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

CONCERNING

BENZOIC ACID AND SODIUM BENZOATE

adopted by the SCCNFP during the 20th plenary meeting
of 4 June 2002

1. Terms of Reference

1.1 Context of the question

Cosmetic products marketed in the EU may only contain those preservatives which are listed in Annex VI of the Cosmetics Directive 76/768/EEC, "List of preservatives which cosmetic products may contain".

The preamble of the Annex states that preservatives marked with the symbol (+) may also be added to cosmetic products in concentrations other than those laid down in the Annex for other specific purposes apparent from the presentation of the products.

Benzoic acid, its salts and esters bear the symbol (+) and can therefore be used in cosmetics at higher concentrations, as long as they are not employed as preservatives.

In its opinion of 17 February 1999 concerning the restrictions on materials listed in Annex VI of Directive 76/768/EEC on cosmetic products, the SCCNFP stated that those substances indicated by (+) in Annex VI, when incorporated into cosmetic formulations for non-preservative functions, should be subjected to the same restrictions in usage levels and warnings as when used for preservative effects.

If a preservative marked with the symbol (+) is added for non-preservative purpose to a cosmetic product in a concentration higher than that laid down in the Annex VI, data to substantiate its safety should be submitted to the SCCNFP.

1.2 Request to the SCCNFP

The SCCNFP was requested to review the data submitted to support the safety of benzoic acid, its salts and esters, when used at concentrations other than those laid down in Annex VI to Directive 76/768/EEC as preservatives, for other specific non-preservative purposes apparent from the presentation of the products and to answer the following question :

* Can benzoic acid, its salts and esters be safely used for non-preservative purposes in cosmetic rinse-off products at a maximum concentration of 2.5 % and in cosmetic oral-care products at a maximum concentration of 1.7 %?

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.

Only toxicological data for benzoic acid and its salt sodium benzoate have been made available for review. Therefore, there is no review of other salts of benzoic acid or any of its esters. These will require separate evaluation when the necessary data have been made available.

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. Chemical name

Benzoic acid (INCI name)
Sodium benzoate (INCI name)

2.1.2. Synonyms

Benzoic acid
Benzene carboxylic acid; benzene formic acid; carboxybenzene; benzene carboxylic acid; phenylcarboxyl acid; phenylformic acid

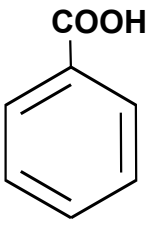
2.1.3. Trade names and abbreviations

2.1.4. CAS no.

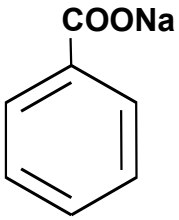
Benzoic acid : 65-85-0
Sodium benzoate : 532-32-1

2.1.5. Structural formula

Benzoic acid



Sodium benzoate



2.1.6. Empirical formula

	Benzoic acid	Sodium benzoate
Emp. Formula :	$C_7H_6O_2$	$C_7H_5O_2Na$
Mol. weight :	122.13	144.11

2.1.7. Purity, composition and substance codes

No data provided.

2.1.8. Physical properties

		Benzoic acid	Sodium benzoate
Appearance	:	solid	solid
Melting point	:	122 °C	> 300 °C
Density	:	1.321 g/cm^3 at 20 °C	

2.1.9. Solubility

		Benzoic acid	Sodium benzoate
In water	:	2.91 g/l at 20 °C	556 g/l at 20 °C

2.2. Function and uses

Benzoic acid, its salts and esters are used as preservatives (up to 0.5 %, calculated as acid) and currently as disinfectants (up to 2.5 %, calculated as acid) in cosmetic products.

Other uses for benzoic acid and its salts include regulated use as food preservatives, most suitable for foods, fruit juices, and soft drinks in an acidic pH range. In the EU, there are regulations controlling the maximum levels of benzoic acid and its salts for use in foodstuffs ready for consumption and the specific purity criteria of food additives. The levels are expressed as the free acid.

