OPINION OF THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS INTENDED FOR CONSUMERS

CONCERNING

THE USE OF BENZOYL PEROXIDE (BPO) HYDROQUINONE (HQ), HYDROQUINONE METHYLETHER (MEHQ) IN ARTIFICIAL NAIL SYSTEMS

adopted by the SCCNFP during the 20th Plenary meeting

of 4 June 2002

1. Terms of Reference

1.1 Context of the question

Annex II of the European Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products currently include Benzoyl peroxide (BPO), entry 382, and 4-methoxyphenol (synonym for Hydroquinone methylether) entry 178. Annex II is the List of substances which must not form part of the composition of cosmetic products.
Hydroquinone (HQ) is in Annex III- Part 1. List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down- to European Council Directive 76/768/EEC of 27 July 1976.

Request for amendment of Annex II and Annex III of the European Cosmetics Directive (76/758/EEC) in order to allow restricted use of benzoyl peroxide, hydroquinone and hydroquinone methylether in artificial nail systems.

1.2 Request to the SCCNFP

Request for deletion from Annex II and inclusion of benzoyl peroxide and hydroquinone methylether in Annex III- Part 1. List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down- to European Council Directive 76/768/EEC of 27 July 1976.

Request for amendment of Annex III- Part 1. List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down- to European Council Directive 76/768/EEC of 27 July 1976 to include restricted use of Hydroquinone in artificial nail systems.

Annex III Ref. No.	Substance	Restrictions			Conditions of use and warnings to be printed on the label
		Field of application and/or use	Maximum authorised concentration in the finished cosmetic product	Other limitations and requirements	
a	b	c	d	e	f
14	Hydroquinone [(1)]	(c) Artificial nail systems	200 ppm (after mixing	Professional use only	- for professional use only - Avoid skin contact - read use directions carefully

/	Benzoyl peroxide (BPO)	Artificial nail systems	0.7% (after mixing)	Professional use only	- for professional use only - Avoid skin contact - read use directions carefully
/	Hydroquinone methylether (MeHQ)	Artificial nail systems	200 ppm (after mixing	Professional use only	- for professional use only - Avoid skin contact - read use directions carefully

(1) These substances may be used singly or in combination provided that the sum of the ratios of the levels of each of them in the cosmetic product expressed with reference to the maximum level authorised for each of them does not exceed the value given in column d.

- Do the safety profiles documented in the attached submission support the use of benzoyl peroxide, hydroquinone and hydroquinone methylether in artificial nail systems?

  - Considering the mode and frequency of application as well as the application site of artificial nail systems

  - Is exposure to artificial nail systems containing benzoyl peroxide at a maximum concentration of 0.7% (after mixing) considered safe for the consumer?
  - Is exposure to artificial nail systems containing hydroquinone and/or hydroquinone methylether at a maximum concentration of 200 ppm (after mixing) considered safe for the consumer?

- Are benzoyl peroxide and hydroquinone methylether safe for use in cosmetic products?
  - In the opinion SCC/XI/103/88-EN, recommended that benzoyl peroxide was not permitted for use in cosmetic products as the risk that it could promote skin tumours at low doses was not acceptable.
  -. Hydroquinone methylether, as 4-methoxyphenol has been prohibited since the first publication of the Cosmetics Directive, but no reason was given.

- Does the SCCNFP propose any restrictions or conditions for the use of benzoyl peroxide and hydroquinone methylether in cosmetic products?

- The opinion SCCNFP/0078/98 permitted the use of 1,4-Dihydroxybenzene, Colipa A21, (Hydroquinone) as a "rinse-off" product when as a "coupler" in oxidative hair dye mixtures, diluted to 0.15% from 0.3% ‘in the bottle’.
- Does the SCCNFP propose any further restrictions or conditions for the use of hydroquinone in cosmetic products?

1.3. Assessment background

The SCNFP can only assess the safety of substances for which appropriate data has been submitted for evaluation.

