

## OTC MEDICINES EVALUATION SECTION

### ASSESSMENT OF NEW TOPICAL EXCIPIENT

#### Butyloctyl salicylate

This is an assessment of a new topical excipient butyloctyl salicylate (salicylic acid, 2-butyloctyl ester; colourless or pale yellow liquid; trade name: HallBrite BHB; CAS No. 190085-41-7) submitted by [REDACTED] on behalf of [REDACTED]. Butyloctyl salicylate is present in a topical product [REDACTED] at a concentration of 1% (10 mg/g). The excipient is reported to function as a skin conditioning agent.

The sponsor has not provided any statement regarding marketing status of the excipient in other countries or adverse effects associated with the use of the excipient.

The sponsor has not provided any toxicity study but has provided a report of the Cosmetic Ingredient Review (CIR, 2003) Expert Panel<sup>1</sup> on several salicylates, including butyloctyl salicylate. Also, a Product Information (PI) Sheet and a Material Safety Data Sheet (MSDS) have been provided for HallBrite BHB (butyloctyl salicylate).

According to the CIR (2003), butyloctyl salicylate was of low acute oral ( $LD_{50} > 5000$  mg/kg; no deaths) and dermal ( $LD_{50} > 2000$  mg/kg; no deaths) toxicity in rats.

In a skin irritation study reviewed by the CIR (2003), the primary dermal irritation of butyloctyl salicylate was determined in rabbits according to the Federal Hazardous Substances Act (FHSA) methods (Leberco Celsis Testing 1996). In this study, butyloctyl salicylate caused very slight to well-defined erythema and oedema. One animal had "blanched skin" at the test site and two had flaking skin. The primary irritation index (PII) was 2.12. According to the FHSA, butyloctyl salicylate was not a "primary" dermal irritant in rabbits. However, the MSDS submitted by the sponsor as well as the PI for butyloctyl salicylate state that butyloctyl salicylate is not a primary irritant but has the potential for moderate irritation when applied at 100% concentration under occlusive conditions (PI 2.12). Based on these, the OTCMS evaluator considers butyloctyl salicylate as a moderate skin irritant.

In an eye irritation study reviewed by the CIR (CIR, 2003; Leberco Celsis Testing, 1996 using FHSA methods), butyloctyl salicylate produced minimal conjunctival irritation in 3 of 6 animals; all eyes were normal by day 3. Butyloctyl Salicylate was a minimal irritant.

In a guinea pig maximization test (reviewed by the CIR, 2003; Huntingdon Life Sciences, 1998), induction concentrations of butyloctyl salicylate were 5% in propylene glycol given intradermally and 100% butyloctyl salicylate applied topically. The challenge was performed 14 days after the last induction dose by applying patches of 50% and 100% butyloctyl salicylate to two separate sites. Five male guinea pigs, were used as control (vehicle + FCA for induction; test substance for challenge). During induction, the test sites were evaluated 24 h after dosing and during challenge, the sites were evaluated 24 and 48 h after patch removal. None of the animals challenged with 100% butyloctyl salicylate had a sensitisation

<sup>1</sup> Cosmetic Ingredient Review Expert Panel (2003). Safety assessment of salicylic acid, butyloctyl salicylate, calcium salicylate, C12-15 alkyl salicylate, capryloyl salicylic acid, hexyldecyl salicylate, isocetyl salicylate, isodecyl salicylate, magnesium salicylate, MEA-salicylate, ethylhexyl salicylate, potassium salicylate, methyl salicylate, myristyl salicylate, sodium salicylate, TEA-salicylate, and tridecyl salicylate. Int J Toxicol. 2003; 22 Suppl 3:1-108.

response. The "severity indices" at 24 and 48 h were 0.4 and 0.2, respectively, for the test group and 0.6 and 0.3, respectively, for the control group. One of 10 animals challenged with the lower concentration ie. 50% butyloctyl salicylate had a "clear dermal response". The "severity indices" at 24 and 48 h were 0.3 and 0.4, respectively, for the test group and 0.0 and 0.1, respectively, for the irritation control group (Huntingdon Life Sciences 1998). The CIR concluded that butyloctyl salicylate was not a skin sensitiser.

