CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification: Hexyl salicylate

EC Number: **228-408-6**

CAS Number: **6259-76-3**

Index Number: **-**

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1 RATIONALE FOR READ-ACROSS

A read-across is proposed from data on salicylic acid (SA), sodium salicylate (NaS) and methyl salicylate (MeS) for classification for fertility and developmental toxicity.

The justification for this read-across consists on a similar metabolism pathway. Indeed, HS, MeS, NaS and SA were all metabolized initially to free salicylate (by hydrolysis for HS), then mainly to salicyluric acid and conjugated salicylic acid compounds, with a small proportion of oxidative metabolites. This scenario is consistent with the scenario 1 (analogue approach for which the read-across hypothesis is based on (bio)transformation to common compound) of the Read-across Assessment Framework.

Figure AII - 1: Biotransformation of HS, MeS and NaS into SA

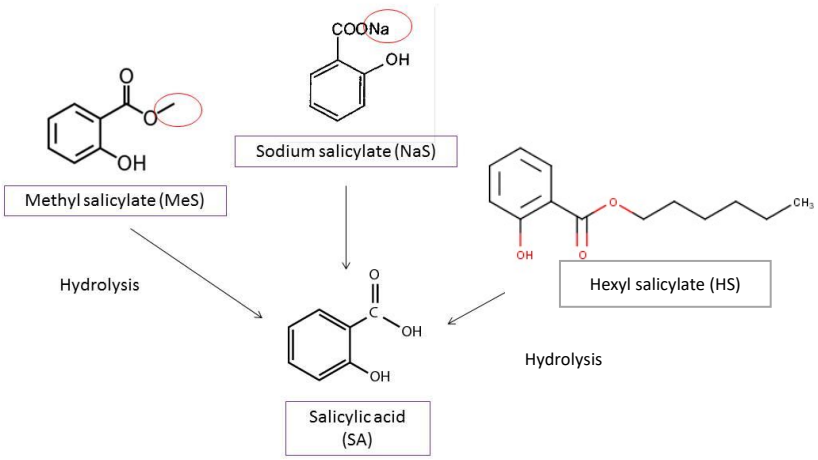


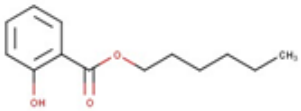
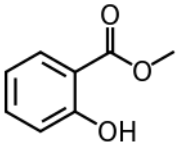
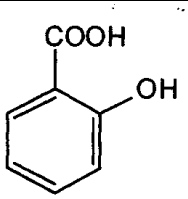
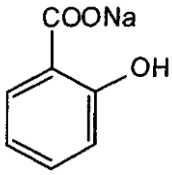
Table AII - 1: Read-across scenario

	Parent substances	(Bio)transformation	Common compound	Non-common compound
Target	Hexyl salicylate (HS)	HS → SA + hexanol	Salicylic acid (SA)	Hexanol
Source	Methyl salicylate (MeS)	MeS → SA + methanol	Salicylic acid (SA)	Methanol
Source	Sodium salicylate (NaS)	NaS → SA + sodium	Salicylic acid (SA)	Sodium
Source	Salicylic acid (SA)	-	Salicylic acid (SA)	-

2 DATA MATRIX

In order to assess the relevance of this read-across, physico-chemical and toxicological data of HS, MeS, SA and NaS were compared. Data on HS were based on the Evaluation Report submitted by the Netherlands. Data on methyl salicylate were based on French Evaluation during SeV process (ongoing process). Data on SA and NaS were based on the available CLH report on SA but also from a literature research and on registration data published on ECHA website. It should be noted that most of the reported data are of low quality (studies not following guideline, only small parameters examined…). This was summarized in the table below.

Table AII - 1: Comparative data on physico-chemical parameters and human health endpoints

Endpoints	Hexyl salicylate	Methyl salicylate	Salicylic acid	Sodium salicylate
CAS number	6259-76-3	119-36-8	69-72-7	54-21-7
Structure				
Classification	No harmonized classification	No harmonized classification RAC September 2019: Acute Tox 4 – H302; Repr. 2 – H361d, Skin Sens. 1B – H317, Aquatic Chronic 3 – H312 Classification not yet included in an ATP.	Acute Tox 4 – H302 Eye Dam. 1 – H318 Repr. 2 – H361 (ATP13)	No harmonized classification
Solubility	2 mg/L at 23°C (Sev)	0.67g/L in water at ambient T, miscible in chloroform, ether, anhydrous methanol, ethanol, benzene, CCl4, oils (Sev)	Slightly soluble in water (2.17 mg/ml at 20°C); soluble in organic compounds 0.262% at 25°C in CCl_4, 0.775% at 25°C in benzene, 27.36% at 21°C in propanol, 34.87% at 21°C in ethanol, 396% at 23°C in acetone (Merck 2006)	Soluble in water 125g/100ml in water, 17g/100ml in methanol (Merck 2006)
Log P_{ow}	5.5 (Sev)	2.55 (Sev)	2.26 (Hansch, Leo 1995)	No data
Vapour pressure	7.7 x 10^{-5} kPa at 23°C (Sev)	10 Pa at 22°C 100 Pa at 51°C (Sev)	8.2.10^{-5} mmHg at 25°C (Daubert, Danner 1989)	No data
ADME	Salicylates were metabolized into salicylic acid. During this first step of metabolism, hexanol is formed after hydrolysis of hexyl salicylate, methanol after			