Safety assessment is specific and not generic.

1.4 Statement on the toxicological evaluation

The SCCNFP is the scientific advisory body to the European Commission in matters of consumer protection with respect to cosmetics and non-food products intended for consumers.

The Commission's general policy regarding research on animals supports the development of alternative methods to replace or to reduce animal testing when possible. In this context, the SCCNFP has a specific working group on alternatives to animal testing which, in co-operation with other Commission services such as ECVAM (European Centre for Validation of Alternative Methods), evaluates these methods (doc. n° SCCNFP/0546/02).
The extent to which these validated methods are applicable to cosmetic products and its ingredients is a matter of the SCCNFP.

SCCNFP opinions include evaluations of experiments using laboratory animals; such tests are conducted in accordance with all legal provisions and preferably under chemical law regulations. Only in cases where no alternative method is available will such tests be evaluated and the resulting data accepted, in order to meet the fundamental requirements of the protection of consumer health.

In the interest of consumer's health protection, the SCCNFP highlights the important requirement of ensuring that files for evaluation are submitted complete.
The files should include, as well as the results procured by the applicants themselves, all relevant published literature and other findings to the applicant's best ability, and also "grey material" available elsewhere. Subsequently, should additional data or information be acquired by Industry and/or other agencies, this should be transmitted to the Commission, for review as necessary.

2. Toxicological Evaluation and Characterisation

2.1. General

2.1.1. Primary name

BPO	HQ	MeHQ
Benzoyl peroxide IUPAC Dibenzoyl peroxide IARC	Hydroquinone, 1,4-Dihydroxybenzene	Hydroquinone methylether

2.1.2. Synonyms

BPO	HQ	MeHQ
Benzoic acid, peroxide; benzoperoxide; benzoyl superoxide; diphenyl-glyoxal peroxide	Benzene, p-dihydroxy-; p-Benzenediol; 1,4-Benzenediol; Benzohydroquinone; Benzoquinol; Dihydroxybenzene; p-Dihydroxybenzene; 1,4-Dihydroxybenzene; Dihydroxybenzene (OSHA); p-Dioxobenzene; p-Dioxybenzene; Hydroquinol; Hydroquinole; alpha-Hydroquinone; p-Hydroquinone; Hydroquinone (ACGIH:OSHA); p-Hydroxyphenol; Pyrogentistic acid; Quinol; beta-Quinol	4-Methoxyphenol; P-Guaiacol; Hydroquinone monomethyl ether; Hydroxyanisole; p-Hydroxyanisole; 4-Hydroxyanisole; p-Hydroxymethoxybenzene; Mequinol; p-Methoxyphenol; Mono methyl ether hydroquinone; Phenol, p-methoxy

Ref. : AR 1

2.1.3. Trade names and abbreviations

BPO	HQ	MeHQ
BPO	HQ; Arctuvin; Eldopaque; Eldoquin; NCI-C55834; Phiaquin; Tecquinol; Tequinol;	MEHQ, Leucobasal; Leucodine B; Novo-Dermoquinona;

	USAF EK-356	PMF; USAF AN-7

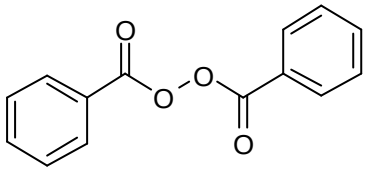
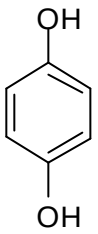
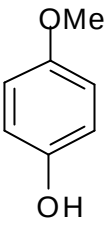
Ref. : AR 1

2.1.4. CAS no.

BPO	HQ	MeHQ
94-36-0	123-31-9	150-76-5

Ref. : AR 1

2.1.5. Structural formula

 Benzoyl peroxide	 Hydroquinone	 Hydroquinone methylether

2.1.6. Empirical formula

	BPO	HQ	MeHQ
Emp. Formula	$C_{14}H_{10}O_4$	$C_6H_6O_2$	$C_7H_8O_2$
Mol weight	242.24	110.12	124.15