In a 28-day oral toxicity study (reviewed by CIR, 2003), groups of 5 Sprague-Dawley CD rats/sex were dosed with 15, 150, or 1000 mg/kg/day butyloctyl salicylate in corn oil for 28 days, while a control group was given vehicle only (Huntingdon Life Sciences 1998). At the end of the study, histological examination was restricted to the control and 1000 mg/kg/day groups. In the HD group, excessive salivation was observed in one HD female during week 2, and in 2 males and 2 females during week 3; one of the females also had "slight red stains on the snout" during week 3. Another HD female had lacrimation during week 3. In the HD group, prothrombin and activated partial thromboplastin times were increased. There were no treatment-related effects on body weights, feed consumption, motor activity, functional observational batteries, organ weights or histology. The no-observable-effect level (NOEL) was 150 mg/kg/day (Huntingdon Life Sciences 1998).

According to the CIR (2003), the mutagenic potential of butyloctyl salicylate in DMSO was determined in a standard plate incorporation assay and a preincubation assay using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and *E. coli* strain CM891 (WP2uvrA/ pKM101; Huntingdon Life Sciences 1998). Doses of  $\leq$  5000  $\mu$ g/plate were tested without and with metabolic activation. Negative and positive controls gave expected results. Butyloctyl salicylate was not mutagenic (CIR, 2003).

An *in vitro* mammalian chromosome aberration test was performed using human lymphocytes to determine the mutagenic potential of butyloctyl salicylate in DMSO (CIR, 2003; Huntingdon Life Sciences, 1998). Doses of 20 to 500  $\mu$ g/plate were tested without metabolic activation and of 500 to 2500  $\mu$ g/plate were tested with metabolic activation. Negative and positive controls gave expected results. No reproducible increases in the frequency of metaphases with aberrant chromosomes were observed; with a 3-h treatment, 20-h sampling time, a significant increase was observed in one of two cultures treated with 2500  $\mu$ g/plate with metabolic activation. The CIR (2003) concluded that butyloctyl salicylate was not clastogenic.

An OTCMS evaluation of tridecyl salicylate, a structurally-related chemical, revealed that tridecyl salicylate was of low acute oral and dermal toxicity; was a moderate skin sensitiser (maximisation test in guinea pigs) but was not a skin irritant in humans. Tridecyl salicylate was a slight eye irritant in rabbits. In *Salmonella typhimurium*<sup>2</sup>, tridecyl salicylate (10-10,000  $\mu$ g/plate; with and without 'metabolic activation', details of metabolic activation were not provided) was not mutagenic. Based on the evaluation of data submitted by two sponsors, and taking the CIR into consideration (including exposure calculations), the OTCMS approved a maximum of 5% tridecyl salicylate in topical products.

According to the CIR report, there were no significant toxic effects at ~500 mg/kg/day of tridecyl salicylate in a 15-week dietary study in rats. In a 2-year dietary study in rats, bone lesions were seen at 2% (~1000 mg/kg/day) but not at 0.7% (~350 mg/kg/day). Liver damage was seen in dogs exposed to 150 mg/kg/day in one study; kidney and liver weights were

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<sup>2</sup> Strains TA98, TA100, TA1535, TA 1537 and TA1538. Positive controls (sodium azide, 9-AA, 2-NF and 2-AA) were reported to increase the number of revertant colonies.

increased in another study at the same exposure, but no liver or kidney abnormalities were seen in a study at 170 mg/kg/day.

The CIR considered several skin sensitisation studies conducted in animals and humans. The clinical studies are shown in the table below. It appears that salicylic acid is unlikely to cause any skin sensitisation or photosensitivity at 2% although there may be sensitising reactions in people susceptible to skin allergy or in people prone to salicylate allergy.

