Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Salicylic acid

EC Number: 200-712-3
CAS Number: 69-72-7

CLH-O-0000001412-86-110/F

Adopted

10 March 2016

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10 March 2016

CLH-O-0000001412-86-110/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonized classification and labelling (CLH) of:

Chemicals name: **Salicylic acid**

EC number: **200-712-3**

CAS number: **69-72-7**

The proposal was submitted by **Novacyl S.A.S.** and received by the RAC on **17 October 2014.**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonized System (GHS).

PROCESS FOR ADOPTION OF THE OPINION

Novacyl S.A.S. has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **28 October 2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **12 December 2014**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Radu Branisteanu**

Co-rapporteur, appointed by RAC: **Anna Biro**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2. The RAC opinion on the proposed harmonized classification and labelling was reached on **10 March 2016** and was adopted by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	**No current Annex VI entry**										
Dossier submitter's proposal	xxx-xxx-xx-x	Salicylic acid	200-712-3	69-72-7	Acute Tox. 4 Eye Dam. 1	H302 H318	GHS07 GHS05 Dgr	H302 H318			
RAC opinion	xxx-xxx-xx-x	Salicylic acid	200-712-3	69-72-7	Repr. 2 Acute Tox. 4 Eye Dam. 1	H361d H302 H318	GHS08 GHS07 GHS05 Dgr	H361d H302 H318			
Resulting Annex VI entry if agreed by COM	xxx-xxx-xx-x	Salicylic acid	200-712-3	69-72-7	Repr. 2 Acute Tox. 4 Eye Dam. 1	H361d H302 H318	GHS08 GHS07 GHS05 Dgr	H361d H302 H318			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Background: Toxicokinetics and read-across

Supplementing the database with read-across from structural analogues

The class of salicylic compounds has been widely studied but limited information is available for salicylic acid itself. In particular, no study could be identified specifically addressing the adverse effects of salicylic acid on sexual function and fertility in adult males and females. To overcome the information gaps, the Dossier Submitter (DS) performed a read across to salicylic acid from sodium salicylate (NaS), methyl salicylate (MeS), and o-acetyl salicylic acid (ASA). The justification provided relies on toxicokinetic data.

Short description of key information

Upon oral administration in rats, salicylic acid, MeS, NaS and ASA are all rapidly absorbed even at high concentrations. A publication by Davison (1961) has compared the oral absorption and metabolism of MeS and NaS in rats and humans with that of ASA.

Several publications demonstrated that salicylic acid is the initial metabolite (hydrolysis product) for the related salicylates: ASA, NaS, MeS. Salicylic acid is found in blood both bound to plasma albumin and as the unbound (free) moiety. Therefore, many studies use the term "plasma (serum) salicylate" as an equivalent. Unless specified otherwise, the plasma (serum) salicylate levels refer to the total (*i.e.* bound and free) concentration. This expression will be used also in this document.

Plasma analyses in rats showed rapid hydrolysis to free salicylate for MeS, NaS and ASA, resulting in comparable plasma concentrations of salicylate at 60 minutes post dosing. However, in humans hydrolysis of MeS to salicylic acid was slower and less complete. The publications of Rainsford *et al.* (1980) and Tjalve *et al*. (1973) revealed that salicylic acid was found in the stomach, liver, kidney, lungs, bone marrow, intestine, inflamed paws and spleen of rats; the *in vivo* distribution of ASA and the methyl ester of ASA (AME) were very similarly to that observed with salicylic acid. Tjalve *et al.* (1973) confirmed that there was no difference between the distribution of salicylic acid compared to ASA in mice after injection. In mice, rats, monkeys and humans, salicylic acid was found in the placenta and readily passed into the foetus.

Studies reported by Emudianughe (1988) and McMahon *et al.* (1989), both performed on rats, demonstrated that salicylic acid is metabolised to two major urinary metabolites, salicyluric acid and salicyl-glucuronic acid and oxidative metabolites (2,3- and 2,5 -dihydroxybenzoic acid) and other conjugated salicylic acid compounds (salicyl ester glucuronide or salicyl ether glucuronide). All these metabolites as well as unchanged salicylic acid are eliminated almost entirely via the urine.

