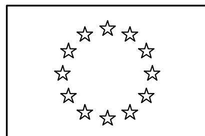

EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

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

SCIENTIFIC COMMITTEE ON CONSUMER PRODUCTS

SCCP

Opinion on

4-Amino-m-cresol

COLIPA N° A74

Adopted by the SCCP during the 5th plenary meeting
of 20 September 2005

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1. BACKGROUND

4-Amino-m-cresol (COLIPA[1] n° A 74) is listed in Annex III, part 2, no 38 of the Cosmetics Directive 76/768/EEC.

Submission III is an updated dossier submitted in line with the second step of the strategy on the evaluation of hair dyes: http://pharmacos.eudra.org/F3/cosmetic/doc/HairDyeStrategyInternet.pdf

2. TERMS OF REFERENCE

1. *On the basis of currently available information, the SCCP is asked to assess the risk to consumers of 4-Amino-m-cresol when used in hair dye formulations.*

2. *Does the SCCP recommend any further restrictions with regard to the use of 4-Amino-m-cresol in 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

4-Amino-m-cresol (INCI)

3.1.1.2. Chemical names

Chemical name	:	4-Amino-3-methylphenol (IUPAC)
CAS name	:	Phenol, 4-amino-3-methyl
Synonyms	:	2-Amino-4-hydroxy toluene
		4-Hydroxy-2-methylaniline
		4-Hydroxy-o-toluidine

3.1.1.3. Trade names and abbreviations

Trade name	:	Jarocol 4A3MP (Robinson), Oxy-rot
COLIPA n°	:	A74
Colour Index	:	/

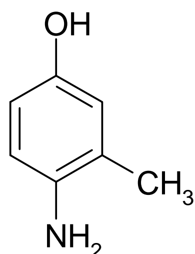
[1] COLIPA - European Cosmetics Toiletry and Perfumery Association

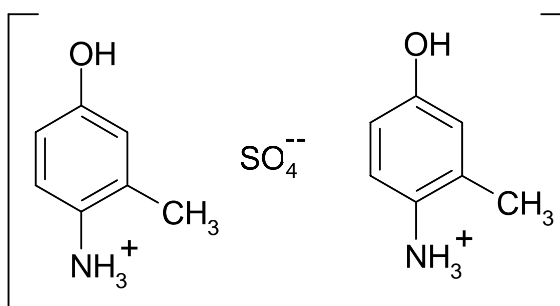
3.1.1.4. CAS / EINECS number

CAS : 2835-99-6
EINECS : 220-621-2

4-Amino-3-methylphenol hemisulfate
CAS : /
EINECS : /

3.1.1.5. Structural formula





4-Amino-3-methylphenol 4-Amino3-methylphenol hemisulfate

3.1.1.6. Empirical formula

Empirical Formula : C_7H_9NO

3.1.2. Physical form

Grey powder

3.1.3. Molecular weight

4-Amino-3-methylphenol : 123.16
4-Amino-3-methylphenol hemisulfate : 172.16

3.1.4. Purity, composition and substance codes

The identity of 4-Amino-3-methylphenol was established by NMR.
The quantification of 4-Amino-3-methylphenol and 4-Amino-3-methylphenol hemisulfate was performed by HPLC, IC and NMR as described in the following table.

Batch/Lot Identification	4-amino-3-methylphenol content % (w/w)				Content determined as	Solvent residues % (w/w)	
	HPLC*	IC	Titration	^{1}H-NMR		Methanol	Ethanol
16.03.1984, FOF (ex.Fluka 08329)	103.6	-	100.6	99.8±00	Free base	-	Traces
19.03.1984 FOF	98.8	96.8	-	94.5±0.1	Hemisulfate	0.6	3.2
16-384, TOX	99.7	99.6	-	94.6±0.0	Hemisulfate	Traces	0.4
26603, TOX	97.6	-	99.1	97.7±0.1	Free base	-	0.2
16384, Seibersdorf (CS62)	98.9	100.0	-	95.8±0.1	Hemisulfate	-	0.3
R00052978, CH:127 Robinson, 03.04.2000	101.4	-	99.9	99.7±0.0	Free base	-	-
Projekt 224616, 25.02.1991	105.6	-	100.5	99.8±0.0	Free base	-	-
Projekt 176005, 20.12.1989	100.5	101.3	-	96.5±0.1	Hemisulfate	0.2	1.7
123-124, (R99052801), Standard ,Robinson	100.6	-	100.2	99.9±0.1	Base	-	-

* HPLC-peak purity was determined by comparable peak areas at 210 nm, 254 nm and 295 nm. Determination was performed using peak area at 295 nm.

3.1.5. Impurities / accompanying contaminants

Impurities

3-Methyl phenol: not detected (GC detection limit 2 ppm)
Sulfanilic acid: not detected (HPLC detection limit 50 ppm)
4-Nitro-3-methylphenol: not detected (detection limit 70 ppm)

The maximum possible contamination of above mentioned compounds, used as raw material for the synthesis, in 4-amino-3-methylphenol is declared by the applicant to be:

3-Methyl phenol: <100 ppm
Sulfanilic acid: <1000 ppm
4-Nitro-3-methylphenol: <300 ppm

3.1.6. Solubility

Water : 1.2 % (w/w)

Ethanol : 5.5 % (w/w)
DMSO : > 10 % (w/w)

3.1.7. Partition coefficient (Log P_{ow})

Log P_{ow} : 0.51

3.1.8. Additional physical and chemical specifications

Organoleptic properties	:	/
Melting point	:	178 – 180 °C (decomposition)
Boiling point	:	not detectable (decomposition)
Flash point	:	/
Vapour pressure	:	< 3.3 10^{-5} hPa (20 °C)
Density	:	/
Viscosity	:	/
pKa	:	/
Refractive index	:	/
Storage	:	dark, at room temperature

Stability:

- 4-Amino-3-methylphenol in aqueous medium is unstable: 30% loss in 48 h at 25°C, >50% loss at 50°C.
- Stability of 4-Amino-3-methylphenol hemisulfate is described as unlimited, but its stability in aqueous medium is not described.
- 10% (w/v) 4-Amino-3-methylphenol in DMSO was stable up to 7 days test period.
- 4-Amino-3-methylphenol in phosphate buffer (0.3%, pH 5.9) showed a linear degradation to 71% in 7 days at room temperature.
- 4-Amino-3-methylphenol in water/acetone (4% w/v) showed a linear degradation to 81% in 7 days at room temperature.
- 4-Amino-3-methylphenol was unstable in receptor fluid (PBS) used for dermal absorption study.
- Stable in a formulation stored for 25 months at room temperature (study not submitted).