Non alcoholic drinks	150 mg/l
Alcoholic drinks	200 mg/l
Jams & jellies	500 mg/kg
Aspic	500 mg/kg

Ref. : AR 1, AR 2

In the United States, benzoic acid and sodium benzoate are on the FDA list of substances that are generally recognised as safe (GRAS). Both may be used as antimicrobial agents, flavouring agents and as adjuvants with a current maximum level of 0.1% in food. The FDA has not determined whether significantly different conditions of use would be GRAS. The FDA have sought fully up-to-date toxicology information.

Ref. : AR 3

Benzoic acid is used in oral medicines up to 0.15%, in parenteral medicines up to 0.17% and in topical drugs up to 0.2%. Benzoic acid is used as an active ingredient in anti-fungal cream with salicylic acid (3.0%) up to 6%.
Sodium Benzoate, expressed as benzoic acid, is permitted in oral medicines up to 0.5%, in drugs parenterally administered up to 0.5% and in cosmetics up to 0.5%.

Ref. : AR 4, AR 5

Benzoic acid is also an intermediate in the synthesis of phenol and caprolactam. Other end products include sodium and other benzoates, benzoyl chloride, and diethylene and dipropylene glycol dibenzoate plasticizers. Sodium benzoate is primarily a preservative and corrosion inhibitor (e.g., in technical systems as an additive to automotive engine antifreeze coolants).

TOXICOLOGICAL CHARACTERISATION

2.3. Toxicity

2.3.1. Acute oral toxicity

Benzoic acid

Rats : LD_{50} 1700 mg/kg
LD_{50} 2530 mg/kg

Mice : LD_{50} 1736 mg/kg
LD_{50} 2370 mg/kg

Ref. : 1, 2, 3, 4 and cited in 45

Sodium benzoate

Rats : LD_{50} 2100 mg/kg, calculated as acid (rats fasting 18 h pre-treatment)
LD_{50} 3140 mg/kg (only abstract available)
LD_{50} 3450 mg/kg, calculated as acid (rats not fasted)
LD_{50} 4070 mg/kg

Ref. : 5, 6, 7 and cited in 45

2.3.2. Acute dermal toxicity

Benzoic acid

Rabbit : $LD_{50} > 10\,000$ mg/kg
$LD_{50} > 10\,000$ mg/kg

Ref. : only cited in 45

2.3.3. Acute inhalation toxicity

Benzoic acid

Rats : $LC_{50} > 0.026$ mg/l/h

Ref. : only cited in 45

2.3.4. Repeated dose oral toxicity

Sodium benzoate

Groups of 6 male and 6 female Sherman rats were given 2 % (approx. 2.0 to 2.4 g/kg bw) or 5 % (5.7 g/kg bw for females and 7.8 g/kg bw for males) sodium benzoate in the diet for 28 days.
In the 5 % dose group, all females rats died by day 11 and. males by day 13.
In the 2 % dose group a slight significant body weight depression was observed in male rats.

Ref. : 37

28 young rats were given 5 % sodium benzoate in the diet for 21 days.
19 animals died within 14 days, the others within 21 days.

Ref. : 41

5 adult rats were given 5 % sodium benzoate in the diet for 35 days.
4 rats died between day 28 to 35.

Ref. : 41

Dose levels from 0.016 to 1.09 g sodium benzoate/kg bw were given to groups of 10 rats (5 male and 5 female) for 30 days with the diet. No dose related adverse effects were observed.

Ref. : 7

0.5, 1, 2, 4, and 8 % sodium benzoate in drinking water were administered for 35 days to groups of four female and four male Swiss albino mice.
In the 8 % dose level (approx. 24 g/kg bw/d) all mice died within 3 weeks. In the 4 % dose level (approx. 12 g/kg bw/d) 3 male and 3 female mice died within the 35-day observation period. The bodyweight of the surviving mice was substantially reduced. The 2 % dose level was chosen for a chronic toxicity (carcinogenicity) study.