In summary, the toxicokinetics of salicylic acid and the selected salicylates indicate that following absorption, the initial metabolic step for MeS, NaS and ASA is hydrolysis to free salicylate. Since salicylate is the principal species circulating in plasma at comparable concentrations, it follows that data from the selected salicylates are acceptable for read across to salicylic acid.

RAC notes that read across from close structural analogues to salicylic acid has been previously used by The Scientific Committee on Cosmetic Products and Non-Food Products intended for consumers (SCCNFP).

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

Summary of the studies on acute toxicity

A study report by BioFax (1971) was chosen as key study. This study did not follow a published test guideline (TG) but it was reported as being similar to OECD TG 401. The tests were performed in male rats with salicylic acid of unspecified purity, administered (probably by gavage) at a concentration of 25% in corn oil. The result was an LD_{50} of 891 mg/kg bw. The signs of intoxication were hypoactivity and muscular weakness. At necropsy, inflammation of the gastrointestinal tract was reported in the dead animals. Publications by Hasegawa *et al.* (1989) and Schlede *et al*. (1995) on NaS were chosen as supporting studies. Both were performed with a protocol similar to OECD TGs and gave values for LD_{50} of 1580 mg/kg bw and between 500 and 2000 mg/kg bw, respectively. In summary, all LD_{50} values were in the range 500 - 2000 mg/kg bw, demonstrating that salicylic acid is harmful via the oral route (Acute Tox. 4; H302).

Discussion

All three studies have limitations as reflected by the Klimisch score of 2. The key study and one of the supporting studies (Hasegawa *et al.,* 1989) presented experimental results obtained with salicylic acid. The second supporting study, Schlede *et al.* (1995), is an acute toxic class method assay collaborative study using sodium salicylate; the study was included because read across from sodium salicylate to salicylic acid was considered justified. The DS chose a conservative value for comparison with the classification criteria.

Comments received during public consultation

Four out of five comments supported the DS proposal, i.e. Acute Tox 4 via the oral route.
One comment disagreed with the proposal and recommended no classification. The reason for the disagreement was the low reliability of the key study.

Assessment and comparison with the classification criteria

Two salicylic acid and one NaS studies (all considered as "reliable with restrictions") have been included in the assessment; all the LD_{50} values are in the range of 300-2000 mg/kg. Therefore RAC considers that the argumentation presented by the DS supports the proposal and agrees with classification of salicylic acid as **Acute Toxicity Category 4, H302** (Harmful if swallowed) according to the CLP criteria.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier submitter's proposal

Summary of the studies on eye irritation

Three *in vivo* studies (all having a Klimisch reliability score of 2) were presented for evaluation of this endpoint.

The publication by Sugai *et al*. (1991) was chosen as the key study. The primary eye irritation potential of salicylic acid was evaluated according to the Draize method. Under the conditions of this study, salicylic acid induced severe irritation not recovering within 21 days of treatment. Draize scores for cornea and conjunctivae were 54.1 and 10.3, respectively.

In the study report (BioFax, 1971), chosen as a supporting study, the primary eye irritation potential of salicylic acid was evaluated with a method similar to a Draize test. In this study, salicylic acid induced severe irritation. Mean scores for cornea, iris and conjunctivae were 51.5, 40.3 and 38.7 at 24 h, 48 h and 72 h, respectively.

In a publication by Ohno *et al.* (1999), a Draize eye irritation test was conducted with NaS. Average scores at 24 h after application for cornea, iris and conjunctiva were 21.7, 3.3 and 12.7, respectively. This publication was considered acceptable as a supporting study.

An *in vitro* Bovine Corneal Opacity/Permeability (BCOP) test evaluated salicylic acid as part of a program to develop alternatives for *in vivo* eye irritation tests (Gautheron, 1992). Results for opacity but not permeability were reported for salicylic acid tested at up to 10%. Based on the following opacity readings, salicylic acid was considered a severe irritant: 0.1%: 7.2 +/- 1.7; 1%: 70.2 +/- 8.4; 5%: 88.2 +/- 5.1; 10%: 98.7 +/- 7.4.

