EUROPEAN COMMISSION

Directorate-General for Health & Consumers

Scientific Committee on Consumer Safety

SCCS

OPINION ON

Polysilicone-15

COLIPA n° S74

Scientific Committees
on consumer safety
on emerging and newly identified health risks
on health and environmental risks

The SCCS adopted this opinion at its 7th plenary meeting

of 22 June 2010

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 Safety (SCCS), 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).

SCCS

The Committee shall provide opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

Scientific Committee members

Jürgen Angerer, Ulrike Bernauer, Claire Chambers, Qasim Chaudhry, Gisela Degen, Gerhard Eisenbrand, Thomas Platzek, Suresh Chandra Rastogi, Vera Rogiers, Christophe Rousselle, Tore Sanner, Kai Savolainen, Jacqueline Van Engelen, Maria Pilar Vinardell, Rosemary Waring, Ian R. White

Contact
European Commission
Health & Consumers
Directorate C: Public Health and Risk Assessment
Unit C7 - Risk Assessment
Office: B232 B-1049 Brussels
Sanco-Sc6-Secretariat@ec.europa.eu

ISSN 1831-4767 ISBN 978-92-79-12744-1
doi:10.2772/24945 ND-AQ-09-016-EN-N

ACKNOWLEDGMENTS

Prof. J. Angerer
Dr. U. Bernauer
Dr. C. Chambers
Prof. G. Degen
Dr. S.C. Rastogi
Prof. V. Rogiers
Prof. T. Sanner (Chairman)
Dr. J. van Engelen (rapporteur)
Prof. R. Waring
Dr. I.R. White

Keywords: SCCS, scientific opinion, UV-filter, S74, polysilicone-15, directive 76/768/ECC, CAS 207574-74-1, EC 426-000-4

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on polysilicone-15, 22 June 2010

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1. BACKGROUND

Dimethicodiethylbenzalmalonate (CAS n° 207574-74-1) was introduced as an UV-filter in the Cosmetics Directive (2002/34/EC) based on the SCCNFP [1] opinion (SCCNFP/0079/98) adopted during its 7th plenary meeting of 17 February 1999.

Dimethicodiethylbenzalmalonate has meanwhile got the INCI-name polysilicone-15, and it is currently authorized as an UV-filter, in annex VII, entry 26, in a concentration up to 10% without any further regulations.

Taken into consideration the MoS of 1600, the current authorisation for the substance covers the use of this UV-filter in sunscreen products, but also in other cosmetic products.

The company has informed the Commission that polysilicone-15 was tested via inhalation route in an acute exposure scenario. Outcome of the study will classify polysilicone-15 as toxic by inhalation. In order to evaluate whether this classification will have any influence on the current authorisation, the Commission has asked for the study in order to have it evaluated by the SCCP.

The requested information is contained in the current submission.

2. TERMS OF REFERENCE

1. *Does the SCCS have any scientific concerns for the continued use of Polysilicone-15 in cosmetic products in a concentration up to 10%, taken into account the new provided scientific data on inhalation?*

[1] The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers, the predecessor of the current SCCS

3. OPINION

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

3.1.1.1. Primary name and/or INCI name

Polysilicone-15 (INCI-name)

3.1.1.2. Chemical names

Benzylidene malonate polysiloxane
Dimethico-diethylbenzalmalonate
α-(Trimethylsilyl) ω-[(trimethylsilyl)oxy)poly[oxy(dimethyl)-silylene]-co-[oxy(methyl)(2-{p-[2,2 bis(ethoxycarbonyl)vinyl]-phenoxy}-1-methyleneethyl)silylene]-co-[oxy(methyl)-(2-{p-[2,2-bis(ethoxycarbonyl)vinyl]phenoxy}prop-1-enyl)-silylene]

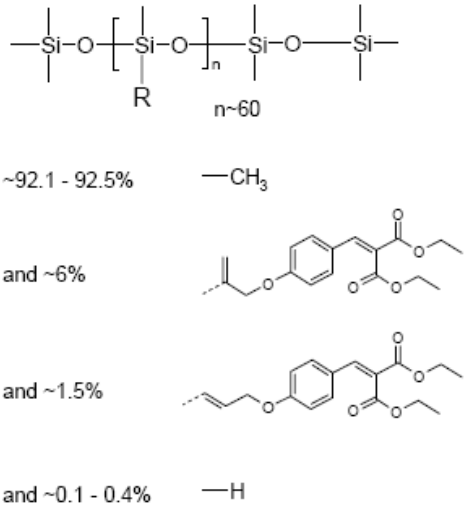
3.1.1.3. Trade names and abbreviations

PARSOL ® SLX

3.1.1.4. CAS / EC number

CAS: 207574-74-1
EC: 426-000-4

3.1.1.5. Structural formula



3.1.1.6. Empirical formula

Formula: $C_{196}H_{490}O_{84}Si_{65}$

3.1.2. Physical form

Clear, slightly yellow, viscous liquid

3.1.3. Molecular weight

Molecular weight: 5987 (molecular weight of the main homologue)

3.1.4. Purity, composition and substance codes

Composition
A polysiloxane with cinnamate functions attached to the extent of 4 in every 60 polymeric units. The composition and molecular weight are thus variable.

Purity
Not appropriate for polymers

Manufacturer's code
RO 84-5690/001; also Giv/Ro 84-5690.

3.1.5. Impurities / accompanying contaminants

See point 3.1.4. Purity, composition and substance codes

3.1.6. Solubility

≤ 0.1 mg/l (water, 20 °C)

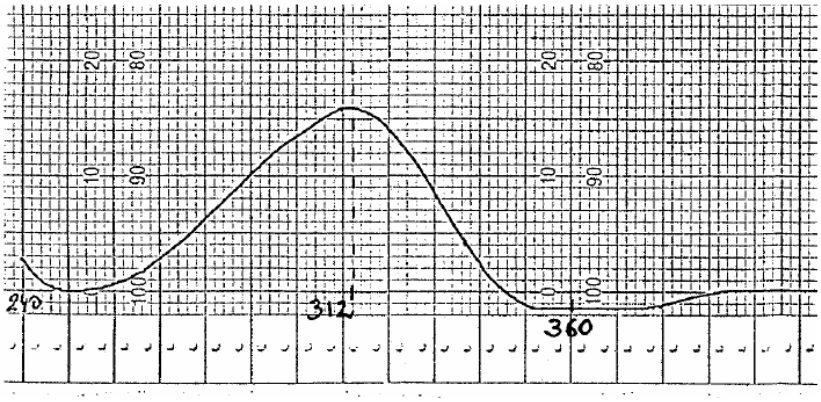
3.1.7. Partition coefficient (Log P_{ow})

Log P_{ow}: > 6 (30 °C)

3.1.8. Additional physical and chemical specifications

Melting point:	> 210°C, under 101 hPa
Boiling point:	> 210°C (1013 hPa)
Flash point:	/
Vapour pressure:	< 20 Pa (20 °C)
Density:	1.023 g/cm³ (20°C)
Viscosity:	774 mPa.s (25 °C) 315 mPa.s (50 °C)
Surface tension:	73 mN/M (20 °C)
pKa:	/
Refractive index:	/

Absorption spectrum



3.1.9. Homogeneity and Stability

No data submitted

General Comments to physico-chemical characterisation

/

3.2. Function and uses

Polysilicone-15 is used as an UV-filter in cosmetic sunscreen products as well as in other cosmetic products at a maximum concentration of 10%.