Ref. : 36

2.3.5. Repeated dose inhalation toxicity

The available safety tests are not considered sufficient to support the safety of these ingredients in formulations where inhalation is a route of exposure. Inhalation toxicity data are needed to complete the safety assessment of these ingredients where inhalation can occur.

Ref. : AR 7

Benzoic acid
Ten CD rats per sex per group were exposed to 0, 25, 250, or 1200 mg benzoic acid dust aerosol/m^3 (analytical concentration; mass aerodynamic diameter [MAD]/sigma g (standard deviation): 0, 4.6/3.1, 4.4/2.1, 5.2/2.1; mass median aerodynamic diameter [MMAD]: 4.7 µm) for 6 h per day and 5 days per week over 4 weeks. Various serum biochemical, haematological, organ weight, and histopathological examinations were conducted. At >25 mg/m^3, an increased incidence of interstitial inflammatory cell infiltrate and interstitial fibrosis in the trachea and lungs in treated animals compared with controls was seen. Although the number of these microscopic lesions was higher in treated animals than in controls, there was no clear dose dependency for this effect. A concentration of >250 mg/m^3 resulted in upper respiratory tract irritation, as indicated by inflammatory exudate around the nares, and significantly decreased absolute kidney weights in females. In the highest dose group, one rat per sex died, and the body weight gain was significantly decreased in males and females compared with controls. In addition, a significant decrease in platelets (males/females), absolute/relative liver weights (males), and trachea/lung weights (females) was noted.
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Sodium benzoate
Studies concerning repeated exposure by inhalation to sodium benzoate were not identified in the available literature.

Ref. : AR 8

2.3.6. Sub-chronic oral toxicity

Benzoic acid

50 male and 50 female mice received 80 mg benzoic acid/kg bw/d by oral intubation for 90 days. At the end of the 90 day trial, 14 of the surviving mice were subjected to a restricted dietary intake (90 % restriction) and continued dosing (80 mg benzoic acid/kg bw/d) by oral intubation for up to 5 days. Weight loss and mortality was higher in the treated group compared with controls.
Also at the end of the 90 day trial, a further10 mice were tested for their tolerance to CCl_4 (test on liver detoxifying capacity) by giving a single dose (0.1 ml CCl_4) in by oral intubation at the end of the test. Mortality was higher in the treated group with reduced tolerance to CCl_4 compared with the control group.
The quality of the data are not sufficient to be conclusive.

Ref. : 38

Sodium benzoate

Groups of 4-5 male and 4-5 female rats received 0, 1, 2, 4, and 8 % sodium benzoate (0.6, 1.3, 2.6 and 6.3 g/kg bw/d) in the diet for 90 days.
4/8 animals died (average 13 days to death) in the 8 % dose level group, the average weight gain of the surviving rats was reduced and the relative liver and kidney weight was significantly increased. Moreover, frequent pathological lesion were noted (7/16).
Data are insufficient to justify NOAEL 4 % in the diet (2.6 g/kg bw/d).

Ref. : 6

2.3.7. Chronic toxicity

Benzoic acid

25 male and 25 female mice were given 40 mg/kg bw/d for 17 months. Benzoic acid was fed in a paste prior to the main feed.
The weight of liver, kidney and testes relative to body weight in mice sacrificed at the end of the test period were lower in the group receiving sorbic acid (40 mg/kg bw/d) than in the group treated with benzoic acid. No further details were given.

Ref. : 38

10 male and 10 female rats received 40 mg benzoic acid/kg bw/d for 18 months. Benzoic acid was fed in a paste prior to the main feed.
The rats developed some tolerance to a lethal dose of benzoic acid given terminally (25 % mortality after 4000 mg/kg bw compared to 100 % mortality on the control group given one dose of 3600 mg/kg bw). No further details were given.