General comments on analytical and physico-chemical characterisation

- UV-spectrum of 4-amino-3-methylphenol is not submitted, the purity of the substance by HPLC is determined at 295 nm. However, quantification is performed at 272 nm in dermal absorption study.
- HPLC analysis of 4-amino-3-methylphenol (oxyrot # 23533, study n° G2003/2005, p. 24) revealed two significant impurities (peak area 4% and 6% of total peak area). These impurities have not been identified.

3.2. Function and uses

4-Amino-3-methylphenol is used as an oxidative hair dye at a maximum concentration of 1.5% after mixing with peroxide.

3.3. Toxicological Evaluation

3.3.1. Acute toxicity

3.3.1.1. Acute oral toxicity

Guideline: /
Species/strain: Wistar rats, CF1 mice
Group size: Rats: 5 male and 5 female
Mice: 6 females
Test substance: 4-Amino-m-cresol (10% in gummi arabicum)
Batch: Not indicated
Purity: Not indicated
Doses: Rat, females: 800, 900, 1000, 1100 and 1200 mg/kg bw
Rat, males: 700, 800, 900, 1000 and 1100 mg/kg bw
Mouse, females: 750, 800, 850, 900, 950 and 1000 mg/kg bw
Observation: 14 days
GLP: No

The method is not mentioned in the report but comparable to OECD 401.
The test substance was administered orally by gavage to the groups of male and female rats and the groups of female mice. Mortality and clinical signs were checked daily during the 14-day observation period. Body weights were recorded and all animals were submitted to a gross necropsy at the end of the observation period.

Results
In the treated animals, reduction of the physical activity was noted. Deaths occurred within 2- 48 hours after substance administration. At necropsy no macroscopic organ changes/damages were noted.

Based on the observed mortality rates, the following LD_{50} figures were calculated by the method of Spearman-Kärber:

LD_{50} rat ♀: 1010 mg/kg bw
LD_{50} rat ♂: 870 mg/kg bw
LD_{50} mouse ♀: 908 mg/kg bw

Remark
Although there is no information on the batch that was tested, and the study was not carried out according to GLP, the outcome of this study is considered acceptable.

Ref.: 16

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	:	/
Species/strain	:	White guinea pigs, strain Pirbright Specific Pathogen Free (SPF)
Group size	:	15 females
Test substance	:	4-Amino-m-cresol (3 % aqueous dilution thickened with 0.5 % tylose)
Batch	:	/
Purity	:	/
Application	:	Open application by brush on the clipped flank region daily for 5 consecutive days
GLP	:	not in compliance

A 3 % dilution of 4-Amino-m-cresol in 0.5 % aqueous tylose was applied onto the clipped flank region of 15 albino guinea pigs, by means of a brush, daily for 5 consecutive days. The skin was not covered, but animals were restrained from movement in order to avoid contact with the treated area (3 x 4 cm) for the first 5 hours after application. The skin was evaluated according to the Draize-scheme for erythema and oedema 5 hours after each application.

Results
No skin reactions at all were observed at any observation time point. In addition, no clinical signs or unusual behaviour of the treated animals was noted.
A 3 % dilution of 4-amino-m-cresol in 0.5 % aqueous tylose showed no irritant effects to the guinea pig skin after repeated application under the test conditions.

Ref.: 17

3.3.2.2. Mucous membrane irritation

Guideline	:	/
Species/strain	:	White guinea pigs, strain Pirbright (SPF)
Group size	:	5 females
Test substance	:	4-amino-m-cresol (1.5 % in 50 % propylene glycol)
Batch No.	:	/
Purity	:	/
Application	:	0.1 ml, permanent contact
GLP	:	Not in compliance

0.1 ml of a 1.5 % dilution of 4-Amino-m-cresol in 50 % propylene glycol was applied into the conjunctival sac of the left eye of 5 female guinea pigs; the right eye served as control. The eyes

were not rinsed and evaluated and scored according to the Draize scoring system 0.5, 1, 2, 3, 4, 6, and 7 h after application. Further readings by means of fluorescein-instillation took place 24 h and 48 h after substance application.

Results
No ocular irritant effects were noted at any observation time point after 4-Amino-m-cresol as a 1.5 % dilution in 50 % propylene glycol was instilled into the eyes of guinea pigs without rinsing in 4 of the 5 tested animals. The conjunctival erythema was seen in one animal without any other macroscopic effect.

Conclusion
4-Amino-m-cresol at 1.5 % may have minimal ocular irritant potential.

Ref.: 18

3.3.3. Skin sensitisation

Maximisation test

Guideline	:	/
Species/strain	:	With guinea pigs, strain Pirbright, Hoe: DHPK (SPF)
Group size	:	20 animals for treatment, 10 for positive and 10 for negative control
Test substance	:	4-Amino-m-cresol
Batch No.	:	/
Purity	:	/
Concentrations	:	Intradermal induction: 3 % test substance in distilled water and in Freund’s complete adjuvant (FCA)/arachidis oil Dermal induction: 3 % test substance in white vaseline, occluded, pre-treatment with 10 % sodium lauryl sulfate in white vaseline Challenge: 1, 2 and 3 % test substance in distilled water occluded
GLP	:	Not in compliance

The dermal sensitisation potential was evaluated in guinea pigs, strain Pirbright, Hoe: DHPK.

A topical range-finding study was conducted on two guinea pigs per dose group. The animals were treated dermally under occlusive conditions with a 1, 1.5, 2 and 3 % dilutions of the test item in distilled water. No skin reactions were observed at these test concentrations. Therefore, twice the maximum intended on-head concentration of 3 % for hair dye formulations was used as the test concentration for the intradermal and topical induction as well as maximum concentration for the challenge phase.