Ref. : AR 1

2.1.7. Purity, composition and substance codes

BPO	HQ	MeHQ
No data on the purity is provided. BPO has to be stabilised, otherwise it degrades to benzoic acid in water with in days. The stabiliser(s) is(are) not identified	Not provided	Not provided

2.1.8. Physical properties

	BPO	HQ	MeHQ
Appearance	White granular crystalline solid; faint odour of benzaldehyde	Not provided	white crystalline chips
Melting point	105 ^{0}C		55 - 57 ^{0}C
Boiling point	May explode when heated		243 ^{0}C
Density			
Rel. vap. dens.			
Vapour Press.	<13 Pa at 20 ^{0}C		<0.01mm 20 ^{0}C
Log P_{ow}			

Ref. : 4 g, AR 2

2.1.9. Solubility

BPO	HQ	MeHQ
Soluble in all organic solvents, particularly benzene, chloroform and ether. Slightly soluble in alcohol and vegetable oils. Slightly soluble in water.	Soluble in water, alcohol chloroform and ether.	Not provided

Ref. : 4g, AR 3

2.2. Function and uses

Artificial Nail System

Benzoyl peroxide is used as a chemical initiator for polymerisation of the powder component of dry acrylic polymers and pigments of the 2 component artificial nail systems. It is at a maximum concentration in the powder of 2% and as maximum concentration of 0.7% at the start of the polymerisation process.
Hydroquinone and/or hydroquinone methylether are the stabiliser or inhibitor in the liquid component of acrylate monomers primarily methylacrylates of the 2 component artificial nail systems. Either hydroquinone and hydroquinone methylether, under in use condition as an stabiliser/inhibitor in the two

component artificial nail system, is at a maximum concentration 200 ppm (0.02%). After mixing 2 parts liquid to 1 part powder the final concentration is reduced to around 133 ppm or 0.0133%.

Ref. : 1

A brush is wetted in the liquid component containing the stabiliser and acrylate monomers. The wetted brush is then dipped into the powder with the initiator to obtain an 'asprin sized' bead. The liquid : powder ratio is about 2:1. The two components are mixed into a 'slurry bead', which is applied to the centre of the nail plate and then shaped. The polymerisation is completed in 5 min - 15 min. Contact is to the keratin of the nail plate. The hydrophobic methylacrylate has low adhesion affinity to the keratin, thus hydrophilic nail primers are necessary.

Ref. : 3, AR 4

Other uses

Benzoyl peroxide is used at concentrations up to 10% topical treatment of acne. It is probably the most widely used first-line drug in the management of mild acne.

Ref. : AR 3, AR 5

Benzoyl peroxide is used as a chemical initiator for polymerisation of acrylates (including dental cements and restoratives) and other polymers; bleaching agent in foodstuff; rubber curing.

Ref. : 4 g

Hydroquinone and hydroquinone methylether are both used in topical drug preparations as depigmenting agents for the skin in hyperpigmentation conditions. Hydroquinone is used in preparations up to 4%. Higher concentrations have been used but cause irritation. Hydroquinone methylether is used in preparations up to 20%.

Ref. : AR 3

Hydroquinone and hydroquinone methylether are used as inhibitors, to increase the shelf life, preventing premature polymerisation of the methylacrylate-based liquid portion of a two component polymer systems.

Ref. : 1

TOXICOLOGICAL CHARACTERISATION

2.3. Toxicity

Hydroquinone

No new data was provided. The opinion, SCCNFP/0078/98, on 1,4-dihydroxybenzene (hydroquinone) had concluded that hydroquinone is unlikely to pose a toxic and/or carcinogenic risk when applied topically.

Ref. : 8

Hydroquinone methylether

No toxicological information was provided.