Ref. : 38

2.4. Irritation & corrosivity

2.4.1. Irritation (skin)

Benzoic acid

Covered contact with neat benzoic acid for 24 h caused mild irritation in rabbits (only abstract available).

Ref. : 8, cited in 46

Single application of 500 mg benzoic acid on rabbits, response scored at 24 h and 72 h. Irritation score: 1.66/8.00 (only abstract available).

Ref. : 9, cited in 45

The flank site of 3 albino rabbits was exposed to 0.5 g of benzoic acid moistened with 0.25 ml Milli-RO water for 4 h using semi-occlusive dressings. Primary skin irritation index: 0.5 (only abstract available).

Ref. : 10, cited in 45

Chamber test (20 min/occlusive), open test (30 min): 15 µl of 5 % benzoic acid in petrolatum, 15 atopic and 16 non-atopic patients. The compound caused non-immunological contact urticaria. The atopics showed redness in both the Chamber test, 73 % and the open test, 80 %. Non-Atopics showed 80% redness in both the Chamber test and in the open test. There was no statistical difference between atopics and non-atopics.

Ref. : 15

Chamber test (72 h/occlusive): 0.1 ml of 7.5 % and 15 % benzoic acid in ethanol on scarified skin, 30 % benzoic acid in ethanol on normal skin (6 volunteers).

Results :

Scarified skin	:	7.5 % in ethanol : moderate irritant
		15.0 % in ethanol : marked irritant with erosions
Normal skin	:	30 % in ethanol : lowest irritant concentration

Ref. : 16, 17

Sodium benzoate

Test was carried out according to OECD guideline 404.
Results : no irritation effects on rabbits tested.

Ref. : 11, citation in 45

Application of 500 mg sodium benzoate/rabbit for 24 h; responses were scored at end of treatment and after 48 h.
Results : not irritating.

Ref. : 12, citation in 45

2.4.2. Irritation (mucous membranes)

Benzoic acid

Test was carried out according to OECD guideline 405.
Results : mild irritation on rabbit eyes.

Ref. : 20, citation in 45

Instillation of 50 mg into the conjunctival sac of 2 rabbits.
Results : moderate irritation.

Ref. : 21, citation in 45

Sodium benzoate

Application of 50 mg sodium benzoate/rabbit for 24 h; responses were scored at 24 h, 48 h and 72 h; postexposure observation time: 7 d.
Results : not irritating.

Ref. : 12, citation in 45

Test was carried out according to OECD guideline 405.
Results : Draize score 9.3.

Ref. : 22, citation in 45

2.4.3. In-use-test

Sodium benzoate:

A dish-washing & hand-cleaning product (no concentration given in the report; but given as 2.35% sodium benzoate in the Colipa submission, RIS-No. 1Z210086000A, Batch: MA 99-65) was tested for 28 days, application at least once a day, by 24 healthy volunteers with normal and 25 healthy volunteers with dry skin. 4 out of 49 had unwanted effects suggesting irritation. No details are given of their skin condition before application.

Ref. : 18

A dish-washing & hand-cleaning product (no concentration given in the report; but given as 2.35% sodium benzoate in the Colipa submission, Rez.Nr.: ES-99-147A) was tested for 28 days, in an use-test application at least once a day, by 25 volunteers with normal and 25 volunteers with dry skin. 8 had suffered from skin diseases: atopic eczema (5), neurodermatitis (2), others (1). 4 out of the 50 had unwanted effects suggesting irritation. No details are given of their skin condition before application.

Ref. : 19

2.4.4. Non-immunologic contact urticaria

Benzoic acid

Benzoic acid (5.0 % in petrolatum) was tested in an open test on 29 atopic and 74 non-atopic persons.