In the main study, 20 animals were intradermally induced on day 1 with 0.05 ml of a 3 % dilution (w/v) of 4-amino-m-cresol in distilled water. Freund's complete adjuvant was injected in parallel. Six to eight hours later the animals were topically pre-treated with 10 % sodium lauryl sulfate in vaseline to cause a slight inflammation. Thereafter, animals were topically exposed to 3 % of 4-amino-m-cresol in white vaseline (0.5 ml/2x4 cm) on the flank under occlusive conditions for 24 h. Then, a second intradermal injection with 3 % of 4-amino-m-cresol in FCA/arachidis oil was performed. Animals were challenged on day 16 by applying about 0.5 ml of a 1, 2 and 3 % dilution of 4-amino-m-cresol in FCA/arachidis oil to the flank region (2x4 cm) under

occlusive patch conditions for 24 h. Approximately 24 and 48 hours after the challenge phase, the test sites were evaluated for signs of any elicited sensitisation.

The same procedures were carried out on concurrent vehicle and positive control groups except that the solutions of the test article were replaced by distilled water (vehicle control) and 0.005 % (intradermal) and 0.025 % (topical) 1-chloro-2,4-dinitrobenzene (DNCB) (positive control), respectively.

Results
No dermal irritation was observed during the "induction phase" for the control or the treated groups. Following challenge with 1, 2 and 3 % of 4-amino-m-cresol diluted in FCA/arachidis oil no sensitisation reactions were noted at 24 and 48 hours after patch removal. With the concurrent positive control, DNCB, the skin reactions noted at challenge concentrations of 0.5 and 1 % demonstrated the sensitivity of the system.

Conclusion
4-Amino-m-cresol did not cause a skin sensitising effect under the described conditions of testing. Based on these findings, 4-Amino-m-cresol was considered as non-sensitising.

However, the test design was inadequate. Specifically the concentration used for both the epidermal induction and challenge were not based on the required thresholds for a minimum irritating/maximum non-irritating concentration, but on twice the maximum intended use concentration. Furthermore, the study has reporting deficiencies.

Ref.: 19

Local Lymph Node Assay (LLNA)

Guideline	:	OECD 429 (2002); US National Institute of Health publications No. 99-4494 (1999)
Species/strain	:	Mice CBA/J
Group size	:	5 females
Test substance	:	4-Amino-m-cresol
Batch No.	:	123-124
Purity	:	95.8 % (HPLC)
Concentrations	:	0.5, 1.5, 5.0 and 10.0 % (w/v) in DMSO and 0.5, 1.5, 3.0 and 5.0 % in aqua/acetone (1:1) mixed with olive oil (4:1)
GLP	:	In compliance

The skin sensitising potential of 4-Amino-m-cresol was investigated in CBA/J mice by measuring the cell proliferation in the draining lymph nodes after topical application on the ear.
Twenty five µl of 0 (vehicles only), 0.5, 1.5, 5 and 10 % of 4-amino-m-cresol in DMSO and 0.5, 1.5, 3 and 5 % in a mixture of aqua/acetone (1:1) with olive oil (4:1) (equal to the maximum solubility) were applied to the surface of the ear to each of five female CBA/J mice per group for three consecutive days. For the highest test concentration in water/acetone, the pH value was adjusted to pH 11 in order to obtain a homogenous solution. After application, the ears were dried by means of a hair dryer for 5 minutes. p-Phenylenediamine (PPD) at 1 % in DMSO was used as the positive control in parallel under identical test conditions. Even though this is not the

conventional material used as a positive control, it was regarded as the most adequate control for oxidative hair dye precursors.
Animals were checked for morbidity/mortality at least once daily. Observation for clinical signs was done daily before and at least once after dosing. Body weight was determined on day -2 and on day 5.
On day 5, the mice received an intravenous injection of 250 µl phosphate buffered saline containing 23.6 µCi of [H^3] methyl thymidine. Approximately five hours later, the mice were sacrificed by CO_2-inhalation and the draining auricular lymph nodes were removed and weighed. After preparing a single cell suspension for each mouse, cells were precipitated by TCA and the radioactivity was determined (incorporation of [H^3] methyl thymidine in the pellets) by means of liquid scintillation counting as disintegration per minute (dpm).
The mean dpm per treated group was determined and the stimulation index (test item compared to the concurrent vehicle control) was calculated.

Results
There were no abnormal clinical signs or mortality throughout the study period. Body weight development was not affected by the treatment.
Lymph node weights were increased after treatment with 4-amino-m-cresol as compared to the vehicle controls indicating an immune response in both vehicles.
The mean stimulation indices were affected in a dose-dependent manner by the treatment with 4-amino-m-cresol. With the test item in DMSO, mean stimulation indices of 0.9, 3.1, 6.5 and 6.7 were obtained for the 4 test concentrations of 0.5, 1.5, 5 and 10 %, respectively. An EC3 value (equal to the concentration inducing a stimulation index of 3) of 1.45 % was calculated.
In the second vehicle (aqua/acetone/olive oil), the indices were 1.5, 1.7, 4.7 and 6.9 for the 4 test concentrations of 0.5, 1.5, 3 and 5 %, respectively. An EC3 value of 2.15 % was calculated from these findings.
The responses noted in both groups for 4-amino-m-cresol are considered positive with EC3 values of 1.45 % and 2.15% indicative of a moderate sensitiser.
The positive control (PPD, 1 % in DMSO) caused a stimulation index of 4.3 and an increase in lymph node weight by a factor of 1.3 which demonstrated the sensitivity of the test system used.

Conclusion
4-amino-m-cresol induced a biologically relevant immune response in local lymph nodes after dermal application to the mouse ear with either vehicles used. EC3 values of 1.45 % and 2.15 % were calculated for DMSO and aqua/acetone/olive oil, respectively. The concurrent positive control demonstrated the sensitivity of the assay.

Based on these findings 4-amino-m-cresol is evaluated to be a skin-sensitiser under the described test conditions. 4-amino-m-cresol would be categorised as a moderate sensitiser according to the relative skin sensitisation potency classification scheme published in the ECETOC technical report on contact sensitisation (Reference: 20).