Comments received during public consultation

All five comments received were in favour of the proposed classification, *i.e.* Eye Damage Category 1 (causes serious eye damage). However, one of the comments recommended that the DS complete the dossier with tables showing all the findings of the studies.

Assessment and comparison with the classification criteria

The assessment is based on three *in vivo* studies (two with salicylic acid and one with NaS) and one *in vitro* study (performed with salicylic acid). The NaS study was also taken into account. Taken together, the results indicate that salicylic acid causes severe eye damage; the DS mentions the crystal mechanical irritation and chemical properties as causes for the damage. The irritation did not recover within 21 days following treatment.
RAC considers that the argumentation presented by the DS supports the proposal and agrees with the classification of salicylic acid as **Eye Damage Category 1, H318** (causes serious eye damage) according to the CLP criteria.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

The animal data on fertility and development presented by the DS was sufficient to evaluate both endpoints. With respect to human data, the information was not separated between the two endpoints and the DS presented them together.

Effects on fertility, animal data

The assessment of salicylic acid is based on read-across data from studies on MeS and ASA. The studies used in the assessment are summarised in the table below:

Summary of the fertility studies taken into assessment

Study design, test material, species	***Doses***	***Conclusions***
3-generation study (Collins *et al*., 1971), MeS, male and female Osborne-Mendel rats	500, 1500, 3000 and 5000 ppm (equivalent to 22.5, 67.5, 135, 225 mg/kg bw/d as salicylic acid) in the diet	No statistically significant decrease in fertility index was reported at any dose for any generation.
2-generation study (Abbott & Harrisson, 1978), MeS, male and female Wistar rats	2500 and 5000 ppm (equivalent to 113 and 225 mg/kg bw/d as salicylic acid) in the diet	Non-significant decrease in mating performance for the first generation.
2-generation study (Abbott & Harrisson, 1978), MeS, male and female mice	2500 and 5000 ppm (equivalent to 324 and 648 mg/kg bw/d as salicylic acid) in the diet	No adverse effects were reported on any reproductive parameter.
2-generation study,(NTP, 1984a) continuous breeding protocol , MeS, CD-1 mice	25, 50 and 100 mg/kg bw/d (22.5, 45 and 90 mg/kg bw/d as salicylic acid) by gavage	No effects on fertility were reported.
1-generation study (NTP, 1984b), continuous breeding protocol , MeS, CD-1 mice	100, 250 and 500 mg/kg bw/d (90, 225 and 450 mg/kg bw/d as salicylic acid)	No effect on fertility index.
Fertility test, (Schardein *et al*., 1969), ASA , male and female rats	A single dose level of 0.4% in the diet (210 mg/kg bw ASA, equivalent to 161 mg/kg bw as salicylic acid)	ASA did not significantly affect male or female fertility. This dose caused moderate bw depression in males and severe bw depression in females.

Note: all the studies in the table above have a Klimisch reliability score of 2

The studies showed a number of deficiencies in relation to current TGs in terms of parameters studied, but the results were consistent. No statistically significant effect on fertility was reported in any study. In addition, 2-year chronic toxicity studies in rats and dogs (Webb, 1963) showed no abnormalities in sexual organs (testes/prostate or ovaries/uterus).
The adverse effects on reduced viability of offspring reported primarily in rats represent developmental toxicity rather than a reduction in the fertility of either males or females.

Developmental effects: animal data

The developmental effects presented are from studies with salicylic acid, ASA or NaS. Since the interspecies differences are a key element in the discussions of the developmental effects, the studies will be presented according to the species rather than the test material.