3.3. Toxicological Evaluation

3.3.1. Acute toxicity

3.3.1.1. Acute oral toxicity

Taken from SCCNFP/0079/98

Rat
A group of 5 male and 5 female Wistar SPF animals was tested by the administration of a suspension of the active ingredient once by gavage. The investigation was carried out in accordance with GLP, and EU and OECD guidelines.

Following a preliminary range finding experiment, a dose of 2000 mg kg bw was chosen. The active ingredient was suspended in 0.5% sodium carboxymethylcellulose; the volume of administration was 5 ml/kg bw. The dose was administered to animals which had been fasted for 17 hours. Observation was for 14 days. Clinical signs were observed on 3 occasions on the first day of the experiment, and daily thereafter (except weekends). Body weights were recorded every 3 days. Following sacrifice, the animals were subjected to necropsy.

No deaths occurred. No clinical abnormalities were observed. The weight gain of the animals was what would be expected of this strain. No abnormalities were found at autopsy. The LD_{50} was estimated at greater than 2000 mg/kg bw.

Ref.: 1

3.3.1.2. Acute dermal toxicity

Taken from SCCNFP/0079/98

Rat
A study according to GLP and EU and OECD guidelines was carried out in groups of 5 male and 5 female SPF animals of the Wistar strain. The backs and flanks of the animals were shaved with an electric clipper over an area of about 16 cm² (about 10% of the body surface). Pure active ingredient was applied to this area and covered with an occlusive dressing for 24 hours, after which the dressing was removed and the area washed with ethanol 70% in warm water. Clinical observations etc., were carried out as in the experiment recorded in reference 1 (above). Observation was for 14 days; after sacrifice, necropsy was carried out.

There were no deaths, and no clinical abnormalities, No skin lesions were seen. The increase in body weight was what would be expected in this strain of animal. Necropsy was normal. The LD50 was estimated at greater than 2000 mg/kg bw.

Ref.: 2

3.3.1.3. Acute inhalation toxicity

Toxicity following inhalation was investigated in a GLP and OECD 403 guideline compliant acute inhalation study using HanWistar rats. At ambient temperature, the test substance was too viscous for aerosol generation. Therefore, the test material was to a temperature of 55°C prior to nebulisation. Groups of five male and five female HanWistar rats were exposed by nose-only, flow-past inhalation to the generated aerosol at chemically determined mean concentrations of 0.285 mg/l air (Group 1) or 1.838 mg/l air (Group 2) for 4 hours. Two gravimetric measurements of particle size distribution produced mass median aerodynamic diameters (MMAD) and geometric standard deviations (GSD) of 2.64

µm (GSD 2.63) and 3.03 µm (GSD 2.49) for Group 1, and 2.67 µm (GSD 2.74) and 2.66 µm (GSD 2.73) for Group 2. Mortality and clinical signs were checked on the day of exposure, and twice (mortality) or once (clinical signs) days until day 15. Body weight was recorded on day 0, 4, 8 and 15. Necropsy was performed on the day that the animals were found dead or on day 15.

Results
In Group 1, two of ten animals were found dead on the day after the exposure. In Group 2 nine of ten animals were found dead, one or two days after exposure. There were no clinical signs during or after the inhalation exposure in Group 1. In Group 2, clinical signs were only seen from the day after the exposure. The clinical signs consisted of restlessness and ruffled fur, both findings slight to marked in degree, and of tachypnea and hunched posture and were followed by premature death or had cleared within 3 to 5 days in the one survivor of this group. This survivor remained free from clinical signs from five days after exposure onwards. There were no relevant, adverse effects on body weight development in the survivors of Groups 1 and 2. Necropsy did not reveal any macroscopic pathology changes in any of the survivors either of Group 1 or Group 2. In the two decedents of Group 1 the lungs were dark red discoloured and incompletely collapsed, and in the nine decedents of Group 2 the lungs were dark red discoloured.
No LC50 of Parsol SLX was calculated from this study, but was estimated to be between 0.285 and 1.838 mg/l air.

Ref.: 9 (Subm. II), 12 (Subm. II)

3.3.2 Irritation and corrosivity

3.3.2.1. Skin irritation

Taken from SCCNFP/0079/98

Man
A repeated insult patch test was carried out in a panel of 103 subjects (83 females and 20 males), using a modified Shelanski and Shelanski procedure. Eleven subjects failed to complete the study, for reasons unrelated to the testing procedures. The protocol lists various exclusion criteria, including a history of allergy or skin disease likely to interfere with the test, and previous participation in a test of this sort in the preceding 3 months. GCP rules were followed, and the subjects gave informed consent to the procedure.

The active ingredient was used in a 10% solution in liquid paraffin. Applications were made to the upper outer arm, and the dressings were occlusive. Provision was made for the use of an alternative site if a defined level of reaction was exceeded, but this appears to have been done once only, in which case sunburn had made it difficult to read any reaction and a new site was used instead. A problem with the study appears to have been a number of reactions to the plaster used to hold the patches in place, but these, it seems, were not generally so severe as to prevent reading of the sites; however, in 3 subjects it was severe enough to warrant the use of a new site for subsequent applications. The protocol originally seems to have called for the application of more than 8 induction patches, but following discussion with the sponsors 8 patches were deemed sufficient (the text states that a "Deviation from protocol log" contains details of this, but this log is not provided in the documents presented). Not all subjects achieved the full number of induction patches, but the trial lists decided that 6 or 7 induction patches (achieved in 11 subjects) could be accepted in the study.

The induction patches were applied over 3 weeks; each application was of 0.4 ml, and each site was inspected 24, 48, and 72 hours after each application (in some cases it was necessary to replace the 72 hour reading by a 96 hour reading). After the final induction patch a 2 week rest period was allowed, and the challenge patches were then applied, one

to the original site and another to a new site on the opposite arm, for 24 hours. These sites were inspected 48 and 96 hours after the application.

Results
No adverse reactions were found to any application. There were several deviations from the protocol, but none of these seemed sufficiently marked to make the results untrustworthy. The author concludes that the active ingredient shows no evidence of a potential for the production of sensitisation or irritation in this test.

Ref.: 10

Rabbit
A test was carried out in accordance with GLP, and EU and other relevant guidelines. One male and 2 female animals of the NZW White strain were used. The active ingredient, without dilution, was used as the test material. Its pH was determined to be 5. About 24 hours before treatment, areas of the skin on the dorsum about 10 X 10 cm were prepared by clipping. The sites were inspected before treatment to ensure that the skin had not been damaged by the preparation. An area of about 6 cm^2 had 0.5 ml of the active ingredient applied, following which the area of application was covered by a semi-occlusive dressing. The area of application was such as to preclude any ingestion of the material after removal of the dressing. After 4 hours, the dressings were removed and the area of application washed with warm water. Reading was at 1, 24, 48 and 72 hours after removal of the dressing. Clinical observations were carried out daily during the experiment, and body weights recorded before the experiment, 1 day after, and at termination of the experiment. Necropsies were not carried out. A conventional scoring system was used to record the reactions.