Results
Contact urticarial reactions to benzoic acid were seen in 27/29 (93 %) of the atopics and in 64/74 (87 %) of the non-atopics. In the Chamber test, 20 min occlusion (recorded 10 min later) 0.1 % benzoic acid in petrolatum and 0.05 % benzoic acid in water elicited reactions. When water was the vehicle, the reactions were oedematous.

Ref. : AR6

2.5. Sensitisation

Benzoic acid

Mouse Ear Swelling test: 20% benzoic acid in acetone for induction and challenge. No sensitising effects.

Ref. : 13

Patch test (48 h/occlusive) according to the ICDRG recommendations: 5 % benzoic acid in petrolatum, 627 patients. 8 patients showed positive reactions (1.3% of the tested). Some reactions may be interpreted as allergic but may have been irritant.

Ref. : 14

25 human volunteers were given five 48 h patch tests (during the 10 d period) with 2 % benzoic acid in petrolatum. None gave positive reactions when challenged 10-14 d after the induction phase by a final 48 h closed patch test with 2 % benzoic acid in petrolatum (only abstract available).

Ref. : 23, cited in 46

10 persons allergic to benzoyl peroxide were tested by a 48 h patch test with 5 % benzoic acid in a petrolatum. No reactions at 48, 72 and 96 h.

Ref. : 24

5203 patients with suspected contact dermatitis were patch tested with benzoic acid (no details were given). 34 patients (0.7 %) showed allergic reactions.

Ref. : 25

2.6. Reproduction toxicity

Sodium benzoate

Sodium benzoate at doses of 0, 1.75, 8, 38 and 175 mg/kg bw was administered by gavage to groups of at least 20 pregnant albino CD outbred mice and White albino rats on gestation day 6 to 15. Groups of 21 to 22 pregnant hamsters were dosed with 0, 3, 14, 65 or 300 mg/kg bw on gestation days 6 to 10. Groups of 10 Dutch-belted rabbits were artificially inseminated and then dosed by oral intubation with 0, 2.5, 12, 54 or 250 mg/kg bw on gestation days 6 to 18. Caesareans were performed on mice, rats, hamsters and rabbits on days 17, 20, 14 and 29, respectively.

There was no clearly discernible effect on nidation or on maternal or foetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

The NOEL in these studies were in all species identical with the highest dose tested :

mice and rats	NOEL : 175 mg/kg bw
hamsters	NOEL : 300 mg/kg bw
rabbits	NOEL : 250 mg/kg bw

Ref. : 39

Benzoic acid

In a study to determine the teratologic effects, benzoic acid was administered in a single dose of 510 mg/kg bw to 7 pregnant Wistar albino rats at day 9 of gestation. The malformations and resorption rates were comparable to those in control animals.

Ref. : 40

2.6.1. Multi-generation reproduction toxicity

Benzoic acid

A four generation study with benzoic acid was conducted in rats. Males and females of the first and second generation were fed 0.5 or 1.0 % benzoic acid in the diet (approx. 0.25 or 0.5 g/kg bw d). The third generation was treated for 16 weeks and generation 4 was treated until breeding.

There were no unfavourable side-effects on growth, food utilisation, duration of life, procreation, feeding of the offspring, weight of organs and histological pattern of organs in the 1 % dose group. In the 0.5 % group there was a significant prolongation of lifetime.
NOAEL : 500 mg/kg bw

Ref. : 41

2.7. Toxicokinetics (incl. Percutaneous Absorption)

Benzoic acid

^{14}C-labelled benzoic acid (4 - 40 µg/cm^2 dissolved in acetone) was applied to excised human skin in a static diffusion chamber. Samples of penetrated amounts were measured in 1- 2 hr interval over the first 24 hrs and 3-6 hrs interval over the remaining days. A median of 44.9 % of the applied benzoic acid was found in the receptor phase 48 hrs after application.

Ref. : 34

Percutaneous absorption of benzoic acid was studied in the Mexican hairless dog and in man. ^{14}C-labelled benzoic acid was injected subcutaneously and applied dermally to the neck skin of dogs. Human data were obtained from earlier investigations.