Studies in Rats

In a pre-natal developmental toxicity study (Tanaka *et al*., 1973a, *reliability 2*), salicylic acid was administered to pregnant Wistar rats at levels of 0.06%, 0.1%, 0.2% and 0.4% in the diet (50.7 +/- 0.6, 77.4 +/- 1.0, 165 +/- 2.1, 205.9 +/- 18.9 mg/kg bw/d, respectively) on gestation days (GD) 8-14. The two lower doses (*i.e.* 50.7 and 77.4 mg/kg bw/d) caused neither maternal nor foetal effects. A marked body weight loss of dams was observed in the 0.4% group at the beginning of salicylic acid administration, but a gradual increase in bw was then observed after GD 11 day. This decrease in bw was assumed to be due to a decrease in food intake, but no deaths were observed. No marked changes were noticed in other groups. Very low uterine weights of foetuses and significantly lower placental weights were obtained in the 0.4% group, but there were no marked differences in the number of corpora lutea or in the rate of nidation in all groups. The dose of 0.2% (165 mg/kg bw/d) caused foetal effects (foetal anomalies and growth retardation) in the absence of maternal effects. This dose resulted in a maternal serum concentration of about 116 microgram/mL. The highest dose of 0.4% (205.9 mg/kg bw/d) induced maternal effects expressed as temporary body weight loss with toxic symptoms (salivation, piloerection) and the following foetal effects: high fetal mortality (no live foetuses in 9/15 dams examined), high frequency of complex anomalies (cranioschisis, myeloschisis, pes varus, oligodactyly etc.) and dose-related foetal growth retardation. At the dose of 0.2%, the body weight and length and the tail length were statistically significantly decreased. At the dose of 0.4% litter size and body weight and length as well as tail length were statistically significantly decreased. The general conclusion of the authors was: "*It is clear from the results obtained in the present and previous experiments that salicylic acid through oral route has a teratogenic effect on rat*". Also, "*none of the metabolites of salicylic acid produce congenital anomalies. The teratogenic effects of salicylic acid may be attributable to a direct action of the compound on fetal tissues as relatively well distribution was found in foetus and amnionic fluid in the present experiment*".

The derived no adverse effect levels (NOAELs) were: maternal - 0.2% (165 mg/kg bw/d) and developmental - 0.1% (77.4 mg/kg bw/d).
A parallel study by gavage (Tanaka, 1973b) at 75, 150 and 300 mg/kg bw/d gave similar results, with NOAEL (maternal) of 150 mg/kg bw/d and NOAEL (development) of 75 mg/kg bw/d.

In an experimental segment II study (Gupta *et al*., 2003, Klimisch score 1), ASA was administered by oral gavage both in single and multiple dose studies.

In the single dose study the dosage was as follows: GD9 (0, 250, 500 and 625 mg/kg bw), GD10 (0, 500, 625 and 750 mg/kg bw), GD11 (500, 750 and 1000 mg/kg bw). No maternal deaths were noted in any dose group; there were no treatment related clinical signs or necropsy findings. Dose-dependent decreases in body weight gain and food consumption were observed for dams dosed on the days when treatment was administered. Body weight gains were decreased for the duration of the study, whereas the food consumption remained decreased for 2 days after the administration of ASA. The decrease in body weight gain was only partly due to reductions in food consumption as the magnitude of this change was minimal compared with the body weight gain decrements. The decrease in foetal weight and the number of foetuses contributed to the decrease in body weight gain. A dose-dependent decrease in the number of viable foetuses was

observed in dams administrated ASA on each day with the exception of 500 mg/kg dose group on GD11 although the decreases were not always statistically significant. An increase in resorptions with an associated increase in post-implantation loss was observed in the mid- and high-dose groups on GD10 and GD11. The number of viable foetuses decreased in almost all dose groups, with accompanying decreases in uterine weight in all dose groups on GD9 and GD11 and in the mid- and high-dose groups on GD10. Significant increases in malformations were reported only from 500 mg/kg for GD9 administration or from 625 mg/kg for GD10 or GD11.