2.3.1. Acute oral toxicity

Benzoyl peroxide

Low toxicity
Oral LD_{50} in rat : 7710 mg/kg
Oral LD_{50} in mouse : 5700 mg/kg
Hydroquinone methylether
Oral LD_{50} in rat : 1600 mg/kg

Ref. : AR 1

2.9. Carcinogenicity

Benzoyl peroxide

The SCC in a second additional opinion on BPO, dated 19.1.1988, concluded that the use of BPO was unacceptable because of the risk of BPO promoting skin tumours at low doses.
BPO was shown to be a tumour promoter in SENCAR mice after exposure to a single topical dose of 20 nmol of the tumour initiator DMBA. BPO was 0.2ml in 100mg/ml in acetone for 51 weeks. All treated mice showed epidermal hyperplasia.

Ref. : 4c

The FDA review suggested that though these results showed BPO to be a promoter, the studies were not adequate as the SENCAR mice are sensitive to carcinogens. The results were not confirmed by other laboratories using similar dosing regimens and the same mouse strain. This suggested that BPO may not be a complete carcinogen. Additional studies were requested.
A two year carcinogenicity in rats and mice have been negative to date. There are no signs of cutaneous cancer, after 52 weeks of topical BPO in carbopol gel to F344 rats and B6C3F1 mice. In mice, at the highest dosed, 25 mg/day, some developed ulceration during the first year. The macroscopic and microscopic cutaneous effects suggested that the Maximum tolerated dose (MTD) was exceeded. Similar response were seen in the second year at 15 mg/day, again suggesting that the MTD was exceeded. Animals which developed ulcers were removed from the experiment. 5 mg/day would seem to be the MTD in mice.
There was no evidence of photocarcinogenicity induced by BPO in carbopol gel, even at the highest dose 50 mg/ml in SKH1(hr/hr) albino hairless mice with UVR (600 RBU) stimulation 3 times a week for 40 weeks.
In conclusion, the interim results of the animal studies uphold the view that the use of BPO in acne treatments pose no human health concerns above currently accepted standards for similar OTC drug products. No additional labelling warning against theoretical or rodent tumour promotion concerns are warranted.
IARC has classified BPO as a group 3 carcinogen based on inadequate evidence in humans for carcinogenicity and limited evidence in experimental animals.

Ref. : 4g, 4a, 4d

The final results of the two year carcinogenicity of topical BPO in carbopol gel in mice have been received. It is unclear if the rat study mentioned above has been completed.
After 104 weeks, treatment related histomorphological alterations were noted in the treated skin at the 1 and 5 % BPO dose levels. These included mild acanthosis and hyperkeratosis in both sexes, minimal to mild subepidermal subacute inflammation and sebaceous gland hyperplasia in males at both dose levels and minimal subepidermal subacute inflammation and minimal to mild sebaceous gland hyperplasia in females at 5% dose level. At higher doses there were no microscopic observations for treated or untreated skin in the group at the higher dose of 25% for 52 weeks, reduced to 15% for the remainder of the experiment or in the group with the higher dose of 25% for 52 weeks and then treatment discontinued. Both high dose groups showed no residual effect of treatment. Thus it was concluded that under the conditions of the study there was no indication of oncogenicity from daily topical exposure of mice to benzoyl peroxided gels at concentrations up to 25%.

Ref. : 13

2.10. Special investigations

Analytical procedures

Standard BPO titration: Reaction with potassium iodide, followed by titrating iodine with sodium thiosulphate. This is reliable to 0.01%. Sensitivity is increased by changing to oxygen free atmosphere.

Residual BPO measurement.: The nail polymer matrix is cross linked and not soluble in acetone, but swells in acetone releasing free BPO. BPO is thermally labile and degrades at a rate dependent on the solution temperature. In this analysis, complete BPO extraction occurred after 3h at 35^0C.