Ref.: 21

3.3.4. Dermal / percutaneous absorption

3.3.4.1. Percutaneous penetration *in vitro*

Guideline	:	OECD–Draft Guideline Skin absorption: in vitro method" (2000); COLIPA-Guideline for "In Vitro Assessment of Percutaneous Absorption and Penetration of Cosmetic Ingredients (1999)
Tissue	:	Porcine back skin (thickness: 840 µm)
Method	:	Diffusion teflon-chambers
Test substance	:	4-Amino-m-cresol tested at a concentration of 1.5 % in a commercial hair dye formulation.
Batch no	:	123-124 (4-amino-m-cresol)
Purity	:	95.8 % (HPLC)
Concentration	:	1.5 mg/cm² tested as part of hair dye formulation (Batch 85506028)
No. of chambers	:	6 (five for the formulation containing the dye stuff and one for the blank formulation)
GLP	:	In compliance

Skin absorption of 4-amino-m-cresol at the maximum concentration intended for hair colorants, was investigated with pig skin (Schweizer Edelschwein, female 115 kg) prepared from the back and the flanks (840 µm thick) of animals. Dye (1.5 mg) was applied to the skin in a commercial hair dye formulation (400 mg aqueous cream formulation containing 1.5 % dye applied to 4 cm² skin).
The integrity of the skin was monitored at the beginning of the experiment using tritiated water.
A Teflon-diffusion chamber was used. The receptor solution (physiological phosphate buffer containing NaCl and antibiotics) was pumped through the receptor chamber at a rate of 5 ml/h. Six chambers per experimental group were investigated.
Thirty minutes after substance application, the test item was removed by washing the skin twice with 4 ml water, then once with 4 ml washing solution (shampoo-formulation diluted to approximately 16.7 %) and again twice with water. The washing solutions were combined and the amount of dye was determined by HPLC.
4 ml fractions of the receptor fluid were collected at 16 and 24 hours and stored at –20° C until analysis. At termination of the experiment, the skin was extracted and the dye content quantified.

Results
All samples/tissue extracts were analysed by HPLC. The limit of quantification of the applied method was 5 ng/HPLC-injection.
The integrity of each skin sample was demonstrated with tritiated water, resulting in penetration rates of 0.7 to 1.1 % of the applied dose. These figures were within the limit of acceptance (≤ 1.5 %).
A total recovery of 96.1 ± 3.0 % of the applied dose was obtained. However, preliminary stability tests showed that only about 5 % of the initial quantity of the applied dose could be recovered after 16 h in the receptor fluid, indicating a moderate to rapid decrease of 4-Amino-m-cresol when added to the receptor fluid or brought into skin contact (in a mounted Franz cell, 32° C).
The majority of 4-Amino-m-cresol remained on the skin surface representing 95.6 ± 3.1 % of the applied dose.

Because of the above mentioned findings, the quantification of the skin penetration by analysis of skin-extracts and the receptor fluid is not meaningful. 4-amino-m-cresol was not detected in the receptor fluid. Thus, the limit of detection (equal to 132 ng/cm²) was used to estimate the content for this compartment, i.e. 0.3 µg/cm² (equal to <0.02 % of the applied dose). However, due to the instability of the test item in the receptor fluid, this approach might not reflect the real conditions. Similarly, the content quantified in the skin 8.0 ± 2.2 µg/cm² (equal to 0.5 ± 0.2 % of the applied dose) might not reflect the real conditions, due to the limited stability of the test item upon skin contact.
Therefore, the bioavailable fraction was calculated as either the difference between the amount applied (1500 µg) and the amount found in the combined rinsings (1433.5 µg), i.e. 66.5 µg/cm², or the difference between the total recovery (1441.8 µg) and the combined rinsings, i.e. 8.3 µg/cm². Based on the above calculations a maximum amount of 8.3 to 66.5 µg/cm² of 4-Amino-m-cresol (equal to 0.6 to 4.4 % of the applied dose) may be bioavailable.

Conclusion
The huge variation obtained within the above approach clearly demonstrates that this way of calculation does not provide a suitable skin penetration rate for the risk assessment of 4-Amino-m-cresol. The study is considered inadequate.

Ref.: 22

3.3.4.2. Percutaneous absorption *in vivo*

Guideline	:	/
Species/strain	:	Pigmented rats, strain PVG
Group size	:	6 rats per treatment group (3 males and 3 females)
Test substance	:	^{14}C-4-Amino-m-cresol hemisulphate (ring-labelled). Radioactive purity 96.5 %, specific activity: 57 µCi/mg
Batch No.	:	CFQ4065, 4-Amino-m-cresol hemisulphate
Purity	:	/
Doses	:	Solution in DMSO: 150 mg/ml, 0.1 ml/animal; 1.611 mg/cm^2. Commercial formulation with peroxide: 1.5 %, 1 g/animal, 1.516 mg/cm²
Treatment period	:	Single cutaneous application under occlusive conditions in DMSO (24 h contact) and as part of a formulation with hydrogen peroxide (0.5 h contact); total study period 72h
GLP	:	Not in compliance

^{14}C-4-Amino-m-cresol was dermally applied to groups of three male and three female pigmented rats strain PVG (body weight 142 - 171 g at arrival; 8- 14 week old). The application area was 9 cm² and the test substance was applied at concentrations of 15 % in DMSO and of 1.5 % in a commercial formulation with hydrogen peroxide, for 24 h and 30 min contact, respectively. The mean dosages of the dyestuff applied were 1.611 mg/cm² and 1.516 mg/cm², respectively. During the exposure time the treated skin area was securely sealed by an occlusive plaster.
Thereafter, the test substance was scraped off (formulation only) and the skin was rinsed with a shampoo formulation and warm water. After rinsing, the area was covered with an aluminium foil strip and securely sealed by an occlusive plaster to further prevent licking of the treated area during the 72 h in the metabolism cages.
Urine and faeces were collected daily (0-24, 24-48 and 48-72 h after administration) from the metabolic cages. Exhaled carbon dioxide was removed every 24 hours for the 72 h post-dosing period.

Animals were killed 72 hours after the application and the application sites, blood and organs were taken and analysed for radioactivity. The radioactivity in the remaining carcass was also determined.