Results
There were no abnormal clinical signs. Body weights were as would be expected in this strain. The skin at the area of application showed very slight erythema at 24 hours in one female animal. Otherwise, no effect was noted. The cumulative mean score for irritation was 0.11. The active ingredient showed no evidence of having an irritant action on the skin.

Ref.: 4

3.3.2.2. Mucous membrane irritation

Taken from SCCNFP/0079/98

Rabbit
A study according to GLP, and EU and OECD guidelines was carried out in a group of 2 female and 1 male NZW White rabbits. The active ingredient, as supplied by the manufacturer, was found to have a pH of 5. Examination of the eyes of the animals at the beginning of the experiment was normal.

A volume of 0.1 ml of the active ingredient, without dilution, was applied to the left conjunctival sac of each animal, and the lids held closed for about 1 second. The right eye was untreated, and served as a control. Reading was at 1, 24, 48 and 72 hours. Rinsing was not carried out. A conventional scoring system was employed.

There was hyperaemia of the sclera and conjunctiva, and watery discharge, from the eyes of all animals at 1 hour; at 24 hours, there was slight reddening of the conjunctiva and sclera; at 48 hours, the eyes were normal in 2 animals, but slight reddening of the conjunctiva was seen in one animal. At 72 hours, no abnormalities were seen. The mean cumulative scores at each observation were, respectively, 1.67, 1.67, 0.33, 0. The mean score over 24 to 72 hours was 0.67 (maximum 13) so that, according to the protocol, the active ingredient was deemed to be non-irritant.

Ref.: 3

3.3.3. Skin sensitisation

Taken from SCCNFP/0079/98

Guinea pig

A Magnusson Kligman maximisation test was carried out in albino guinea pigs of the Himalayan spotted strain. The work was carried out in accordance with GLP and EU and OECD guidelines. A preliminary investigation was carried out to determine maximally tolerated doses of the active ingredient for the induction and challenge applications. (a) Two guinea pigs had intradermal injections in the flanks of 3 concentrations of the active ingredient in ethanol: 5%, 3% and 1%. Reactions were observed after 24 hours. The injections areas showed grade 1 erythema and oedema at all concentrations, and in accordance with the protocol, 5% was the concentration chosen for the main study. (b) Four animals were prepared by clipping and shaving both flanks. For each animal, 4 patches of filter paper 4 X 4 cm were saturated with each of the following: undiluted active ingredient, 30% active ingredient, 10% active ingredient, and 3% active ingredient (the diluting material being ethanol). These were applied two on each flank; the positions of the various dilutions were varied to exclude possible site related differences in response. The sites were then covered with aluminium foil and occlusive dressings for 24 hours. Reading was at 24 and 48 hours. No reactions were seen at any concentration, and the maximum concentration was chosen to be undiluted active ingredient. Concentrations of 30%, 10% and 3% were also used in the main test, however.

The main study
Thirty male animals were used: 20 test and 10 (negative) controls.
(a) Intradermal induction. An area about 6 X 8 cm was prepared in the scapular area, and three pairs of intradermal injections of 0.1 ml volume were made at the borders of a 4 X 6 cm area. For the test animals the injections were: 50/50 Freund's complete antigen (FCA)/physiological saline; 5% active ingredient in ethanol; 5% active ingredient emulsified in a 50/50 FCA/physiological saline. For the control animals, 50/50 FCA/physiological saline; ethanol; 50/50 ethanol emulsified in a 50/50 mixture FCA/physiological saline. (The author notes that the EU guideline requires that the third pair of injections should be formulated with FCA only. The method chosen, which is consistent with the OECD guidelines, was chosen to "decrease the site effects of FCA when applied alone.")

(b) Epidermal induction. On day 7, the scapular area was prepared, and treated with 10% sodium lauryl sulphate in liquid paraffin, rubbed in with a glass rod. On day 8, a 2 X 4 cm patch of filter paper saturated with undiluted active ingredient was applied to the area in the test animals, and covered with an occlusive dressing for 48 hours; the application of the active ingredient was omitted in the control animals. The sites were read at 24 and 48 hours after the removal of the dressings.

(c) Challenge. On test day 22, sites on both flanks were prepared and 4 patches of filter paper, saturated with active ingredient, were applied. The concentrations of active ingredient used were (%): 100, 30, 10, and 3. Impervious dressings were then applied for 24 hours. Readings were at 24 and 48 hours after removal of the dressings. A conventional scale was used to quantitate the reactions.

(d) Results. The skin at the injection sites showed oedema, erythema, encrustation, and finally necrosis. These reactions were essentially the same in both test and control animals. The epidermal induction sites showed no lesions. The challenge sites also showed no lesions.

(e) Other observations: there were no deaths. Clinical observation showed no evidence of systemic toxicity. There was no effect on body weights. Necropsy was not carried out.

(f) Positive controls. No contemporaneous positive control experiment was carried out. A maximisation test in the same strain of animal had been carried out in the same laboratory some 8 months previously, according to OECD guidelines, using 4-aminobenzoic acid ethyl ester (benzocaine) as the sensitiser. The results were positive, according to the protocol, although not all animals showed reactions, and the reactions seen were erythema only; no animal showed oedema. The author reports that similar investigations had been carried out in the laboratory, using benzocaine a second time, nickel sulphate, and 2-mercaptobenzothiazole; the results are not presented in this report, as the experiments had not been formally completed and had not then been subject to quality assurance. Presumably the results supported the conclusion that the methods used were satisfactory.

Under the circumstances of the experiment, the active ingredient showed no capacity to produce sensitisation.

Ref.: 5

3.3.4. Dermal / percutaneous absorption

Taken from SCCNFP/0079/98

The authors present a rather unusual view of the problem of percutaneous absorption. He begins by stating: "Skin penetration of [the active ingredient] is rather an efficacy target, than a safety one [presumably on the grounds that any UVF absorbed is to that extent no longer a protective agent]… Percutaneous absorption …is not a fixed value… but is depending on many factors like vehicle, concentration, exposure time, number of applications, skin type, skin surface condition, etc. It is therefore indispensable to compare the skin penetration with a "bench mark" molecule under identical conditions. Parsol MCX (2-ethylhexyl-p-methoxycinnamate) was used for this purpose."