Detection techniques used were titration, Gel Permeation Chromatography, Gas Chromatography and Supercritical Fluid Chromatography (SFC). SFC column detection limits at 267 nm were determined for the standards as :

BPO	200 ng
HQ	240 ng with a single peak around 5 minutes retention time
MeHQ	206 ng with 2 peaks of unequal intensity centred around 9 minutes retention time.

The analytical detection limit for both hydroquinone and hydroquinone methylether is 10 ppm.

Ref. : 2d, 10, 11

Polymer preparation for some of these extractions was different from that in the artificial nail systems. In the artificial nail system, the powder to liquid ratio is 1:2. In some analysis, the powder to liquid ratio was 2:1. No reason was given.

Ref. : 2d, 3

In use penetration

Systemic exposure should be minimal from penetration of BPO, HQ or MeHQ through the nail plate, since penetration through the nail plate is known to be limited from studies on topical anti-fungal drugs. Professional application of the artificial nail to the nail plate should not allow contact with skin. However, without due care, there could be skin contact at the cuticle and the side of the nails.

Ref. : 2b, 2c, 2e, AR 4

In use simulation

The data provided is not directly an 'in use' application of the artificial nails, but was designed to show the possibility of leaching residual benzoyl peroxide from the polymer. No detection limit was given, but none was detected!

The artificial nail system seemed to contain approximately 0.1% residual BPO after 15 min, there was no further reduction by 24 h. To assess the quantity of BPO that could migrate from the finished nail system, finished nail samples were soaked in water at 35^0C for 1, 2 and 5 days. No leaching of BPO from the polymer was detected.

Detection of hydroquinone in the finished nail system extracts was difficult. The SFC/UV results showed a single peak at approximately 4.9 minutes retention time in the extract chromatogram. This matched well with the retention time of HQ standard. However the peak was much more symmetrical in the extract than in the standard trace. The assignment of this peak to HQ in the extract should be viewed cautiously as a number of co-extractables were observed.

Three additional peaks were found in the extract chromatograms at approximately 9.8, 10.6, and 10.8 minutes which did not match the retention times for any of the standards for the other components, benzoyl peroxide and hydroquinone methylether, of the artificial nail systems. Although these peaks were not examined with a spectrometric detector, it may be postulated that these peaks are due to the oxidation products of the hydroquinones. Further study may be warranted.

Ref. : 3, 9

The approved method for detection of and identification of hydroquinone, hydroquinone monomethylether and others in Directive 95/32/EC, pages 169 -175 was not used. The reason was that this method was not appropriate to quantify traces in a solid matrix such as artificial nails during or after hardening

Ref. : AR 5, Letter from Colipa with submission II

2.11. Safety evaluation

The 2 components of the artificial nail systems are mixed into a "slurry" bead, which is applied professionally only to the centre of the nail plate and then shaped. The ratio of powder to liquid is 1:2. The polymerisation is completed in about 5 - 15 min. Contact is to the keratin of the nail plate. The hydrophobic methylacrylate has low adhesion affinity to the keratin, thus hydrophilic nail primers are necessary. Penetration through the nail plate is nil or minimal. Contact with skin is nil or minimal. Benzoyl peroxide, hydroquinone and hydroquinone methylether are at low concentrations and are mainly consumed rapidly during polymerisation. The remaining residual is trapped in the hardened polymer

matrix. Possible systemic exposure, through the nail plate, is slight. Even if the nails are bitten, the quantity that might be absorbed would be very low.

The artificial nail systems are applied to the nail plate every 4-6 weeks with a refill application 2-3 weeks. Full application is 4.05g of polymer and 1.1g for the refill. Exposure to BPO is estimated to be less than 4 mg for the full application and less than 1 mg at the refill application. For hydroquinone or hydroquinone methylether, this is an estimated topical exposure of less than 40µg for the full application and 10µg at the refill application.