Ref. : AR 9

Excretion of benzoic acid in man was rapid, almost complete by day 3. In the dog, excretion was less extensive and greatly prolonged. This was accounted for by the persistence of benzoic acid in the skin.
Maximum absorption rate in man was 3.0 %/h, total absorption was 42.6 % of applied dose.

Ref. : 35

2.8. Mutagenicity/Genotoxicity

Benzoic acid

Benzoic acid (up to 10 mg/plate) was tested in the Salmonella/microsome test using *S. typhimurium* TA 92, TA 94, TA 98, TA 100, TA 1535 and TA 1537. No significant increases in the numbers of revertant colonies were detected in any *S. typhimurium* strains at the maximum dose.

Ref. : 26

Benzoic acid (up to 10 mg/plate) was tested in the Salmonella/microsome test using *S. typhimurium* TA 97, TA 98, TA 100, TA 1535, and TA 1537 with and without metabolic activation. Benzoic acid was nonmutagenic in this test.

Ref. : 27

Benzoic acid was tested in the Salmonella/microsome test using *S. typhimurium* TA 98, TA 100, TA 1535, and TA 1537 with and without metabolic activation. Benzoic acid was nonmutagenic in this test (< 0.0099 revertants/nmol).

Ref. : 28

Chromosome aberration test was carried out on benzoic acid (up to 1.5 mg/ml) using Chinese hamster lung fibroblasts. No metabolic activation system was applied. 8 % of the cells treated with benzoic acid (1.5 mg/ml) showed structural aberrations at 48 hrs after treatment.

Ref. : 26, 30

Sodium benzoate

Sodium benzoate (up to 3.0 mg/plate) was tested in the Salmonella/microsome test using *S. typhimurium* TA 92, TA 94, TA 98, TA 100, TA 1535 and TA 1537. No significant increases in the numbers of revertant colonies were detected in any *S. typhimurium* strains at the maximum dose.

Ref. : 26

Sodium benzoate was tested in the *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 in the presence and absence of S9 mix. Sodium benzoate was non-mutagenic in this test.

Ref. : 29

Chromosome aberration test was carried out on sodium benzoate (up to 2.0 mg/ml) using a Chinese hamster fibroblast cell line. No metabolic activation system was applied. 38 % of the cells treated with sodium benzoate showed chromosome aberrations at 48 h.

Ref. : 26, 30, 31

Chromosome aberration test was carried out on sodium benzoate using a pseudodiploid Chinese hamster cell line (DON). No metabolic activation system was applied.
Concentration above 0.002 mol/l showed twofold background effects of chromosome aberrations; no increase in the frequency of sister chromatid exchange was observed.

Ref. : 30, 32

Chromosome aberration test was carried out on sodium benzoate using human embryonic lung culture cells. Sodium benzoate produced no significant increase in the aberration frequency in the anaphase chromosomes when tested at the dosage levels 0, 2.0 µg/ml, 20 µg/ml and 200 µg/ml.

Ref. : 33

0, 50, 500 and 5000 mg sodium benzoate/kg bw was given orally to mice (single dose or once a day for 5 days) in an Host-Mediated Assay. Elevated mutant frequencies were seen with *Salmonella* TA 1530 in the acute intermediate dose level. The subacute and the other acute dose levels showed no increase in mutant frequencies. Test with *Salmonella* G 46 were negative while giving slightly elevated mutant frequencies. Tests with *Saccharomyces* D 3 produced no increases in recombinant frequencies.

Ref. : 33

Chromosome aberration of sodium benzoate was investigated *in vivo* in rats. Five rats per group were dosed with 0, 50, 500 and 5000 mg/kg bw by gastric intubation in an single dose or once a day for 5 days. The animals were killed at 6, 24 and 48 h after dosing in the acute study and 6 h after dosing in the subacute study. Bone marrow metaphase chromosomes were checked for aberrations. Sodium benzoate did not induce chromosomal aberrations in this test system.