Results
Total recovery of the applied radioactivity was 86.7 and 89.8 % and 95.7 and 97.9 % for males and females treated with the commercial formulation and the DMSO solution, respectively.
The amount of radioactivity remaining at the application site (skin) for the formulation represented 2.8 % and 1.73 % of the applied dose for males and females, respectively. The respective figures for the DMSO solution were 7.86 and 6.1 % for males and females.
Absorbed radioactivity was mainly excreted via urine both for the commercial formulation (0.35% males, 0.15 % females) and for the DMSO solution (8.09% males, 5.00 % females). Elimination was fast, with 79.4 - 88.9 % of the total amount being excreted within in the first 24 hours. Excretion via faeces was low for both the formulation (0.01 to 0.02 %) and the DMSO solution (0.27 to 0.58 %). Elimination via expiration was also relatively low at less than 0.2 % for both the commercial formulation and the DMSO solution.
The majority of the applied doses was recovered in the dressings and the washing solutions, representing 83.3 to 87.7 % and 74.4 to 81.6 % of the applied amount for the formulation and the DMSO solution, respectively.
Low levels of radioactivity were detected in all tissues examined for the DMSO solution, except for the thyroid, adrenal and gonads, in which detectable amounts were only found in one sex and/or for some but not all of the animals within one group. The highest levels were noted for the remaining carcass (0.059 - 0.063 % of the applied dose) and the GI-tract content (0.006 - 0.007 % of the applied dose). The levels were generally low and the total residue in tissue minus the application sites, but inclusive of the carcass, represented 0.07 % of the applied dose for both sexes. In general, the tissue distribution did not reveal any sex differences.
Similar findings were noted for the formulation, but the tissue levels were in general lower than the ones noted for the DMSO solution. Again, the highest levels were noted for the remaining carcass and the GI-tract content as observed with the DMSO solution. The figures obtained for males were almost identical to the ones noted with the DMSO solution, whereas for females lower residues were noted. The total residues in tissues (without application sites) and carcass in males and females represent about 0.07 % and 0.02 % of the applied dose, respectively. The higher residue in the carcass in males, a similar tissue distribution was noted for males and females.
Accepting the mean amounts in urine, faeces, exhaled air, residual carcass, and as a worst case assumption the total content of the skin, as potential total bioavailable dose, a cutaneous absorption of 2.73 % of applied dose equivalent to 41.4 ug/cm² was found for a commercial formulation applied under typical use conditions in the presence of peroxide. The respective amount for the DMSO solution is 14.38 % of the applied dose equal to 231.7 µg/cm².
No significant differences were noted between males and females with regard to skin absorption, tissue-distribution and elimination of 4-amino-m-cresol when applied with in either a hair dye formulation chassis or a DMSO solution.

Conclusion
4-amino-m-cresol applied dermally to rats is absorbed to a significant level (14.38%) if applied in DMSO, a known skin-penetration enhancer, but to a lesser amount (2.73 %) when applied in a commercial formulation.
Excretion is predominantly via the urine and to a minor extent via the faeces and lung. Excretion via urine is rapid, with 79.4 to 88.9 % being excreted within the first 24 hours. Low tissue

residue levels were noted in both experiments, indicating, that bio-accumulation potential is low following dermal application. The organ distribution indicated very low levels for the organs investigated.

Based on a worse case assumption, that the total amount found in the rat skin will become bioavailable, a mean absorption rate of 41.4 µg/cm² was found for 4-Amino-m-cresol when applied in a commercial formulation in the presence of peroxide under typical use conditions.

Ref.: 24

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: /
Species/strain: Wistar rat, strain BOR:WISW (SPF/TNO)
Group size: 20 animals per sex and dose; 5 additional animals per sex for the high dose and the control satellite groups
Observation: 90 days (+4 weeks recovery period)
Test substance: Oxyrot (4-amino-m-cresol sulphate)
Batch no: 19384
Purity: 99.7 area% (HPLC), according to submission (not indicated in the test report)
Dose levels: 15, 60 and 120 mg/kg bw/day
GLP statement: not in compliance

Three groups of 20 male and 20 female Wistar rats received the test substance, A74, dissolved in water), daily by oral gavage at doses of 15, 60 or 120 mg/kg bw/day for 90 days. The control group of 20 rats/sex received the vehicle alone (water for injections). For recovery observations, satellite groups of additional 5 animals/sex for control and high dose group were investigated after a 4-week treatment free period. Animals were observed twice daily for mortality/morbidity and once daily for clinical abnormalities. Body weight and food consumption were recorded weekly. A detailed ophthalmological investigation as well as an evaluation of auditory function and reflexes, according to a modified Irwin screen test (FOB) was performed on 5 animals/sex/group with special regard to awareness, co-ordination and autonomous nervous system functions. The investigations were conducted prior to treatment, after week 6, at the end of the treatment period and at the end of week 17 (recovery groups).

Haematology, clinical chemistry and urinalysis evaluations were performed in 20 or 5 animals (urinalysis)/sex/dose at day 0, and after 6 and 13 weeks in all dose groups and after 17 weeks in the recovery group.
At the end of the treatment period, all animals were killed and subjected to a detailed necropsy. Selected organs were weighed. A wide range of organs/tissues of the control and high dose animals was examined histopathologically. In addition, all gross lesions noted were examined microscopically.

Results
One female in the high dose group died in week 11, according to the necropsy this was due to a gavage error.
The only test substance related finding was an increase in absolute spleen weight in high dose females (statistically significant increased) and in high dose males. In the high dose recovery group an increase in absolute spleen weight was not observed.

Conclusion
The No Observable Adverse Effect Level for this study was 60 mg/kg bw/day.

Remark
The study design closely resembles OECD 408, except for data on test substance (purity), stability and homogeneity (these are not provided). It is only stated that as a salt, the substance is 'unlimitedly stable'.

Ref.: 25

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, TA1535, TA1537, TA102
Replicates	:	Two independent tests with and without S9 mix (Experiment I: plate incorporation test; exp. II: preincubation test)
Test substance	:	WR 23533 OXYROT A074 in DMSO
Batch n°	:	123-124
Purity	:	HPLC: 97.8 area % (254 nm) and 99.2 area % (300 nm)
Concentrations	:	Experiment I: 3 - 5000 µg/plate Experiment II (without S9 mix): 1 – 1000 µg/plate Experiment II (with S9 mix): 3 – 2500 µg/plate
GLP	:	Quality Assurance Statement included

A74 (WR 23533 OXYROT) has been investigated for the induction of gene mutations in *Salmonella typhimurium*. Liver S9 fraction from rats induced with phenobarbital/ß-naphthoflavone was used as the exogenous metabolic activation system. Toxic effects (i. e. reduction in the number of spontaneous revertants) occurred at higher concentrations with and without metabolic activation in nearly all strains used. Negative and positive controls were in accordance with the OECD guideline.
Results
A74 did not induce gene mutations in *S. typhimurium* in the absence or presence of S9 mix. Despite some deviations from historical control data for mutant frequencies of controls, the test

conditions are considered to be appropriate. Reference mutagens (positive controls) revealed a clear increase in revertant colonies.
A74 is considered to be non-mutagenic in the bacterial gene mutation assay with *S. typhimurium*.