In the multiple dose study the dosage was of 0, 50 mg/kg bw/d (38 mg/kg bw/d as salicylic acid), 125 mg/kg bw/d (96 mg/kg bw/d as salicylic acid), 250 mg/kg bw/d (192 mg/kg bw/d as salicylic acid). Maternal toxicity was reported as a dose-dependent decrease in maternal body weight that was statistically significant at the mid-dose (85% of control) and high-dose (52% of control). Hence, the decreases in food consumption were partly responsible for the decrease in body weight. Irregular respiration and sporadic salivation were noted in the dams at 250 mg/kg bw/d. One dam given 125 mg/kg bw/d was killed as moribund on GD13 due to severe weight loss and associated inappetence. At necropsy, this dam showed no unusual findings and no other mortality was noted. The foetal toxicity was expressed as a dose-dependent decrease in the number of foetuses. This was due to the dose-dependent decrease in the numbers of viable foetuses across the dose group. The malformations were statistically significantly increased only in the high dose (250 mg/kg) group and included ablepharia, craniorachischisis, bent forepaw, kinked tail, protruding tongue, gastroschisis, ectopic adrenal, ventricular septal defect (VSD), diaphragmatic hernia, hypoplastic kidney and hypoplastic testis.

Fritz and Giese (1990, Klimisch score 2) performed a gavage study on 17-19 females per dose with NaS during GD 6-15. The dosage was 30, 60 and 90 mg/kg bw/d. The maternal toxicity was seen only at the highest dose and was described as some reduction in food consumption. The foetal toxicity could be observed at the mid dose (in the absence of maternal toxicity) as a dose-related delay in growth. At the highest dose the foetal toxicity was described as a dose-related delay in growth and malformations in 30% of the foetuses, the most common malformation being cranio(rachi)schisis (22.7% of the foetuses).

Nakatsuka and Fujii (1979, Klimisch score 2) treated SD rats with ASA on GD 7-17 with 3 doses: 50, 100 and 200 mg/kg bw/d. Neither maternal nor foetal toxicity were present at the lowest dose. At the middle dose, dose-dependently decreased foetal bodyweight was described in the absence of maternal toxicity. At 200 mg/kg bw/d maternal toxicity was described as significantly decreased bodyweight and the foetal toxicity as: increased number of foetal resorptions and malformed survivors, dose-dependently decreased foetal bodyweight, 21 foetuses (8.5%) with gross malformations, significantly delayed ossification and increased frequency of skeletal malformations (mainly absence, fusion, fragmentation or deformation of vertebral and costal bones) or variations.

Schardein *et al*. (1969, Klimisch score 2) treated rats with ASA at doses of 99 mg/kg bw/d (0.2 % in diet), 224 mg/kg bw/d (0.4% in diet) and 250 mg/kg bw/d (by gavage) during GD 6-15. Maternal toxicity was reported at 0.2% in diet (29% food intake depression with a 52% weight gain depression) and 0.4% in diet (17 % food intake depression and a 90% weight gain depression). Fetal toxicity was registered at all doses with skeletal malformations at 99 mg/kg bw/d and 100% resorptions at the two higher doses.

Studies in Rabbits

ASA was administered by oral gavage to pregnant New Zealand White (NZW) rabbits at 125, 250 or 350 mg/kg bw/d on GD 7-19 (Cappon *et al*., 2003, Klimisch score 2). Maternal body weight gain was significantly reduced in the mid and high dose groups from GD 7 to 13. Food consumption was also reduced in these groups. Three does given the high dose and one given

the mid dose died during the study. There were no treatment-related effects on corpora lutea, implantation sites, pre-implantation losses or embryofoetal mortality. There were no treatment-related visceral or external anomalies. Reduction in mean foetal weight at 350 mg/kg bw/d was the only developmental adverse effect reported at this maternally toxic dose.

In a supporting study (Schardein *et al*., 1969, Klimisch score 2), rabbits received ASA at 200 or 250 mg/kg bw/d on GD 6-13 or GD 6-18. ASA induced maternal toxicity. A single kit of a dam had hydrocephaly. There were no skeletal malformations among those examined, but the limited number (9) could have precluded finding such defects. There were no significant findings in kits of the control dams. Under the conditions of this test, ASA induced maternal toxicity and foetotoxicity.