The study was carried out according to GLP and OECD guidelines. A modified Franz cell was used, and both rat skin and domestic pig skin was used. The area of application was 5 cm2. The application rate was 2 mg/cm2 of formulation. The receptor chamber was continuously stirred, and was maintained at a temperature of 32°C. The composition of the receptor fluid is not given. The active ingredient was incorporated into an o/w lotion at a concentration of 5%. (a) "Naked" rat skin: after 16 hours, none was found in the receptor fluid. Stripping yielded 1.4% of the amount of active ingredient applied. The author states that the stripping procedure was halted when "the skin shines and a moderate afflux of moisture indicates the total removal of the horny layer." The remaining skin was then homogenised and the content of active ingredient analysed. This gave a yield of 0.4%. Finally, the amount recovered from the skin surface amounted to 98.2%. (b) Pig skin. The percentages found in the chamber, strippings, remaining skin, and surface were, respectively (percentage of amount applied) 0, 0.2, 2.1, and 97.7. Thus, a little more was found in the pig skin than in the rat skin. Further studies were carried out with the active ingredient formulated in isopropyl myristate: the figures from pig skin were 0, 0.4, 2.6 and 97%. Using petrolatum as a vehicle, the figures were 0, 0.5, 1.4 and 98.1%. Figures for a formulation in an o/w lotion "+ emulsion" were similar to the above. Repeated applications of a lotion formulation at 0, 2, 4 and 6 hours with estimation of penetration at 24 hours showed results very little different from those found following a single application. Finally, if the skin were stripped before being mounted in the cell, the amount in the receptor fluid was 0.5% and in the remaining skin 5%. The author regards this as an indication of increased absorption of the active ingredient if applied to damaged skin.

The comparison compound was studied in much the same way as described above for the active ingredient. In all tests, the amounts found in the receptor fluid, the stripped skin, and the stratum corneum were higher. In rat skin, the most marked increase was in the stripped skin and the receptor fluid, while in pig skin, the greatest increase was in the stratum corneum.

It is difficult to interpret this interesting report, as no details are given of the number of experiments performed, the statistical analysis carried out, etc. On the face of it, it would appear that about 2% of an applied amount is found in the stratum corneum + the stripped skin, and none in the receptor fluid.

Ref.: 7

3.3.5. Repeated dose toxicity

3.3.5.1. Repeated Dose (14 days) oral / dermal / inhalation toxicity

See point 3.3.5.2. Sub-chronic toxicity

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

Taken from SCCNFP/0079/98

Rat, oral (gavage)
The experiments were carried out in SPF rats of the Wistar strain. In a 14 day preliminary study (not carried out according to GLP) 5 groups, each of 6 female animals, were treated as follows (mg/kg bw/day): 0, 12, 60, 250 and 1250. The active ingredient was suspended in rape seed oil. On and after day 5, the lowest dose was replaced by a dose of 1800 mg/kg bw/day. Daily clinical observations were carried out, food consumption was measured, haematological and blood chemistry tests were also carried out. The animals were subjected to necropsy on sacrifice at the end of the experiment, and organ weights were recorded. No abnormalities were seen, and on the basis of these findings the doses for the definitive experiment were chosen.

For the main experiment, which was carried out according to GLP, and EU and OECD guidelines, the groups were: Group 1 (control) 20 male and 20 female; group 2 (low dose) 10 male and 10 female; group 3 (mid dose) 10 male and 10 female; group 4 (high dose) 20 male and 20 female. The doses of active ingredient were, respectively (mg/kg bw/day) 0, 60, 220, & 1000.
The active ingredient was made up in rape seed oil in such concentrations that the volume administered was 5 ml/kg bw/day. Dosing was by gavage, 7 days a week, for 90 days. At the end of this period, treatment of 9 male and 10 female animals of groups 1 and 4 was suspended, and these animals were observed for a further 28 days.

Daily clinical observation was carried out. Body weights and feed consumption were recorded. Ophthalmoscopic examination was carried out in weeks 1 & 12. Haematological examination was carried out in all animals at the end of treatment or of the recovery period, as appropriate. A wide range of variables was measured; (the differential white cell count was omitted in groups 2 and 3 unless an abnormality were found in group 4 animals). Similarly, a wide range of biochemical investigations in the blood was carried out at the same times. Urinary investigations were carried out in week 13. All animals were subjected to post mortem examination after sacrifice. Organ weights were recorded, and a large range of tissues fixed for histological examination. This examination was, in general, carried out in animals of groups 1 and 4 only, unless any abnormality suggested it should be carried out in individual animals of other groups. The suspensions for administration were prepared weekly, and the concentration of the active ingredient in the suspensions was determined (by the manufacturer) and found to be satisfactory.

Results
No dose related clinical abnormalities were noted, but 2 animals died: one group-4 animal, in which no cause for death could be found at necropsy, and one group 1 animal; in that case the death was attributed to obstructive uropathy, known to be an occasional finding in this strain of rat. Body weight and body weight gain were not affected by the treatment; nor

was food consumption. Ophthalmoscopy was stated not to show any dose related abnormalities, but no details are given.

Haematological examination showed some changes, but no definite dose related changes were observed, and the investigators considered that no biologically significant changes had been found. Clinical chemistry investigations in animals at the end of dosing are stated to have shown some falls in serum total bilirubin, aspartate aminotransferase, and serum alkaline phosphatase; A/G ratios were also lower. These changes were found to have reverted to normal in animals of the recovery group, and it was concluded that these changes were compensatory to the increased metabolic load associated with dosing. These statements are not easily confirmed from the tables, as statistical analysis in the tables is not supplied. However, inspection shows no evidence of changes other than those mentioned. Urine analyses were normal.

There was a slight increase in absolute and relative liver weights in the high dose groups, both male and female; this was attributed to the increased metabolic load in these animals. Again, statistical data are not supplied in the tables.
Necropsy did not show any dose related organ changes. Histological examination did not show any dose related changes. In the case of mid dose animals in the main study, and of recovery animals, organs were examined histologically only if changes had been found in the organs of the high dose groups.

The study seems to have been carefully carried out, and the NOAEL is put at 1000 mg/kg bw/day.

Ref.: 6

3.3.5.3. Chronic (> 12 months) toxicity

No data submitted

3.3.6. Mutagenicity / Genotoxicity

3.3.6.1 Mutagenicity / Genotoxicity *in vitro*

Taken from SCCNFP/0079/98

Reverse mutation assay

Two versions were used, viz. standard plate incorporation assay
pre-incubation assay

Indicator cells	Endpoint	Res. - act.	Res. +act.	Activation		Dose range
				Tissue	Inducer	
S. typh. TA 97 TA 98 TA 100 TA 102 TA1535 TA 1537 *E. coli* WP2uvrA	point mut. " " " " " " 	- - - - - - -	- - - - - - -	Rat liver S9 fraction	Phenobarbital/ β-naphthoflavone (combined treatment)	standard plate incorporation assay: 46 - 4553 µg/plate [1] preincubation assay: 50 - 5000 µg/plate [1] vehicle: ethanol
Test substance: Parsol SLX; batch No. 248452 GLP statement: Yes According to OECD 471 (1983): yes[2] [1] In a preliminary tyoxicity experiment, conducted in strain TA100, the compound was not toxic. The max. concentration was selected to be 5000 µg/plate, generally accepted as highest concentration for non toxic compounds. The test substance formed precipitates on the plates at the concentrations of 4553 and 5000 µg/plate. [2] In accordance with the guidelines, each study was repeated in an independent confirmatory experiment.						