Ref.: 26

***In vitro* mammalian cell gene mutation test**

Guideline	:	OECD 476
Cells	:	L5178Y mouse lymphoma cells (*tk*$^{+/-}$)
Replicates	:	One test without metabolic activation; 2 independent tests with S9 mix; single cultures per concentration; 8 analysable concentrations.
Test substance	:	4-Amino-3-methyl-Phenol (A74), dissolved in cell culture medium (RPMI with 3% horse serum)
Batch n°	:	127
Purity	:	HPLC: 94.7 area % (according to submission)
Concentr. Tested	:	0.048 – 6.25 µg/ml without metabolic activation 0.391 – 47.5 µg/ml with metabolic activation (first experiment) 0.5 – 40 µg/ml with metabolic activation (second experiment)
GLP	:	Quality Assurance Statement included

A74 has been investigated for induction of gene mutations at the *tk*-locus in L5178Y mouse lymphoma cells after exposure for 4 hours without and with metabolic activation. Liver S9 fraction from phenobarbital/ß-naphthoflavone-induced rats was used as the exogenous metabolic activation system. Test concentrations were based on the level of toxicity (1.42% – 2.72% relative total growth). Negative and positive controls were in accordance with the OECD guideline.

Results
In the first experiment with S9 mix a slight increase in mutant frequency was measured for 25 and 47.5 µg/ml (mutation factor 1.76 and 1.37, respectively). In the second experiment no induction of mutants was observed up to a concentration of 30 µg/ml and a marginal effect was measured at 40 µg/ml (mutation factor 1.13). In the experiment without metabolic activation, A74 concentrations of 3.125 and 6.25 µg/ml slightly increased the mutant frequency (mutation factor 1.82 and 2.85, respectively). However, at the highest concentration (6.25 µg/ml) a strong cytotoxic effect was measured (relative total growth was reduced to 1.42%). The positive controls clearly induced mutations in all experiments. Colony sizing was performed but is not useful in case of negative test results.

Under the experimental conditions used, A74 did not lead to a clear and/or reproducible induction of gene mutations at the *tk*-locus. Some isolated small mutagenic effects were determined which lack biological significance. All in all, the test indicates that A74 is not mutagenic in cultured mammalian cells.

Ref.: 27

Unscheduled DNA synthesis (UDS) test *in vitro*

Guideline	:	/
Cells	:	Hepatocytes from 8-12 week old male Wistar rats
Replicates	:	One test with 6 parallel cultures
Test substance	:	Cos 291 (A74) dissolved in DMSO
Batch n°	:	Cos 291 (equal to 19384), according to submission (not indicated in the test report)
Purity	:	99.7 area% (HPLC) according to submission (not indicated in the test report)
Concentr. Tested	:	1 - 100 µg/ml
GLP	:	Statement of compliance included

A74 has been tested in the *in vitro* UDS test with freshly prepared rat hepatocytes. UDS was measured by liquid scintillation counting of incorporated (^{3}H)-thymidine after treatment for three hours. Concentrations higher than 100 µg/ml could not be tested because they inhibited the incorporation of (^{3}H)-thymidine. DMBA was used as a positive control.

Results
A74 (Cos 291) did not induce UDS under the test conditions used. The positive control (DMBA) clearly increased the incorporation of (^{3}H)-thymidine.
The negative result indicates that A74 does not induce DNA damage that is detectable with the *in vitro* UDS test. However, due to the small size of the study and the methodology used (liquid scintillation counting) the result is of limited value and only provides supportive evidence for a lack of genotoxic activity.

Ref.: 28

3.3.6.2 Mutagenicity/Genotoxicity *in vivo*

Mouse bone marrow micronucleus test

Guideline	:	OECD 474
Species/strain	:	Mouse, NMRI
Group size	:	5 males + 5 females
Test substance	:	4-Amino-3-methyl-Phenol (A74) dissolved in 0.9% NaCl
Batch n°	:	127
Purity	:	HPLC: 94.7 area %, according to submission (not indicated in the test report)
Dose levels	:	20, 100 and 200 mg/kg bw (single i. p. injection)
Sacrifice time	:	24 hours (all doses) and 48 hours (200 mg/kg only)
GLP	:	Quality Assurance Statement included

A74 has been investigated for induction of micronuclei in the bone marrow cells of mice. Due to results of preliminary toxicity tests, 200 mg/kg bw was selected as the top dose-level. Negative and positive controls were in accordance with the OECD guideline.

Results
In all treated groups, the relative PCE frequency was not decreased in any dose group. The highest dose (200 mg/kg bw) induced signs of toxicity (palpebral closure, lethargy) within the

first hour after application. No toxic effects were observed at later time points. The mean MNPCE frequencies were not signifcantly increased in any of the groups treated with the test substance. The positive control substance gave the expected result. The study was conducted appropriately.

A74 did not induce chromosome aberrations or damage to the mitotic apparatus in bone marrow cells of mice after intraperitoneal treatment under the test conditions used.

Ref.: 29

An older *in vivo* micronucleus test with NMRI mice has been submitted in addition. A74 (Cos 291, dissolved in DMSO; batch No. and purity not indicated in the test report) was administered by gavage at dose levels of 100, 333 and 1000 mg/kg bw. All doses were evaluated 24 hours after administration, the highest dose was also investigated 48 hours and 72 hours after treatment. 1000 PCE were evaluated for the presence of micronuclei per data point. Cyclophosphamide was used as a positive control.
The PCE/NCE – ratio was reduced after treatment with the highest test dose only at the late preparation time point (72 hours). No induction of micronuclei was measured at any dose and any preparation time point. The positive control substance gave the expected effect. Although this test does not meet the requirements of the actual guideline and the test report is incomplete, supportive evidence is provided for the absence of a mutagenic effect of A74 in the *in vivo* micronucleus test.

Ref.: 30

Rat liver in vivo/in vitro UDS assay

Guideline	:	not available at the time of test performance
Species/strain	:	Rat, Wistar / WU
Group size	:	3 males
Test substance	:	A74 dissolved in DMSO/PEG 400 (1+9)
Batch n°	:	do/1258
Purity	:	> 99% (according to test report)
Dose levels	:	60, 600 and 2000 mg/kg bw, by gavage
Sacrifice times	:	16 hours (dose group: 600 mg/kg bw); 4 hours (dose groups: 60 and 1000 mg/kg bw)
GLP	:	Quality Assurance Statement included

A74 has been investigated for induction of unscheduled DNA synthesis (UDS) in rat hepatocytes *in vitro* following *in vivo* dosing (single oral treatment). No toxic reactions of the animals were observed. Negative and positive controls were included. Only three animals were evaluated per data point and 100 cells per animal were scored.