*Clinical studies on salicylates (CIR, 2003)*

Study	Test system (Reference)	Test substance	Findings (Reference)
<b>Skin sensitisation (predictive studies)</b>			
Maximisation test	Humans, n = 25	Salicylic acid, 20% for induction; 10% for challenge	Not a sensitiser. (Kligman, 1966)
RIPT, 2 studies	Humans, n = 99 or 101	Salicylic acid, 2% (moisturising cream)	Not a sensitiser. Except for a doubtful response or erythema (without oedema) during induction, there were no reactions. (TKL Research Inc, 1993).
RIPT, 2 studies	Humans, n = 193 or 198	Salicylic acid, 2% (gel)	Not a sensitiser. A few subjects (5 during induction and 7 during challenge in the first study; 2 during induction and 5 during challenge in the second study) had scores of + (faint, minimal reaction) or 1 (erythema). (HRL, 1993; 1997).
Maximisation test	Humans, n = 25	Ethylhexyl (octyl) salicylate, 4%	Not a sensitiser. (Anonymous, 1976)
Maximisation test	Humans, n = 27	Methyl salicylate, 8%	Not a sensitiser. (Opdyke, 1978)
<b>Skin sensitisation (Provocative studies)</b>			
Single patch for 24 hours	Eczema patients, n = 230	Salicylic acid, 5%	3 patients had positive reactions (erythema and infiltration for >24 h after patch removal). (Thune, 1969).
Standard test battery from 1979-1983	n = 9701	Salicylic acid 5% in petrolatum	11 (doubtful) positives. Repeat patch tests in 8 of these 11 patients using 0.5%, 1%, 2% and 5% salicylic acid showed positive reaction (to 1-5% salicylic acid) in one patient who had a history of immediate type hypersensitivity to oral salicylates. (Goh an Ng, 1986)
Skin test	Patients with history of aspirin intolerance, n = 31	Intradermal: 0.02 mL of 0.1% sodium salicylate	One positive reaction (Patriarca <i>et al.</i> , 1976)
Prauxnitz and Kustner passive transfer test (PK test)	Patients with history of aspirin intolerance, n = 31	0.1% sodium salicylate for challenge for passively sensitised sites (0.1 mL serum)	No positive reaction (Patriarca <i>et al.</i> , 1976)
Passive cutaneous anaphylaxis test	Patients with history of aspirin intolerance, n = 31	0.05 g sodium salicylate	Two positive reactions (Patriarca <i>et al.</i> , 1976)
<b>Phototoxicity/photosensitisation</b>			
Phototoxicity	10 subjects	2% salicylic acid (cream)	No detectable phototoxicity (Ive Laboratories, 1993)
Phototoxicity (2 studies)	10 subjects	2% salicylic acid (gel)	No phototoxicity (HRL, Inc. 1993)

Photosensitisation (2 studies)	25 subjects	2% salicylic acid (cream)	No detectable photosensitisation (Ive Laboratories, 1993)
Photosensitisation (2 studies)	28 subjects	2% salicylic acid (gel)	No sensitisation or photosensitisation (HRL, Inc. 1993; 1997)

The CIR report also stated that urticarial reactions were increased when sodium salicylate was given to subjects who had reactions to ingested aspirin. In another study in aspirin-sensitive patients with chronic urticaria, positive reactions were seen with sodium salicylate. However, 5% salicylic acid in petrolatum did not induce non-immunological contact urticaria in 110 patients.

The CIR Panel review considered three primary issues associated with the use of salicylates in general: (1) reproductive and developmental toxicity; (2) skin irritation; and (3) increased sun sensitivity (increased UV radiation damage with the use of any exfoliant).

According to the information provided in the CIR report, reproductive and/or developmental toxicity was seen in rats at oral doses of  $\geq 10$  mg/kg/day of salicylic acid or sodium salicylate (Waltman *et al.*, 1973; Fritz and Suter, 1985). Thus, in a study conducted with 12.5 or 25 mg/kg po of sodium salicylate administered on gestation days 20-21, neonatal mortality was increased in a dose-dependent manner. The NOEL for this study appears to be 4.2 mg/kg sodium salicylate ( $\sim 3.6$  mg/kg of salicylic acid). In two other studies in rats, increased gestation period, duration of parturition, bleeding at parturition and/or neonatal mortality were seen at 10 mg/kg of sodium salicylate or salicylic acid, administered on gestation days 20 and 21.

Some reports suggest that reproductive and developmental toxicity to salicylates is associated with exposures to large, therapeutic concentrations of salicylic acid (a metabolite of salicylates). According to the IPCS (1996)<sup>3</sup>, and Campbell and Halushka (1996)<sup>4</sup>, there is no evidence that moderate therapeutic doses of salicylates cause fetal damage in human beings; however, babies born to women who ingest salicylates for long periods may have a significantly reduced weight at birth. In addition, there is an increase in prenatal mortality, anaemia, antepartum and postpartum haemorrhage, prolonged gestation and complicated deliveries. These effects occur when salicylates are administered during the third trimester, and thus its use during this period of pregnancy should be avoided. However, based on consideration of a risk assessment of a representative cosmetic product used on a daily basis, exposure from the cosmetic product was estimated by the CIR to be lower than that following ingestion of a "baby" aspirin (81 mg) on a daily basis. The CIR contended that the reproductive and developmental toxicity from the daily use of a baby aspirin was not significant.