Acceptability
The present study is considered acceptable.

Conclusions
The test substance was not mutagenic in the presence or absence of metabolic activation, when tested in both versions of the reverse mutation assay.

Ref.: 8

Cytogenetic test on Chinese hamster lung cells (Mammalian chromosome aberration test)

Indicator cells	Endpoint	Res. - act.	Res. +act.	Activation		Dose range
				Tissue	Inducer	
Chinese Hamster V79 cells (derived from lung)	Crom. Ab.	-[2]	-[3]	Rat liver S9 fraction	phenobarbital/ β-naphtho-flavone (combined treatment)	50 - 5000 µg/ml [1] solvent: ethanol (final concentration during treatment was 1%)
Test substance: PARSOL SLX; Lot 248452 GLP statement: Yes According to OECD 473 (1983/1997): yes [4] [1] There was no inhibition of the mitotic index both in the presence and absence of metabolic activation; 5000 µg/ml is the maximal recomended concentration. The test substance precipated in the final treatment medium at concentrations between 500 and 5000 µg/ml, forming a homogeneous suspension (up to 2000 µg/ml) or a mixture with oily drops (at 5000 µg/ml). [2] continuous treatment (16 or 27 hrs) or pulse treatment (3 hrs) [3] pulse treatment (3 or 5 hrs) [4] The study was not repeated in a second, independent experiment, but sufficient exposure times were tested.						

Acceptability
The present study is considered acceptable.

Conclusions

The test substance was not clastogenic or aneuploidogenic when tested in Chinese hamster cells *in vitro*, in the presence or absence of metabolic activation.

Ref.: 9

***In vitro* mammalian cell gene mutation assay**

Mouse lymphoma cell mutation test (ML/TK)

Indicator cells	Endpoint	Results - act.	Results +act.	Activation		Dose range
				Tissue	Inducer	
mouse lymphoma cell line L5178Y	gene mut. Thymidine kinase(TK) locus	-	-	Rat liver S-9 fraction	Acrolor 1254	11.7 – 1500 µg/ml[1] vehicle: ethanol
Test substance: PARSOL SLX; batch No. 270033 GLP statement: Yes According to OECD 476 (1997) : yes[2] [1] The solubiliy limit in tissue culture medium was c. 90 µg/ml. The test substance was tested well above its solubility limit up to 1500 µg/ml (the precipitate was removed by post-treatment cell washing). No marked toxicity was observed at any dose level tested in the absence or presence of S-9. [2] In accordance with the guidelines, each study was repeated in an independent confirmatory experiment.						

Acceptability
The present study is considered acceptable.

Conclusions
The test substance did not induce mutation at the TK locus of mouse lymphoma cells in the presence or absence of metabolic activation.

Ref.: 10

3.3.6.2 Mutagenicity/Genotoxicity *in vivo*

No data submitted

3.3.7. Carcinogenicity

No data submitted

3.3.8. Reproductive toxicity

3.3.8.1. Two generation reproduction toxicity

No data submitted

3.3.8.2. Teratogenicity

No data submitted

3.3.9. Toxicokinetics

No data submitted

3.3.10. Photo-induced toxicity

3.3.10.1. Phototoxicity / photoirritation and photosensitisation

Taken from SCCNFP/0079/98

Photo-toxicity

Guinea pig
A study was carried out according to GLP and in accordance with CTFA guidelines. Female SPF animals of the spotted Himalayan strain were used. Ten animals formed the test group and 5 animals the control group.

Both flanks were prepared by the use of electric clippers. The animals were narcotised and 4 circular test sites, 2 cm² in area, were delineated on both flanks. The skin was then pre-treated with 2% DMSO in ethanol to enhance skin penetration. The active ingredient was diluted as required in distilled water, and distilled water was used on the control animals. The active ingredient was applied in concentrations of (%) 25, 50, 75 and 100 on the sites on the flanks of the test animals, and distilled water to the sites prepared on the control animals. The volume of application was 0.025 ml in each case. The sites on the left flank were then irradiated with a nonerythemogenic dose of UVA, 20 J/cm². The right flanks were not irradiated. The source of the radiation was a Philips Actinic "TLD" lamp 36/08, emitting 104 ergs/cm²/second at 320-400 nm.
Reading was at 24, 48 and 72 hours after the application. The protocol called for the radiation to be carried out 2 hours after the application, but it is noted that the interval was longer than this; the deviation was not considered to affect the results.

No lesions of any kind were found at any reading. There were no abnormalities on clinical observation. There were no differences between the groups in body weights. There was no contemporaneous positive control, but a record is given of an experiment in the same laboratory to the same protocol, 2 months earlier, using 8-methoxypsoralen as the active ingredient. This showed strongly positive results with concentrations of the active agent of (%) 0.03, 0.1, 0.3 and 1. Under the circumstances of the experiment, there was no evidence of a photo-toxic effect associated with the active ingredient.

Ref.: 8

Photo-allergy

Man
A test according to the method of Kaidbey and Kligman was carried out in 30 volunteers, 23 female and 7 male. All subjects completed the test. The skin types of the subjects varied from I to III. Exclusions served to ensure that the subjects were suitable for the tests proposed. A xenon arc was used to produce UV radiation, and suitable filtering removed any wavelengths below 290 nm. For the challenge exposure, UVB was also filtered out. The output of the lamp was checked with suitable UV meters.

A MED for unprotected skin was determined for each subject. The area tested was 1 cm². Each dose of UV was 25% greater than the preceding one: the times of exposure were (minutes) 0.8, 1.0, 1.2, 1.5, 1.9 and 2.4. The sites were inspected about 20 hours after the irradiation, and a numerical scoring system used to quantitate the reaction.

Induction
The material tested was a 10% suspension of the active ingredient in a mixture of cyclomethicone and dimethicone copolyol (provided by the sponsors).Two sites, 3 X 3 cm square, were delineated on the upper back of each subject. One of these was a test area; the other was a test material control site, and was not exposed to radiation. Each site was

treated with 10 mg/cm² of the test material, and then covered with an occlusive dressing for 24 hours. These applications were made on days 1, 4, 8, 11, 15 and 18. After removal of the dressing on each occasion, an area of 1 cm² of the test site was irradiated with UVA and UVB. Radiation was 1 MED for the first 2 exposures, 2 MEDs for the next 2 exposures, and 3 MEDs for the final 2 exposures. The test material control site was shielded from radiation. The test and control sites were inspected and assessed on days 4, 8, 11, 15 and 18. It has to be assumed that a third site was prepared and subjected to UV irradiation in the absence of active ingredient; this is not mentioned in the description of the method, but a series of results is given for "UV control site -induction", and these results are also incorporated in the narrative section entitled "Results".