Ref. : 2a, 9

2.12. Conclusions

Benzoyl peroxide, hydroquinone and hydroquinone methylether are technical aids in the polymerisation of polymers such as ethyl and methylacrylates. They are at low concentrations and are mainly consumed rapidly during polymerisation. The remaining residual is trapped in the hardened polymer matrix. This reduces the chance of possible systemic exposure, since penetration through the nail plate is slight. Even if the nails are bitten, the quantity that might be absorbed would be very low.

There is concern that the technique for mixing the two components is open to great operator variation.

Little toxicological data (no data on genotoxicity/mutagenicity) was provided for either hydroquinone or hydroquinone methylether. Assumptions are made but are not corroborated with data. The analytical data for the residual hydroquinone and hydroquinone methylether in the finished nail is inadequate.

Ref. : 9

Nevertheless, the SCCNFP concludes that, due to the very low exposure to the consumer, the risk is minimal.

2.13. Opinion of the SCCNFP

The SCCNFP is of the opinion that the substances are safe for use for the indicated proposes with the restrictions and conditions of use.

Annex III Ref. No.	Substance	Restrictions			Conditions of use and warnings to be printed on the label
		Field of application and/or use	Maximum authorised concentration in the finished cosmetic product	Other limitations and requirements	
a	b	c	d	e	f

14	Hydroquinone [1]	(c) Technical aid in artificial nail systems	200 ppm (after mixing	Professional use only	- for professional use only - Avoid skin contact - read use directions carefully
/	Benzoyl peroxide (BPO)	Technical aid in artificial nail systems	0.7% (after mixing)	Professional use only	- for professional use only - Avoid skin contact - read use directions carefully
/	Hydroquinone methylether (MeHQ)	Technical aid in artificial nail systems	200 ppm (after mixing	Professional use only	- for professional use only - Avoid skin contact - read use directions carefully

[1] These substances may be used singly or in combination provided that the sum of the ratios of the levels of each of them in the cosmetic product expressed with reference to the maximum level authorised for each of them does not exceed the value given in column d.

2.14. References

1. Rohm and Haas Technical Bulletin, 1998, Methacrylic/acrylic monomers: Specifications and Properties.

2 E Jackson, 2000a, Estimation of Risk to Wearers of Artificial Nails from Exposure to Benzoyl Peroxide as a Chemical Initiator in Artificial Nail Systems, Report prepared for NMC; Attachments:

a. Letter to CIR on Penetration of Ethyl Methacrylate Monomer Through the Nail Plate (10/7/99)

b. Sun, Y et al Nail Penetration: Focus on Topical Delivery of Antifungal Drugs for Onychomycosis Treatment (Percutaneous Absorption-Drugs-Cosmetics-Mechanisms-Methodology; 1999) 759-778

c. Gup chup GV and Zatz JL 1999 Structure Characteristics and Permeability Properties of the Human Nail: A Review J.Cosmet. Sci. 11/99) 50, 363-385

d. Summary report ESSTECH, June 22, 2000 : Analysis of BPO content of artificial nail powders (polymers); Analysis of HQ/MEHQ content of artificial nail liquids (monomers)

e. Letter from ESSTECH to E. Jackson, July 20, 2000 :Report of Integrated Analytical Laboratories, LLC.

f. Graph of a Differential Scanning Calorimetery indication that the artificial nail is formed in about 3.5 minutes. The graph measures the exotherm of the heat of reaction. Which is caused by the BPO reaction.