Ref. : 33

A dominant lethal assay was conducted in rats with sodium benzoate. Following dosing by oral intubation (0, 50, 500, 5000 mg/kg bw, single dose or once a day for 5 days) treated male rats, 5 per group, were mated with two females per week for 8 weeks (acute study) or 7 weeks (subacute study). Fertility Index, number of implantations, corpora lutea, pre-implantation losses, resorptions/pregnant female and proportions of females with one or more dead, and two and more and overall dead implants were monitored.
In the acute study all three doses showed at week 8 significant, dose-related decreases, at week 7 significant dose-related increases of average pre-implantation losses. Average resorptions were significant, dose-related increased at the low and high doses of week 2 and the low and intermediate doses of week 7 were significantly increased over the control group. Overall dead implants were significant increased at week 7 for the low and intermediate doses and week 2 for the low dose.
In the subacute study significant increases of average pre-implantation losses were observed at a number of weeks but no significant increases of average resorptions were observed. Overall dead implants were not increased.
The authors considered sodium benzoate to be non-mutagenic in rats in this test system although positive results were obtained.

Ref. : 33

2.9. Carcinogenicity

Sodium benzoate

Sodium benzoate was given in 2 % in drinking water to 50 female and 50 male Swiss albino mice from weeks 5 on for lifespan. The average daily intake of sodium benzoate was 119.2 mg for a female and 124.0 mg for a male (approx. 5.95 - 6.2 g/kg bw/d).
There was no effect of the survival of the treated mice when compared with the untreated control. There were no significant differences between the tumour distribution in sodium benzoate-treated and untreated control mice.

Ref. : 36

Groups of 50 males and 52 female Fischer 344 rats were fed sodium benzoate at 1 or 2 % in the diet (approx. 0.5 or 1.0 g/kg bw/d) for 18 to 24 months. The control group consisted of 25 males and 43 females.
No clinical signs directly attributed to sodium benzoate were observed in treated animals. Differences in the average body weight between the treated and control groups were negligible. 40 rats died during the first 16 months, except for myeloproliferative disorder developed in one female control rat, all other dead animals showed pneumonia with abscess. Around 100 rats including those of the control group died after 16 months of hemorrhagic pneumonia with edema. However no differences in mortality rates between treated and control group was seen. Although a variety of tumours occurred among test and control rats of each sex, tumours in treated rats were similar in type and number of those of the control group.
NOEL: 1000 mg/kg bw/d

Ref. : 42

2.10. Special investigations

Serious metabolic disturbances in premature neonates given intravenous fluids with benzyl alcohol have been attributed to the accumulation of benzoic acid metabolites of the benzyl alcohol. This risk has led to the recommendation that the CNS stimulant, caffeine and sodium benzoate injection should not be given to neonates.

Ref. : AR 10

Benzoic acid can also displace bound bilirubin from albumin, putting neonates at risk from kernicterus.

Ref. : AR 11

Sodium benzoate, 250 mg/kg bodyweight as an intravenous infusion, is used as part of the treatment of hyperammonaemia that occurs as an inborn error in the urea cycle. It is also considered effective in reducing plasma-glycine in non-ketotic hyperglycemia, although it may not be effective in preventing mental retardation.

Ref. : AR 5

2.11. Conclusions

Studies for short-term, sub-chronic, or chronic oral exposure conducted according to current guidelines are not available for benzoic acid or sodium benzoate.
Benzoic acid and sodium benzoate have a low acute toxicity.

Oral subacute toxicity studies (28 days) showed that 2 % sodium benzoate (approx. 1 g/kg bw/d) in the diet is tolerated by rats. In an oral subacute toxicity study in mice (35 days) 2 % sodium benzoate in drinking water was taken to be the no-observed-effect-level (approx. 6 g/kg bw/d).