Challenge
Ten days after the end of the induction procedure, two fresh sites, near the original sites, were delineated; the area of each was 2 X 2 cm. Again, one (a) was a test site and one (b) was a test material control site. The active ingredient, as diluted, was applied in the same manner as previously described, and occlusively covered. In addition, a further similar area (c) was delineated to act as an irradiation control. After 24 hours, the patches were removed and areas (a) and (c) were irradiated with 10 J/cm² UVA. Area (b) was shielded during this procedure. The areas were then examined 24, 48 and 72 hours after irradiation. A numerical scoring system was used, and any reaction noted was presumed due to photosensitisation if the control sites were negative.

Results
There was no adverse reaction to the test material by itself. The induction sites which had been treated with active ingredient and been irradiated showed a reaction, but this was similar to, though somewhat less than the reaction induced by radiation alone; presumably the active ingredient offered some protection against the UV irradiation used in the induction phase of the experiment. In the challenge phase, 9 subjects showed slight erythema 24 hours after the challenge UVA irradiation, but this was exactly replicated in the irradiation control area. Thus it was concluded that the active ingredient showed no evidence of a capacity to produce irritation or photo-sensitisation under the circumstances of the experiment.

Ref.: 11

Guinea pig
Thirty SPF female animals of the Himalayan spotted strain were used: 20 in the test group and 10 in the control group. In addition, 4 female animals were used in a pre-test to determine the highest non-irritant concentration of the active ingredient.
The pre-test was carried out as follows. Both flanks were shaved, and the animals narcotised. Four test sites, each 2 cm² in area, were delineated on both flanks. These sites were then pretreated with 2% DMSO in ethanol. Thirty minutes later, the active ingredient was applied to the sites on the left flank at concentrations of (%) 25, 50, 75 and 100. Dilutions were made with distilled water. Thirty minutes later, the left flank was exposed to 20 J/cm² UVA. Following the exposure, the sites on the right flank were treated identically, except that irradiation was not used. Reading was at 24, 48 and 72 hours after exposure. In the text, it is stated that the highest non-irritant concentration was 75%, but in fact no reaction was seen at any concentration, including 100%.

The main test was carried out according to GLP and CTFA guidelines.
Induction: On the first day, 4 injections of Freund's complete adjuvant diluted 50/50 in physiological saline were used to delineate a previously prepared site in the nuchal area of the test animals. An area of 8 cm² was then marked in the nuchal area, and 0.1 ml of the active ingredient, without dilution, was applied to the area so delineated. This site was then exposed to 1.8 J/cm² UVB radiation and 10 J/cm² UVA. The light sources were: UVA, Philips Actinic "TLD" lamp 36/08, 320-400 nm; UVB, Philips UV-B-SunLamp TL 20W/12, 280-320 nm. The topical application and the irradiations, but not the injections, were repeated on

days 3, 5, 8 and 10. The control animals received the injections as noted above, but no other treatment.
Challenge: Three weeks after the beginning of the induction, both test and control animals had both flanks shaved. The animals were narcotised and 4 test sites 2 cm² in area were delineated on each side. The sites on the left flank were treated with active ingredient in concentrations (%) of 25, 50, 75 and 100; the volume applied was 0.025 ml in each case. The left flank was then irradiated with UVA 10 J/cm². Thereafter, the right flank of each animal was treated with the same concentrations of active ingredient, but this side was not irradiated. The control animals were treated in an identical manner. Reading was at 24, 48 and 72 hours after the exposure.

Results
One animal of the test group died on test day 23. This animal was subjected to necropsy, and it was decided that death had resulted from the narcotising procedure. No clinical abnormalities were found otherwise, and body weights showed no significant differences between test and control groups, although the pre-test animals lost weight between the acclimatisation procedure and the narcosis. This was not felt to be of biological significance. There were marked changes in the skin at the sites of the injections: the sites were initially oedematous and erythematous, and later became necrotic; crusting and desquamation was noted in the later stages of the test. No positive findings were made at the sites of the epidermal induction procedures. The challenge sites, likewise, showed no reaction in either test or control animals.
There was no contemporaneous positive control, but an account is given of a study carried out 6 months previously in the same laboratory, apparently to a similar protocol, using a 3% solution of 3,3',4'5-tetrachlorosalicylanilide in ethanol for induction and 0.003%, 0.01%, 0.03% and 0.1% solutions for challenge. This showed strong positive results at concentrations of 0.01% and above; there were slight reactions in the control animals at the highest concentration of the challenge solution, suggesting some sensitisation.

It was concluded that, under the circumstances of the experiment, the active ingredient under test showed no potential to produce photo-allergy.

Ref.: 9

3.3.10.2. Phototoxicity / photomutagenicity / photoclastogenicity

Taken from SCCNFP/0079/98

Photo-mutagenicity in mutation assay

Indicator cells	Endpoint	UV irradiation [2]	Result - act.	Activation	Dose range
Saccharo-myces cerevisae D7	gene mutation	c. 3 hr: UVA/UVB 3800/75 or 7600/150 mJ/cm²	-[1 3]	No metabolic activation applied	10 - 1000 µg/ml vehicle: ethanol

Test substance: Parsol SLX; Batch No.: 248452
GLP statement: Yes
According to OECD: OECD 480 does not provide explicit quidelines for photomutagenicity studies[3]

[1] A protective effect was evident. The elevated frequencies of convertants induced by the UV exposure decreased in a dose-related manner when the test substance was present in the medium.
[2] Strong positive responses were found with chlopromazin used as positive control
[3] The study was repeated in an independent confirmatory experiment

Saccharomyces cerevisiae D7 strain is capable of showing several events of genotoxic relevance, such as gene-mutation (reversion), mitotic recombination, gene-conversion, etc. It is highly sensitive to all these genotoxic events.

Acceptability
- The substance was not tested in the presence of metabolic activation, but this is not required according to COLIPA guidelines.
- There was no rationale for selecting 1000 µg/ml as the highest dose level. However, it may be assumed that this level was well above the solubility limit.
- This test (in *Saccharomyces cerevisiae*) is a rather unusual mutation assay.
- The present study is considered acceptable.

Conclusions
Under the conditions applied, the test substance was not mutagenic in this photo-mutagenicity test.

Ref.: 13

Photo-clastogenicity

Cytogenetic test on Chinese hamster lung cells exposed to simulated solar radiation
(Photo-mammalian chromosome aberration test)

Indicator cells	Endpoint	Result - act.	Result +act.	Activation		Dose range
				Tissue	Inducer	
Chinese Hamster V79 cells (derived from lung)	Crom. Ab.	-[2, 3, 4, 5]	not conducted	not applicable	not applicable	50 - 5000 µg/ml [1] solvent: ethanol (final concentration during treatment was 1%)

Test substance: PARSOL SLX; Lot 248452
GLP statement: Yes
According to OECD: OECD 473 does not provide explicit quidelines for photo-clastogenixcity studies

[1] There was no inhibition of the mitotic index; 5000 µg/ml is the maximal recomended concentration. The test substance precipated in the final treatment medium at concentrations between 500 and 5000 µg/ml, forming a homogeneous suspension (up to 2000 µg/ml) or a mixture with oily drops (at 5000 µg/ml).
[2] Treatment for 1.5 or 3 hrs including the preincubation and irradiation periods, followed by incubation for another 18 hrs until chromosome preparation
[3] UVA/UVB doses of 100/2.0 or 200/4.0 (exposure duration: 8 min. irradiation unfiltered light) or 500/6.3 mJ/cm (exposure duration: 25 min. irradiation passing through the plastic lid of the culture dish) were employed.
[4] Significant responses were found with chlopromazin used as positive control
[5] At a phototoxic UV dose (UVA 200/UVB 4.0) the occurrence of aberant metaphasis was clearly reduced compared to the negative control, indicating protective effects by the test article as it is expected for a UVB filter.