3. M. Ashraf-Khorasani and L.T. Taylor, 2000, Extraction and Separation of Benzoyl Peroxide. Hydroquinone and Methylether of Hydroquinone from Ethyl and Methyl Methacrylate Copolymer Blend Via Supercritical Fluid Extraction and Supercritical Fluid Chromatography: Report to ESSTECH, July 24, 2000

4. E. Jackson,2000b, Expert Toxicological Opinion on the Tumor Promotion Potential of Benzoyl Peroxide, Report prepared for NMC; Attachments :

a. 2nd Additional Opinion of the Scientific Committee on Cosmetology Relating to the use of Benzoyl Peroxide (19/1/88)

b. Slaga, T.J et al (1988) Skin Tumor-Promoting Activity of Benzoyl Peroxide, a Widely Used Free Radical-Generating Compound. (Science 28/8/81) 213, 1023-1024.

c. Kurokawa, Y, et al. 1984 Studies on the Promoting and Complete Carcinogenic Activities of Some Oxidizing Chemicals in Skin Carcinogenesis. Cancer Letters 1984)24, 299-304

d. Update on Safety Studies with Benzoyl Peroxide (26/2/99; FDA Docket No.81N-0114)

e. Kraus, A L et al 1995 Benzoyl Peroxide: An Integrated Human Safety Assessment for Carcinogencity . Regulatory Toxicology and Pharmacology, 21, 87-107

f. Binder, R. L, et al 1995 Benzoyl Peroxide: Review of Experimental Carcinogenesis and Human Safety Data InGrowth Factors and Human Promotion: Implications for Risk Assessment. 1995 p 245-294

g. Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide (IARC Monographs, 1998) 71, 345-358

5. SCC 1983, report by the Scientific Committeee on Cosmetology on the use of benzoyl peroxide in cosmetic products: X1/450/81-EN; FIN

6. SCC 1984 Additional opinion of the Scientific Committee on Cosmetology concerning the use of benzoyl peroxide in cosmetic products; X1/103/88-EN; FIN

7. SCC 1984, 2nd Additional opinion of the Scientific Committee on Cosmetology relating to the use of benzoyl peroxide in cosmetic products; X1/103/88-EN; Orig Fr.

8 SCCNFP 1999, Opinion of the Scientific Committee on Cosmetic Products and Non-Food Product intended for Consumers concerning 1,4 Dihydroxybenzene (Hydroquinone) a Hair Dye Constituent, SCCNFP/0078/98

9. L.T. Taylor 2000 Explanatory email from Virginia Tech to Allen Johnston (Esstech) on results present in Ref.3. September 2000

10. P.C. Heimenz Polymer Chemistry; The Basic Concents p 395-396 Marcel Dekker Inc., New York and Basel

11. W. Lenz Organic Chemistry of Synthetic High Polymers Interscience Publishers; New York – London- Sydney

12. D. Steinberg 2000, Personal Communication to Colipa on behalf of NMC (Fax dated 11th August 2000) **– not provided**

13 Dermal oncogenicity study of benzoyl peroxide gels in mice. Final report, August 2001. Covance study number 6711-100. Prepared for Consumer Healthcare Products Association (CHPA).

Additional References

AR 1. Registry of Toxic Effects of Chemicals,

AR 2 MSDS

AR 3 Martindale : The Complete Drug Reference 32nd ed. 1999 editors: Parfitt K, Sweetman, S C, Blake P S, Parsons, A V.

AR 4 Faikema,. F.J. and van Buuren,. R.D. 2000 Kunstnagelproducten: Een overzicht van nagelproducten, het gebruik en de daar aan gerelateerde gezondheidsrisico's en wetteliijke aspecten. Rapportnummer NDCOSOO6/

AR 5 Eady, EA et al (1996) The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. Br J Dermatol, 134, 107-23

AR 6 Directive 95/32/EC

AR 7 Rastogi, S.C. 1995 Investigation of residues of benzene in chemical products. Advances in Occupational Medicine and Rehabilitation, 1, 265 -269

AR 8 Rastogi, S.C. 1994 Formation of Benzene by hardeners Containing Benzoyl Peroxide and Phthalates Bull. Environ. Contam. Toxicol. 53:747-752

3. Other considerations

Benzoyl peroxide

The reaction of benzoyl peroxide-phthalate initiators have been shown to be a source of benzene. This could pose a health risk for the consumer and professional at the time of application.

Ref : AR 7, AR 8