	hydrolysis of methyl salicylate; sodium after hydrolysis of sodium salicylate.			
Acute toxicity	LD_{50} oral and dermal > 5000 mg/kg bw	Acute Tox 4 – H302 ATE = 580 mg/kg bw LD_{50} dermal > 2000 mg/kg bw	Acute Tox 4 - H302 LD_{50} oral = 400-3700 mg/kg LD_{50} dermal > 2000 mg/kg bw	LD_{50} oral = 930-1200 mg/kg LD_{50} dermal > 2000 mg/kg bw
	Acute oral toxicity of salicylates is moderate, with toxicity generally decreasing with increasing size of the ester R-group. Likely related to the relative proportion of the molecular weight release as SA followed hydrolysis.			
Irritation	The mean scores for skin irritation do not trigger classification as a skin irritant (registration data)	No dermal irritation (FR SeV)	Moderately to minimally irritant in solutions to animal skin. Mild transient irritant to human skin in formulation. Dermal irritation in repeated-dose toxicity studies (CIR, 2003). No dermal irritation (registration data)	No dermal irritation (registration data)
	No eye irritation (registration data)	Eye Dam 1 required based on *in vitro* study (FR SeV)	Eye Dam. 1	Mildly irritation to eye (registration data)
Sensitisation	One LLNA positive (registration data) Modified Draize test positive (Lapczynski *et al*. (2007)) Maximisation assay negative (Lapczynski *et al*. (2007)) Low incidence of reactions in humans. Classification proposed	Skin Sens. 1B agreed by the RAC in September 2019	One LLNA positive (CIR, 2003). Contradictory results in LLNA, negative in a MEST and QSAR model predict no sensitisation potential of SA (registration data)	QSAR model predict no sensitisation potential of NaS. Only 1 positive reaction among 31 patients (registration data)
Repeated-dose toxicity	No data available for oral route	Target organs: bone and liver (FR SeV)	No target organ reported (registration data), bones (Abbott, 1978)	Target organs: kidney and liver (registration data); bones (Abbott, 1978)
Mutagenicity	Negative in Ames test (registration data)	Negative in bacteria and mammalian cells (FDA, 2006).	Not mutagenic in bacteria and in mammalian cells. Contradictory data for chromosome aberrations (SCCNFP, 2002).	Negative in Ames test and DNA cell-binding assay using Ehrlich ascites cells (CIR, 2003)
	No data available	Negative in a micronucleus assay (FDA, 2006)	Negative *in vivo* in sister chromatid exchange assay and in chromosome aberration assay (Giri, 1996)	Contradictory data for clastogenic effects *in vivo* (Giri, 1996)
Carcinogenicity	No data available	Not carcinogenic in rats by oral route (registration data)	Not carcinogenic in rats by oral route (CIR, 2003).	No *in vivo* data (CIR, 2003)
Toxicity on reproduction	No data available	No effect on fertility (FDA, 2006)	No adequate study on fertility. Inhibition of human sperm	No adequate study on fertility. Increased duration of

			mobility *in vitro* (CIR, 2003). Increased mean gestation period after treatment on GD20 & 21 in rodents (CIR, 2003).	gestation (CIR, 2003)
Toxicity for the development	No data available	Fetal death and malformations (neural tube defect, kidney) (registration data; FDA (2006)). Classification as Repr. 1B proposed by France in a CLH report submitted in 2018 Repr. 2 agreed by the RAC in September 2019, based on a read-across with SA.	Foetal death, growth retardation and malformations (kidney and skeletal) in rats. Classification Repr. 2 – H361 agreed by the RAC in March 2016 based on experimental studies with salicylic acid, methyl salicylate, sodium salicylate and acetylsalicylic acid and on human data with acetylsalicylic acid.	Foetal death, growth retardation and malformations (mainly skeletal) in rats.
	When various salicylates were administered to rats twice on GD9 (subcutaneous route) (Koshakji, 1973), different developmental toxicity profiles were observed depending on the salicylate tested. When comparing molecular structure and developmental findings, it appears that COOH and OH must be adjacent for inducing teratogenic effects. It also appears that substitution of OH group by SH or NH_2, substitution of COOH for $CONH_2$ or addition of OH groups to SA eliminates teratogenic properties.			

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