Acceptability
- The substance was not tested in the presence of metabolic activation, but this is not required according to COLIPA guidelines.
- The present study is considered acceptable.

Conclusions

The test substance was not clastogenic or aneuploidogenic when tested in Chinese hamster cells *in vitro*.

Ref.: 14

3.3.11. Human data

See point 3.3.2.1. Skin irritation, point 3.3.10.1 Photo-allergy

3.3.12. Special investigations

No data submitted

3.3.13. Safety evaluation (including calculation of the MoS)

Taken from SCCNFP/0079/98

Benzylidene malonate polysiloxane (UV Filter)

Based on a usage volume of 18 ml, containing at maximum 10 %

Maximum amount of ingredient applied	I (mg)	=	1800
Typical body weight of human		=	60 kg
Maximum absorption through the skin	A (%)	=	2%
Dermal absorption per treatment	I x A	=	36 mg
Systemic exposure dose (SED)	I x A / 60 kg	=	0.6 mg/kg bw/d
No observed adverse effect level (rat, oral 90 day study)	NOAEL	=	1000 mg/kg bw/d
Margin of Safety	NOAEL / SED	=	1600

For the Margin of Safety after inhalation exposure, see 3.3.14

3.3.14. Discussion

In the present mandate, the SCCS was asked to take the recent acute inhalation data that lead to the classification of Polysilicone-15 as toxic by inhalation into account for the safety assessment. The safety of the substance for dermal application has been assessed in opinion SCCNFP/0079/98**.** The discussion in this section only refers to the safety assessment of the inhalation exposure.

Currently, in the SCCP/SCCS Notes of Guidance there is no indication on how to use acute inhalation studies for the safety assessment of cosmetic ingredients. Therefore a case-by case assessment needs to be applied. From the present acute inhalation study it is difficult to derive a dose-response relationship. The LC50 is estimated between 0.285 and 1.838 mg/l air.
Polysilicone-15 (Dimethicodiethylbenzalmalonate) is currently authorized as an UV-filter, in a concentration up to 10% without any further restrictions (76/768/EEC, annex VII/26). According to the dossier, typical concentrations of Polysilicone-15 in skin care products are in the range of 3% to 5%. In pre-pressurised hair sprays, the concentration of Polysilicone-15 is 0.05% and in pressureless pump sprays 1% at maximum.

Following application of skin care products such as sun milk or day care cream, according to the dossier, there will be no inhalation exposure of the consumer as the products are topically applied only and not sprayed thereby excluding the possibility of the generation of respirable aerosols. For the application of Polysilicone-15 in pressureless pump sprays and

in pre-pressurised hair sprays, the formation of aerosols and, as a consequence, a potential inhalation exposure of the consumer cannot be excluded.
According to the Technical Guidance Document on Risk Assessment (ECB, 2003), it is shown that aerosols with an MMAD greater than 10 - 15 µm are not respirable anymore for humans, i.e. the aerosol particle sizes above this cut-off will deposit in the upper regions of the lungs due to their large particle sizes. Only particles with a size being below 10 to 15 µm reach the gas-exchange region of the lung.

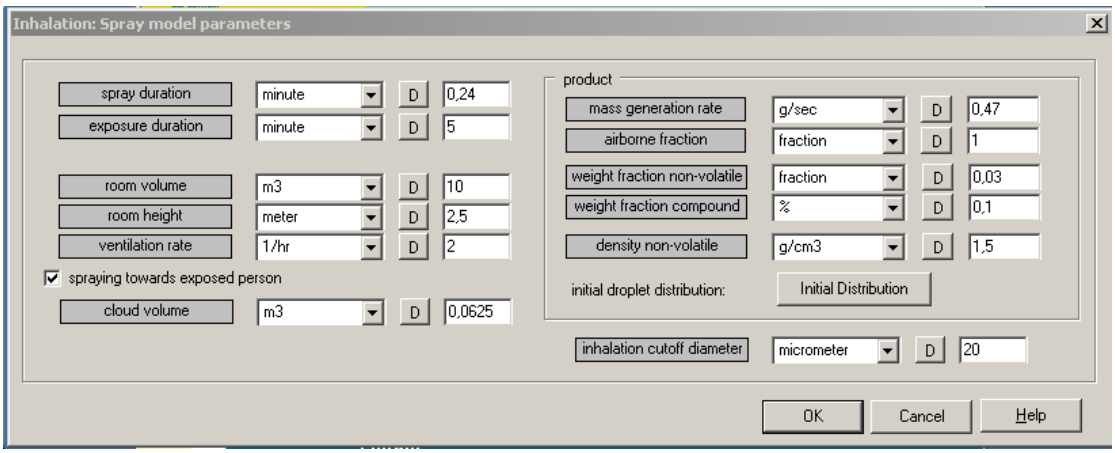
In general, particle sizes generated by pressureless pump sprays are about 120 µm and higher (Westenfelder, 2006). Particle sizes in this order of magnitude are not respirable for humans and will consequently not reach the gas exchange region of the lung. Therefore, consumers can safely use these pressureless pump sprays containing Polysilicone-15 and possible inhalation exposure during this use is not of concern for the consumer. It should, however, be clearly documented in the safety dossier what the typical particle distribution of the specific pressureless pump spray is, so the presence of particles in the inhalable range (<15nm) can be excluded.

Usually, the particle size of aerosols generated from hair spray applications with pre-pressurised hair sprays which use DME (Dimethylether) or propane/butane as propellants, are in the range of 40 – 120 µm (Ref. 11 (Subm. II). Furthermore, an assessment of the consumer risk after application of cosmetics performed by RIVM (Bremmer et al, 2006) demonstrated that the average MMAD of hair sprays typically used by consumers is about 35 µm (see Annex, Table 2 and Figure 2). Only 10% of the generated particles are smaller than 17 to 24 µm.

According to the applicant: " Parsol SLX is used at a very low concentration in these hairs sprays (< 0.1%) and regardless of the intrinsic acute inhalation toxicity potential of Parsol® SLX, the concentration of Parsol SLX in the hair spray is below a level which would trigger any considerations on health effects following inhalation. Based on both, the low concentration of Parsol SLX in the hair spray and the limited exposure towards particles following use of the hair spray (due to the large particle sizes occurring in the spray), the consumer can safely apply hair sprays containing Parsol SLX and a possible inhalation exposure during this use is not of concern for the consumer".