Dermal application of a product containing 1% butyloctyl salicylate can be estimated to be 1.62 mg/kg bw/day of salicylic acid<sup>5</sup>. Assuming only 23% is dermally absorbed<sup>6</sup>, the systemic exposure is 0.37 mg/kg/day (salicylic acid) which is only 10 times lower than the oral NOEL for developmental toxicity in rats ( $\sim 3.6$  mg/kg/day; see above). Since sufficient

<sup>3</sup> International Program on Chemical Safety. Salicylates. 1996; Reference cited: Insel, 1996. [www.inchem.org](http://www.inchem.org)

<sup>4</sup> Goodman & Gilman's The Pharmacological Basis of Therapeutics (9<sup>th</sup> edition), pages 627-628.

<sup>5</sup> 1% butyloctyl salicylate in 18 g of a topical product is equivalent to 180 mg of butyloctyl salicylate or 81 mg of salicylic acid per day; 1.62 mg/kg bw/day of salicylic acid for a person weighing 50 kg.

<sup>6</sup> In humans, total dermal absorption of salicylates was 23% over 5 days; the greatest absorption rate of 0.54%/h was observed at 12-24 h (Feldman & Maibach, 1970, cf. CIR, 2003). However, in humans with active psoriasis and in some animal studies, dermal absorption is much higher (up to  $\sim 80\%$ ). According to Goodman & Gilman's The Pharmacological Basis of Therapeutics (9<sup>th</sup> edition), salicylic acid is rapidly absorbed from the intact skin, especially when applied in oily liniments or ointments, and systemic poisoning has occurred from its application to large areas of skin.

exposure margin does not exist, the use of 1% butyloctyl salicylate in topical products may have the potential to cause reproductive and developmental toxicity.

According to the TGA website (Prescribing medicines in pregnancy, 4th edition), non-steroidal anti-inflammatory drugs (including sodium salicylate) are in 'Pregnancy Category C'<sup>7</sup>: "These agents inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. Continuous treatment with NSAIDs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided".

The CIR Expert Panel was also concerned about increased sun sensitivity for all salicylates since these chemicals are known to have exfoliant action on the skin and repeated administration of salicylates may effectively increase exposure of the dermis and epidermis to UV radiation. On the other hand, salicylates are also known to absorb UV radiation, which would decrease the exposure. The CIR Expert Panel reasoned that the appropriate conclusion would be that salicylates could be used safely as exfoliants, if expressly formulated to avoid increasing a user's sun sensitivity.

High exposure to salicylates can cause 'salicylate intoxication' which is often more serious in small children (<4 years) than in older children, due to an early development of a metabolic acidosis rather than a respiratory alkalosis (Winters *et al.*, 1959, cf. IPCS, 1996).

Overall, in toxicity studies evaluated by the CIR (2003), undiluted butyloctyl salicylate was of low acute oral and dermal toxicity in rats; showed moderate skin potential but only minimal eye irritation potential in rabbits; and was not a skin sensitisier in a maximisation study in guinea pigs. In two studies, butyloctyl salicylate was not genotoxic. In a 28-day oral toxicity study in rats, the NOEL was reported to be 150 mg/kg/day.

The CIR (2003) has evaluated several salicylates, including butyloctyl salicylate and concluded that these chemicals are safe as used "when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection".

The OTCMS has approved (July 2005) the use of tridecyl salicylate at up to 5% in topical products.

Salicylates are absorbed percutaneously and systemic exposure may have the potential to cause reproductive and developmental toxicity. Butyloctyl salicylate should not be used in children below 4 years, in people who are hypersensitive to salicylates, and in asthmatics. However, based on available information on structurally-related chemicals, it appears that butyloctyl salicylate may not have significant toxicity at concentrations up to 1% in topical products.

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<sup>7</sup> Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

## **Recommendation**

Butyloctyl salicylate has been found to be suitable for use as a topical excipient in OTC medicines and is for dermal use only. The maximum concentration of butyloctyl salicylate in products should not exceed 1%. Butyloctyl salicylate is not to be included in topical products intended for use in the eye.

Salicylates have the potential to cause increased sun sensitivity and hence products containing tridecyl salicylate should be formulated in such a way as to avoid this potential.

Products containing butyloctyl salicylate should not be used in:

- children below 4 years
- the last trimester of pregnancy
- people who show hypersensitivity to salicylates
- asthmatics.

Appropriate warning statements may be required on the label for the above warnings.

[REDACTED]  
OTC Medicines Section  
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