 30, 100 and 300 mg/kg bw/d by gavage
Treatment period:	day 6 to 19 post coitum
GLP:	in compliance

Concentration, homogeneity and stability of the test substance in the vehicle were analysed. Mortality and morbidity of the animals were checked twice a day and clinical signs were recorded. Body weights of the dams were recorded on day 0, 3, 6, 9, 12, 15, 18 and 20 pc. Food consumption was determined for the intervals day 0-3, 3-6, 6-9, 12-15, 15-18 and 18-20 pc.
On day 20 of gestation the dams were sacrificed and the common sectio parameter were evaluated: number of corpora lutea and implantation sites, number and distribution of early and late resorptions, number and distribution of dead and live foetuses, placentae and sex. Foetuses were weighed and submitted to external, soft tissue and skeletal examinations.
In the control and low dose group no clinical signs were noted. At 100 mg/kg bw/d orange coloured urine was observed in 7/23 pregnant females while at 300 mg/kg all animals exhibited coloured urine. At 100 (only day 6-9) and 300 mg/kg a statistically significant lower net weight gain was found accompanied by lower amount of feed consumed at 300 mg/kg only. At 300 mg/kg increases in post-implantation loss and early resorptions were observed. Foetal body weight and sex ratio were not affected. No dose-related incidences in external anomalies were recorded and no treatment-related findings of visceral anomalies were reported. At 300 mg/kg 15.7 % of the foetuses (in 50 % of the litters) exhibited supernumerary 14^{th} rib.
The NOEL of maternal toxicity is considered 30 mg/kg bw/d. The NOAEL for both maternal and embryo-foetal toxicity was set at 100 mg/kg bw/day.

Ref.: 12

Comment
It is noted that the effects on the thyroid gland and on the kidneys, as seen in the 90 day study, were not examined.

3.3.9. Toxicokinetics

No data submitted

3.3.10. Photo-induced toxicity

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

(m-AMINOPHENOL)
(Oxidative/permanent)

Maximum absorption through the skin	**A**	**=**	**7.14 µg/cm²**
Skin Area surface	**SAS**	**=**	**700 cm²**
Dermal absorption per treatment	**SAS x A x 0.001**	**=**	**4.998 mg**
Typical body weight of human		**=**	**60 kg**
Systemic exposure dosage (SED)	**SAS x A x 0.001/60**	**=**	**0.083 mg/kg**
No observed effect level (mg/kg) (sub-chronic, oral, rat)	**NOAEL**	**=**	**20 mg/kg**
Margin of Safety	**NOAEL / SED**	**=**	**241**

3.3.14. Discussion

Physico-chemical specifications
Adequate analytical data are reported for one batch only and the stability data of the test material in marketed products has not been provided.

General toxicity
The maximum non-lethal dose of an acute oral toxicity study in rats is > 500 mg/kg bw.
In a subchronic oral toxicity study in rats, the NOAEL was set at 20 mg/kg bw/d, based on effects on thyroid activity and on the kidney.
The NOEL of maternal toxicity is considered 30 mg/kg bw/d. The NOAEL for both maternal and embryo-foetal toxicity was set at 100 mg/kg bw/day.

Irritation, sensitisation
m-Aminophenol at 2% was non-irritating to rabbit skin and non-irritating to rabbit eyes.
m-Aminophenol induced contact sensitisation in a murine Local Lymph Node Assay and was rated to have a strong sensitisation potential.

Dermal absorption
The dermal absorption of m-aminophenol coupled with toluene-2,5-diamine sulphate into a typical hair colouring formulation mixed with hydrogen peroxide at 1.2% (final concentration) was estimated to be at most 4.37 ± 1.79 µg/cm² (1.97 ± 0.68% of the applied dose). The maximum absorption value of 7.14 µg/cm² in a particular cell can be used for calculating the MoS.

Mutagenicity
M-aminophenol was (weakly) positive exclusively in a single *Salmonella* strain (TA98) in the gene mutation tests in bacteria but negative in a gene mutation tests in mammalian cells (*hprt* locus). In *in vitro* tests m-aminophenol induced increases in both chromosomal aberrations and micronuclei. These clastogenic effects of m-aminophenol could not be confirmed in an *in vivo* bone marrow micronucleus test in rats.

Although m-aminophenol showed mutagenic activity in the Ames test, this activity was only observed in strain TA98 in the presence of S9 and was relatively weak. This activity was not

confirmed in an in vitro test gene mutation test in mammalian cells (*hprt locus*) and therefore, additional (in vivo) tests on gene mutations are not necessary.
Since also the clastogenic (or aneugenic) effect of m-aminophenol observed *in vitro* does not lead to clastogenic (or aneugenic) effects in experimental animals under appropriate test conditions, m-aminophenol can be considered as having no mutagenic potential *in vivo*.

Carcinogenicity
No conclusion with regard to carcinogenicity can be made from the studies submitted.

4. CONCLUSION

Based on the information provided, the SCCP is of the opinion that the use of m-aminophenol itself as an oxidative hair dye substance at a maximum concentration of 1.2% 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.

m-Aminophenol itself has no mutagenic potential *in vivo*.
However, studies on genotoxicity/mutagenicity in finished hair dye formulations should be undertaken following the relevant SCCNFP/SCCP opinions and in accordance with its Notes of Guidance.

5. MINORITY OPINION

Not applicable

6. REFERENCES

References in *italics* [17-37] were not submitted as full reports in the present dossier. They consist of reports on preliminary toxicity studies [17, 18], and reports for studies considered to be inadequate [19-37].

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