However, the SCCS is of the opinion that the weight of evidence should be assessed more quantitatively.

Therefore, the exposure to Polysilicone-15 (Parsol SLX) in pre-pressurized hairspray cans was calculated by the ConsExpo 4.1 model (www.consexpo.com), using the default use data for hairspray as presented in the associated database.



During a very short period of spraying a high peak concentration is observed, rapidly declines thereafter. In the model it is assumed that during spraying towards a person, the total amount that is sprayed is distributed in a volume of 1 m3, whereas thereafter there is complete diffusion throughout the room. It has been confirmed within an experimental set-up that very quickly after spraying there is a 'well stirred' situation (Delmaar and Bremmer 2009.).

The peak, and the event concentration during 5 minutes of exposure (= during and after spraying) were calculated. Two situations were simulated: one with a cut-off diameter on 20 um, one with a cut-off diameter of 15um (so only particles with a diameter of 20 resp. 15 um are available for uptake via inhalation).

Using worst case assumptions, as a weight fraction of 0.1% (in practice <0.05%), an airborne fraction 1 and an LC50 of 0.285 mg/l (= 285 mg/m3) the following MOEs were obtained:

Cut off diameter	20 um	MOE (based on LC50=285)		15 um	MOE(based on LC50=285)
Peak	0.2 mg/m3	1425		0.015 mg/m3	19000
Mean Event (5minutes)	0.0177 mg/m3	16101		0.00138	200000

From these worst case scenarios, the most severe case is the one in which it is assumed that all particles with a diameter of <20 um are respirable. In this case the MOE is 1425.

This MOE is obtained by comparing the LC50 from animal experimental exposure during 4h to a peak exposure of a few seconds under realistic use conditions for a hair spray.

When the exposure duration is scaled from 4 hours to 15 minutes (factor of 16) according to a slightly adapted Haber's Rule where $C^n \times t$ = constant (ten Berge 1986), with n=2, an additional factor of 4 in concentration is obtained, resulting in a MOE of 5700. As it can be seen from the table above, the MOE for assessing the peak exposure using a cut-off value of 15 um is much higher, and will also increase a factor of 4 using scaling.

In this present case, using a weight of evident approach, the SCCS is of the opinion that a MOE of 5700 is sufficient to conclude that after inhalation of 0.1% Polysilicone-15 present in a pressurized hairspray there is no risk for the consumer.

4. CONCLUSION

In 1999, the SCCNFP concluded that Polysilicone-15 (Dimethicodiethylbenzalmalonate) is safe for use in cosmetic products as a UV light absorber at a maximum concentration of 10%. In this case only exposure following dermal application was assessed.

In the present assessment, using a weight of evident approach, the SCCS concludes that the use of Polisilicone-15 at a concentration of 0.1% in pressurized hairsprays does not constitute a risk for the consumer.

With regard to the trigger sprays, no risk of the use of Polysilicone-15 is to be expected, as long as the generated particle sizes in the lower tail of the distribution are above the inhalable size (i.e. >15 um).

5. MINORITY OPINION

Not applicable

6. REFERENCES

Submission I, 1998

1. Bremer K.D. (1995) Toxicology Laboratories, Hoffman-La Roche, Ltd., Grenzacherstrasse 124, Basel, Switzerland
2. Bremer K.D. (1995) Toxicology Laboratories, Hoffman-La Roche, Ltd., Grenzacherstrasse 124, Basel, Switzerland.
3. Braun W.H. (1996) RCC, Research and Consulting Company, Ltd., Zelgliweg 1, 4452 Itingen, Switzerland.
4. Braun W.H. (1996) RCC, Research and Consulting Company, Ltd., Zelgliweg 1, 4452 Itingen, Switzerland.
5. Klecak, G (1994) RCC, Research and Consulting Company, Ltd., Zelgilweg 1, 4452 Itingen, Switzerland, and BRL, Biological Research Laboratories, Ltd., Wolferstrasse 4, 4414 Fullensdorf. Switzerland. [It is not clear what part was played by the latter institution].
6. Bremer K.D. (1996) Toxicological Laboratories, F. Hoffman-La Roche Ltd., CH-4070 Basel, Switzerland.
7. Schwarzenbach R (1998) Givaudan Roure RFd Dubendorf, Basel.
8. Arcelin G (1995) RCC, Research and Consulting Company, Ltd., 4452 Itingen and BRL, Biologica Research Laboratories, Ltd., Wofersttrasse 4, 4414 Fullinsdorff, Switzerland. [It appears that the role of the latter was the supply of experimental animals].
9. Arcelin G (1994) RCC Research and Consulting Company, Ltd.,4452 Itingen, Switzerland.
10. Ponti C.T. (1966) Quintiles England Ltd., Ledbury Herefordshire HR8 1LH, U.K.
11. Mulhern M. & Cuthbert J.A. (1997) Inveresk Research, Tranent, EH33 2NE, Scotland.

Submission II, 2008

1. DSM letter to Ms S. Lecrenier, European Commission, Enterprise and Industry DG, BREY 10/180, 1049 Brussels, Belgium
2. Polysilicone-15 – DSM inhalation safety evaluation (2008)
3. Bremmer, H.J., et al (2006) cosmetic fact sheet to assess the risk for the consumer, RIVM report 320104001/2006
4. Cosmetic Ingredient Review (CIR) Expert Panel (2003), Int. J. Toxicol., 22 (2), 11-35
5. European Chemicals Bureau, Technical guidance document on risk assessment, part 1 in support of Commission Directive 93/67/EEC, Commission Regulation (EC) n° 1488/94 and Directive 98/8/EC, EUR 20418 EN/1, pp. 294-295, 2003
6. Hellmann, G. (2006) Parsol SLX: worker safety aspects of manufacturing; DSM Nutritional Products, Ltd, Switserland
7. Opinion of the Scientific Committee on Cosmetic Products and non-Food Products, (1999) SCCNFP/0079/98
8. Silicones Environmental, Health and Safety Council (SEHSC), North America, 2001
9. Thiel et al, 2006, Report n° 2500376, Technical Trial Acute Inhalation
10. Weissenberger, 2006, Parsol SLX: Bestimmung der Viskosität, 2006
11. Westenfelder, H. (2006) Parsol SLX: worker safety and application aspects; DSM Nutritional Products, Ltd, Switserland

12. Wolz E. et al (2004), 4-hours acute inhalation toxicity study in rats, report n° 1017083

Additional References

Delmaar, JC and Bremmer, H (2009) The ConsExpo spray model - Modelling and experimental validation of the inhalation exposure of consumers to aerosols from spray cans and trigger sprays. RIVM report 320104005, RIVM Bilthoven, The Netherlands

ECB, 2003. Technical Guidance Document on Risk Assessment. European Chemicals Bureau, TGD Part I, pp. 294-295, 2003

ten Berge 1986: W.F. ten Berge. (1986). Concentration-time mortality response relationship of irritant and systematically acting vapours and gases. Journal of Hazardous Materials, 13, 301-309