An oral subchronic toxicity study in mice (90 days) showed a minimal effect level of 80 mg benzoic acid/kg bw/d. Data are not sufficient to justify conclusion. In a 90-day feeding study in rats the no-observed-effect-level was 2.6 g sodium benzoate/kg bw/d, compared with other studies this seemed an unlikely NOAEL.

Data from a chronic study in rats are insufficient since no details of the study were given.

Sodium benzoate was tested in mice, rats, rabbits and hamsters for its embryotoxic and teratogenic effects in doses up to 300 mg/kg bw. Based on the results of these studies the No-observed-effect-level can be considered to be 175 mg/kg bw (highest dose in rats and mice).

A limited four generation study with benzoic acid was conducted in rats. Preliminary no-observed-(adverse-)effect level (NO(A)EL) derived from the highest dose of 500 mg/kg body weight per day. However data presented are summarised results and very old (1960. There was no influence on reproduction after application of up to 1 % (approx. 0.5 g/kg bw/d) in the diet.

Sodium benzoate in two long-term studies with rats and mice did not show evidence of carcinogenicity. No carcinogenic data for benzoic acid was given.

There are no adequate studies available on inhalation exposure.

Benzoic acid is a skin and eye irritant in rabbits. It causes irritation but very little allergic reactions on human skin. Benzoic acid causes non-immunological contact urticaria in humans. Sodium benzoate was not irritating on rabbit skin, but very slightly irritating the rabbit eye.

There is no indication that benzoic acid is a contact allergen. There was no data for sodium benzoate.

Benzoic acid and sodium benzoate were tested in the Ames test with a number of different Salmonella typhimurium strains with and without metabolic activation (S9 Mix). None of the tests gave any indication for mutagenic properties. Data came from compiled lists of tested substances, no original data were provided.
Benzoic acid gave equivocal effects in a chromosomal aberration test in Chinese hamster lung fibroblasts, in the absence of a metabolic activation system. No *in vivo* data on genotoxic activity of benzoic acid were provided.
In contrast two studies with sodium benzoate demonstrate positive results with Chinese hamster cells without metabolic activation. Sodium benzoate chromosomal aberrations were not induced *in vivo* in rats. A dominant lethal assay with sodium benzoate in rats did show a genotoxic effect. Therefore, a genotoxic activity of sodium benzoate cannot be ruled out. Data are old and insufficient for an adequate evaluation.

The percutaneous absorption of ^{14}C-labelled benzoic acid was studied *in vitro* with excised human skin. Total absorption was found to be approximately 45 %. These data were comparable to *in vivo* data in human, in which the total absorption of labelled benzoic acid was approximately 43 %.

Data is only given for sodium benzoate, but not the other salts or esters.

Other recommendations

The Scientific Committee on Food stated in its opinion on benzoic acid and its salts expressed on 25 February 1994 that: "An overall no-effect level of 500 mg/kg bw can be taken from the long-term and multigeneration studies. The Committee considers that a 100-fold safety factor is appropriate, giving a temporary ADI of 0 - 5 mg/kg bw, as the sum of benzoic acid and its salts, expressed as benzoic acid. Intolerance to benzoic acid in patients with asthma has been recorded but such observations are not relevant to the setting of an ADI."

Benzoic acid and sodium benzoate are included by the FDA in the list of generally recognised as safe (GRAS) food additives. JECFA (WHO, 1996) has allocated an acceptable daily intake (ADI) for benzoic acid and sodium benzoate of 0 - 5 mg/kg body weight.

There is a major difficulty in coming to scientific based conclusions on consumer health and safety of benzoic acid and sodium benzoate. Much of the data was based on citations in reviews. Original documentation and complete files should have been provided.

2.12. Opinion

The SCCNFP does not find the submission appropriate for a safety evaluation of benzoic acid and sodium benzoate for the applied “other uses” in cosmetic products.

2.13. References

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