Studies in Monkeys

The study of Wilson *et al.* (1977) is not compliant with OECD TGs; its original purpose was to elucidate toxicokinetic aspects, namely the distribution and embryotoxicity of ASA in rats versus monkeys. Since the administration of ASA was performed during the organogenesis period, some conclusions may however be drawn. Unlike other studies, the protocol of administration was twice per day by gavage. For rats the doses were 100, 150, 175 and 200 mg/kg bw (twice daily on GD 9-12) and for monkeys 100 and 150 mg/kg bw (twice daily, for 10 days starting on GD 23). The same doses were given to non-pregnant females of both species for the purpose of determining comparative plasma concentrations.

Maternal toxicity in rats was described as occasional death and weight loss at 200 mg/kg bw twice daily. Foetal toxicity in rats showed significant effects on intrauterine death, growth and malformations rates at 150 mg/kg (twice daily). At this dose, the percentage of dead or resorbed foetuses was 34% and increased to 73% at the highest dose of 200 mg/kg bw twice daily. Also, the percentage of malformed survivors (including those with cardiac, facial, brain, spinal, tail and other skeletal defects) increased from 55% at 150 mg/kg to 100% at 200 mg/kg bw.

In monkeys, the number of aborted or resorbed foetuses was the same (3) at both dosages. At the dose of 100 mg/kg bw twice daily the foetal effects were reported as growth retardation and at 150 mg/kg bw (twice daily), growth retardation and malformations such as gross abnormality, cranioshisis and cystic kidney were reported. At both doses there were also foetuses which were observed to be normal. The conclusion was that 150 mg/kg twice daily is in the teratogenic range.

A comparison of serum concentration of salicylic acid in mothers vs. whole embryo concentration was performed. Unbound salicylate in rat plasma ranged from 30% to 50% of the total plasma concentration and was closely paralleled by the concentration in the rat embryo. Unbound salicylate in monkey plasma was lower, ranging from 17% to 30% of the total plasma concentration and was to some degree paralleled by the concentration in the monkey embryo. The greater embryotoxicity of ASA in the rat compared to the monkey correlated with higher concentrations and longer duration of concentrations in the respective embryos on a day-to-day basis. The general conclusion was that this association only partially explains the difference between species; the mode of action within the embryo must not be neglected.

The study of Wilson *et al.* (1977) has also been considered in the opinion on salicylic acid issued by The Scientific Committee on Cosmetic Products and Non-Food Products intended for consumers (SCCNFP) in 2002.

Conclusion by the dossier submitter

Based on the argumentation presented above, the DS proposed that salicylic acid should not be classified as a reproductive toxicant, either for the fertility or developmental endpoints.

Comments received during public consultation

First public consultation

The German CA agreed with the proposal of the DS for no classification. The French CA commented that based on the level of detail provided, the relevance of the observed effects to humans cannot be concluded. The Belgian CA considered that information provided in two databases -Toxnet (toxicology data network, US) and eMC (electronic Medicines Compendium, UK) - indicates some concerns, mainly related to development and lactation; they recommended that this information should be assessed in depth as this could be supportive evidence for classification. Following detailed argumentation, the Netherlands CA concluded that the developmental effects in rats are not considered secondary to the maternal toxicity. Therefore, based on the teratogenic effects of salicylates observed in rats and the limited evidence in studies with monkeys, but not in rabbits, the Netherlands CA proposed that salicylate should be classified as Repr. 1B; H360D (May damage the unborn child). One comment received during the public consultation period disagreed with the read across from MeS to salicylic acid because it "is not sufficiently justified, only NOAEL/LOAEL are reported for experimental studies."

Second (targeted) public consultation on the reproductive toxicity of salicylic acid

The French CA commented that it is not possible to easily compare the plasma levels between ASA and salicylic acid in animals and humans. Also, there is not enough evidence not to consider the effects seen in animals. Consequently, a classification for salicylic acid is supported.