Results
In none of the groups treated with the test substance there was a significant induction of UDS compared to the negative control group. There were no significant differences in the viability of hepatocytes isolated from rats of different dose groups. The positive control substance agent gave the expected results. The negative test result indicates that A74 does not induce DNA damage that is detectable with the UDS test under the test conditions used in this study.

This study does not meet the requirements of the actual guideline and is therefore of limited value for the evaluation of the in vivo genotoxicity of A74. However, the negative result provides some evidence for the lack of genotoxicity in the rat liver *in vivo/in vitro* UDS test.

Ref.: 31

3.3.7. Carcinogenicity

No data

3.3.8. Reproductive toxicity

3.3.8.1. Two generation reproduction toxicity

3.3.8.2. Teratogenicity

Prenatal development toxicity study

Guideline	:	OECD 414
Species/strain	:	Wistar rat, BORA:WISW-SPF TNO rats
Group size	:	24 females / dose level
Observation period	:	20 days
Test substance	:	Oxyrot (A74)
Batch no	:	19384
Purity	:	HPLC: 94.7 area %, according to submission (not indicated in the test report)
Dose levels	:	0, 10, 40, 80 mg/kg bw/day (in water)
GLP statement	:	in compliance

Three groups of 24 pregnant rats received A74 by oral gavage at doses of 10, 40 or 80 mg/kg bw/day from day 5 through day 15 of gestation. Solutions of test substance were prepared fresh daily. A third group of 24 pregnant rats received the vehicle only (water) and served as a control group. The day of positive proof for sperm in the vaginal smear was designated as day 0 of pregnancy.
Animals were checked daily for clinical signs. Food consumption and body weight were recorded at designated intervals during pregnancy.
On day 20 of pregnancy, the animals were killed and examined macroscopically. Foetuses were removed by Caesarean section. The following litter parameters were recorded: number of corpora lutea and implantation sites, number and distribution of early and late resorptions, and number and distribution of dead and live foetuses, placentae and sex. Foetuses, placentae, gravid uteri and uteri without foetuses were weighed. Foetuses were submitted to external, soft tissue and skeletal examinations.

Results
No treatment-related effects in dams were noted with regard to clinical observations and post-mortem findings. The body weight and the food consumption were not affected by the treatment. Gross necropsy revealed no treatment related effects.

There was no treatment related effect with regard to uterus and placenta weights, the number of corpora lutea, and implantations.
There were no treatment related effects with regard to reproduction e.g. litter size, foetal mortality, foetal body weight, birth position and sex ratio. The skeletal and visceral examination of the foetuses revealed no treatment related findings. Neither a statistically significant difference as compared to the concurrent control nor a dose-dependent increase in any malformation or variation was noted.

Conclusion
In the present study no treatment related effects were seen on maternal toxicity and developmental toxicity parameters up to the highest tested dose of 80 mg/kg bw/day.

Remark
These dose levels were based on the in use concentration of the dye (maximum concentration of dye = 3%, maximum external concentration of 36 mg/person. Assuming 0.2% absorption, 0.072 mg/kg bw intake. Therefore, the study authors conclude that the lowest dose of 10 mg//kg will have a sufficient high safe zone.). This way of dose selection is not according to the OECD guideline and a possible hazard is not adequately identified.

Ref.: 32

3.3.9. Toxicokinetics

Comparative metabolism study in primary hepatocytes of human, rat and mouse

Guideline	:	None
Cells	:	Hepatocytes from male humans (pooled from 3 donors) Hepatocytes from male Sprague Dawley rats Hepatocytes from male ICR/CD-1 mice
Cell density	:	0.88 to 1.2 x 106 cells
Test substance	:	4-amino-m-cresol
Batch no	:	123-124
Purity	:	95.8 area% (HPLC), according to submission (not indicated in the test report)
Test concentration	:	6.6 to 10 µM
Incubation time	:	4 hours
GLP	:	In compliance

The metabolic profile of 4-amino-m-cresol was investigated in vitro by means of cryo-preserved primary hepatocytes from male human donors, male Sprague Dawley rats and male ICR/CD-1 mice.

The metabolic capacity of the hepatocytes was characterised by marker substrates for phase I (general cytochrome P450 activity for humans and rodents and specific activity of 1A1/2 and 2E1) and phase II enzymes (N-Acetyl-transferase 1/2) commonly studied or considered to be relevant for the metabolism of the class of arylamines, to which 4-amino-m-cresol belongs.

Approximately 1 x 106 cells/ml were incubated with 10 µM (mouse hepatocytes) or 6.6 µM (rat, human hepatocytes) of 4-amino-m-cresol for 4 hours. Samples of the supernatant were taken and analysed at 0, 0.5 1.5 and 4 hours. Test conditions were chosen based on range finding

experiments. Incubation was performed in 24 well microtitre plates and cell conditions were microscopically evaluated at each time point. The metabolic stability was assessed by detection of loss of parent compound by means of LC-MS/MS. The metabolic profile was also investigated by LC-MS and metabolites identified/characterised as far as possible.

Results
Cell viability (90%, 95% and 80% in human, rat, and mouse, respectively) was not affected by 4-amino-m-cresol during the incubation period. A slight decrease in viability of about 10 % was noted for the end of the entire incubation period.
The marker enzymes demonstrated the metabolic capacity and the validity of the test system.
As expected, differences in the metabolic capacity between rat, mouse and human hepatocytes were noted for the different Phase I marker reactions. As expected, sulfamethazine N-acetylation was higher in human hepatocytes compared to rat and mouse hepatocytes, reflecting that sulfamethazine is a good marker for human NAT2 but nor for rat and mouse NATs. In contrast, N-acetylation of the model substrate para-amino benzoic acid was comparable in all three species, as it is a good marker substrate for human NAT1 and rat and mouse NAT2.
4-amino-m-cresol revealed a rapid rate of metabolism in rat and human hepatocytes. A decrease of 95.2 % and 89.8 % of the parent compound was detected within 1.5 h incubation for human and rat hepatocytes, respectively. The mouse incubation could not be analysed due to analytical problems.