Assessment and comparison with the classification criteria

Summary of the animal studies

The results of the studies demonstrated that salicylic acid has an embryo-/foetotoxic effect in rats with dose-dependent growth delays, foetal death and malformations. Early developmental effects were clearly seen in the absence of maternal effects. The teratogenicity of salicylic acid may be attributable to a direct action of the compound. This finding is further supported by the mechanistic study of Greenaway (1982) in which teratogenicity of salicylate in rat embryos was shown independent of maternal factors after exposure *in vitro*. However, although there was a general resemblance in terms of skeletal and internal organ abnormalities observed, the pattern of malformations following exposures to salicylic acid and ASA is slightly different, as described in the studies of Tanaka and Gupta. One explanation could be the differences in the experimental protocol, such as the moment of exposure during organogenesis. However, differences in effects following exposure to salicylic acid and ASA were shown in *in vitro* cultured rat embryos (Yokoyama, 1984): the anomalies induced by ASA were systemic (*e.g.* crown-rump length significantly reduced) while those induced by salicylic acid were more localized (*e.g.* facial anomalies).

The study in monkeys also showed teratogenic properties with ASA but with lower magnitude. By contrast, the effects in rabbits were limited to slight growth retardation and were present only at doses much higher than in the rats and monkeys. No skeletal malformations were reported and at the highest dose only one kit of a dam had hydrocephaly.

Overall, salicylic acid was shown to have teratogenic properties but with species differences in potency: strong in rats and lower in monkeys. In contrast, the teratogenic potential in rabbits was practically non-existent.

Developmental effects: human information

Despite its long usage, data regarding human exposure to salicylic acid itself is lacking. To fill the information gap, an assessment was performed using human data on ASA. This approach is appropriate as stated in the read across paragraph above under 'RAC general comments'; however, the fact that ASA is a pharmaceutical product raises a series of limitations to the use of this information due to the range of doses specific to medical usage. ASA is part of a class of medications generically called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Most of the therapeutic effects are common within the group (analgesic, antipyretic, anti-inflammatory activity) but ASA also has an antiplatelet effect. In addition, the mechanism of action differs: unlike the other NSAIDs, ASA inhibits cyclooxygenase (COX) in an irreversible manner, affecting the COX-1 variant more than the COX-2 variant of the enzyme.

Epidemiology. Therapeutic doses of acetylsalicylic acid

The dosage of ASA in prophylactic/therapeutic applications vary according to specific prescriptions/recommendations but guidance ranges for adults are presented by the DS in the following table:

Indicative doses of ASA used in therapy

Indication	**Unit dose strength (mg)**	**Dose regimen**	**Duration**	**Daily dose as ASA (mg/kg bw/d) for a 60 kg person**	**Equivalent dose as SAL (mg/kg bw/d; conversion factor of 0.77)**	**SAC designation**
Treatment of rheumatic fever	350-500	Up to 6500 mg/d in divided doses	Short term (1-2 weeks, then 60-70 mg/kg bw/d for 1-6 weeks)	Up to 108	Up to 83	**"High dose"**
Treatment of severe inflammatory conditions such as osteo- or rheumatoid arthritis, and SLE-associated arthritis	350-500	3000-5400 mg/d in divided doses	Medium to long-term	50-90	38.5-69	
Treatment of mild pain or fever	350-500	Up to 4000 mg/d, 1-2 tablets, 2-3 times per day	Short-term (typically 1 to 4 or 5 days)	11.7-66.7	9-51	**"Standard therapeutic dose"**
Prophylaxis for myocardial infarction, angina stroke etc.	75-350	1 tablet per day	Medium- to long-term	1.25-5.8	1-4.5	**"Low dose"**

Prevention of multiple miscarriage, pregnancy-induced hypertension and other complications of pregnancy	50-150	1-2 tablets once per day	Medium-term: 1st trimester or from 2nd and/or 3rd trimester	1-5	0.77-3.85	

The assessment of "Low doses" in pregnancy

The "low doses" in pregnancy are those referred to in the table above as being indicated for "prevention of multiple miscarriage, pregnancy-induced hypertension and other complications of pregnancy". The (retrospective) cohort study performed by Bard (2012) was provided for this dose range. To further extend the analysis, the DS submitted an additional critical review by the same author (Bard 2015).