The analysis of the formed metabolites revealed an intensive phase II metabolism resulting in sulfation of the phenol group for all three species. In contrast, no indication of N-acetylation was noted for rat or human hepatocytes.

Conclusion
The sensitivity of the HPLC-MS/MS system for the parent compound and potential metabolites was limited and did not allow a detailed analysis of the metabolic profile. However, the data obtained with rat and human hepatocytes treated with 4-amino-m-cresol under identical test conditions indicate, that among those cells there is no significant difference in the metabolic rate/capacity and the metabolic profile.

The results of this comparative in vitro metabolism study in hepatocytes, therefore further support the validity of an extrapolation from rodent (rat) data to the human situation with regard to liver metabolism. However, obviously it does not provide information on comparability of skin and lung metabolism.

Ref.: 33

Bioavailability across intestinal barrier in TC-7 (human intestinal epithelial) cells

Guideline	:	None
Cells	:	Human intestinal epithelial cell line TC-7
Test substance	:	4-amino-m-cresol
Batch no	:	123-124
Purity	:	95.8 area% (HPLC), according to submission (not indicated in the test report)
Test concentration	:	50 µM in HBSS buffer containing 1 % DMSO
Incubation time	:	60 min

Number of experience : two independent experiments
GLP : /

The bioavailability of *4*-amino-m-cresol across the intestinal barrier was investigated in human intestinal epithelial (TC-7) cells *in vitro*. The permeability from the apical (A, pH 6.5) to the basolateral (B, pH 7.4) side was investigated at 37°C in 96- transwell plates with shaking for a 60 min contact time. Analysis of the donor (apical) and receiver (basolateral) samples was done by means of HLPC-MS/MS and the apparent permeability coefficient (P_{app}) was calculated for two independent experiments. ^{14}C-mannitol (about 4µM) was used to demonstrate the integrity of the cell monolayer. Only monolayers revealing a permeability of $< 2.5x10^{-6}$ cm/sec are used. Propranolol, vinplastine and ranitidine were analysed concurrently to demonstrate the validity of the test system.
According to the laboratory's classification system, a low permeability is considered for test items revealing a $P_{app} < 2 \times 10^{-6}$ cm/sec. A P_{app} of $2 - 20 \times 10^{-6}$ cm/sec and a $P_{app} \geq 20 \times 10^{-6}$ cm/sec classify a substance to have a moderate and a high permeability, respectively. Ranitidine, which has a 50 % absorption in humans was used as a low permeability reference compound, as recommended by the FDA.

Results
The total recovery for the reference substances and *4*-amino-m-cresol ranged from 83 to 100 %.
The figures for the reference substances propranolol ($P_{app} = 29.6 \times 10^{-6}$ cm/sec), a high permeability reference compound with 90% absorption in humans, and ranitidine (P_{app}= 0.4 x 10^{-6} cm/sec) were well within the acceptable range for these compounds of 20 –45 x 10^{-6} cm/sec and 0.2 – 2 x 10^{-6} cm/sec, respectively and demonstrated the validity of the assay.
4-amino-m-cresol revealed a P_{app} of 59 x 10^{-6} cm/sec and thus was classified to be of high permeability, indicating nearly 100% absorption from the gastro-intestinal tract.

Conclusion
With *4*-amino-m-cresol a mean permeability in human intestinal epithelial (TC-7) cells of 59 x 10^{-6} cm/sec was obtained, which classifies the test item to be of high permeability. As the absorption from the gastro-intestinal tract is likely to be permeability limited, the high permeability observed in this assay indicates a good absorption of *4*-amino-m-cresol after oral administration.

Ref.: 34

3.3.10. Photo-induced toxicity

3.3.10.1. Phototoxicity / photoirritation and photosensitisation

No data

3.3.10.2. Phototoxicity / photomutagenicity / photoclastogenicity

No data

3.3.11. Human data

No data

3.3.12. Special investigations

No data

3.3.13. Safety evaluation (including calculation of the MoS)

CALCULATION OF THE MARGIN OF SAFETY

Maximum absorption through the skin	**A (µg/cm^2)**	=	**41.4 µg/cm^2**
Typical body weight of human		=	**60 kg**
Skin Area surface	**SAS (cm^2)**	=	**700 cm^2**
Dermal absorption per treatment	**SAS x A x 0.001**	=	**28.98 mg**
Systemic exposure dose (SED)	**SAS x A x 0.001/60**	=	**0.483 mg/kg**
No observed effect level (mg/kg) (rat, subchronic, oral)	**NOAEL**	=	**60 mg/kg**

Margin of Safety	**NOAEL / SED**	=	**124**

3.3.14. Discussion

Toxicity
The No Observable Adverse Effect Level (NOAEL) was 60 mg/kg bw/day (90-day, oral, rat).
No treatment related effects were seen in a prenatal developmental toxicity study on maternal toxicity or on developmental toxicity parameters up to the highest tested dose of 80 mg/kg bw/day.

Irritation
A 3 % dilution of 4-amino-m-cresol in 0.5 % aqueous tylose showed no irritant effects to the guinea pig skin after repeated application under the test conditions. At 1.5 %, it may have minimal ocular irritant potential.

Sensitisation
Local Lymph Node Assay (LLNA): 4-amino-m-cresol is evaluated to be a skin-sensitiser under the described test conditions.

Percutaneous absorption
A mean absorption rate of 41.4 µg/cm^2 was found for 4-Amino-m-cresol when applied in a commercial formulation in the presence of peroxide under typical use conditions (*in vivo* study).

Mutagenicity
4-Amino-m-cresol (WR 23533 OXYROT; A74) did not induce gene mutations in bacteria and mammalian cells *in vitro*. An *in vitro* test capable of detecting chromosomal aberrations is missing. A negative *in vivo* micronucleus test indicates that the substance does not induce chromosome aberrations or damage to the mitotic apparatus in bone marrow cells. However,

exposure of the target cells is not indicated and the use of this *in vivo* test has not been justified. The negative mutagenicity tests are supported by negative results from *in vitro* and *in vivo* UDS tests. On the basis of the genotoxicity tests performed for 4-amino-m-cresol there is no concern about a relevant mutagenic potential of this compound**.**

4. CONCLUSION

The SCCP is of the opinion that the use of 4-Amino-m-cresol itself as an oxidative hair dye at a maximum concentration of 1.5% 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.

However, 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

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