The aim of the study and the analysis was to address the effects of ASA within this dose range on the following endpoints: maternal bleeding, neonatal haemostatic abnormalities, pregnancy duration and labour, prevention of pre-eclampsia and intra-uterine foetal growth retardation, stillbirths and infant mortality, birth weight, birth defects and early childhood development. Particular aspects that raised concern were also analysed; the premature closure of *Ductus arterious*, the occurrence of *gastroschisis* and congenital *cryptorchidism*.

As a final conclusion of the study it was stated that: "*no adverse effect of aspirin treatment can be considered as established, either at low (<150 mg daily) or higher, usual dose*". To further illustrate the overall conclusion with respect to dosages higher than that mentioned above, three epidemiological studies (Slone, 1976; Shapiro, 1976; Kozer, 2002) were cited; the conclusion was that the use of aspirin at up to the maximum recommended therapeutic dose of 4000 mg/d (equivalent to 66.7 mg/kg bw/d as ASA, or 51 mg/kg bw/d as salicylic acid) have largely demonstrated an absence of increased risk of adverse pregnancy outcome in terms of frequency of stillbirth, neonatal mortality, birth defects or developmental delay.

The assessment of "High dose" ASA as prescribed in pregnancy

As already stated, ASA is an NSAID which may be prescribed at "high dose" levels for long-term treatment of a number of severe inflammatory conditions. Only limited information is available regarding the effects of such prescribed medicinal usage of ASA during pregnancy.

In a retrospective survey of 103 patients taking high dose ASA (at least 3250 mg per day) for rheumatoid arthritis or other inflammatory conditions, Lewis and Schulman (1973) reported an increased mean gestational length and increased duration of labour. No malformations was reported, however the study covered ASA exposure only throughout "at least" the last six months of pregnancy, so it cannot be established how many of these patients were also exposed to ASA during the first trimester.

The study of Østensen & Østensen (1996) was not included in the analysis since it had no specific information related to ASA.

Overall, the available data regarding therapeutic doses over 3g/d do not show any association between ASA and malformations in humans.

ASA Overdose during Pregnancy

Two publications (Collins & Turner 1975; Turner & Collins, 1975; reported in detail in Annex 2 of the additional document *"Relevance of plasma levels in humans and rats to establish equivalence of exposure levels"* provided by the DS), describe a prospective study on ASA usage during pregnancy in Australia at doses which were excessive and can be considered as the result of abuse of the substance and toxic. A number of 144 exposed pregnancies were described (6.6% of the Australian-born patients attending the clinics) of which 44% reported ingestion of powders containing ASA at 384 mg (associated with 384 mg of Phenacetin) or 510 mg (associated with Phenacetin, but the quantity was not given) per powder. The subjects took between 2 and 12 doses/day every day throughout pregnancy; 56% used the powders at least once per week. Toxicity to the mother was evidenced by anaemia, ante or post-partum haemorrhage, prolonged labour and increased need for Caesarean and forceps/ventouse. The effects on exposed foetuses were lower birth weight compared to controls. This correlated with the duration of maternal ASA consumption for Group 1 (see below) and increased stillbirth. The data are summarised in the table below.

Summary of developmental effects

No	**Gender**	**Gestation (week)**	**Birth weight (g)**	**Maternal age**	**Salicylate consumption (years)**	**Pregnancy complications**
Group 1						
1	F	37	2305	30	14	None
2	M	39	3050 (macerated)	35	17	Anaemia
3	F	36	2570	38	20	APH, PPH
4	F	36	2490 (macerated)	35	10	None
Group 2						
1	M	29	1920	38	12	APH

APH=ante-partum haemorrhage; PPH=post-partum haemorrhage

The authors commented that the still-births among salicylate users were not all clearly related to pregnancy complications, but all occurred in older women who had been taking salicylates for many years. The two effects correlated with treatment duration were probably more a consequence of the general health of the mothers (among others, the known severe kidney effects of the associated drug Phenacetin) than a direct effect of the ASA treatment.

No increased malformation rate was observed. In this study, depending upon which powder was used and the number of powders taken per day, the ASA dose ranged from 0.8 to over 6 g/d (equivalent to 10-79 mg/kg bw/d as salicylic acid). This level of exposure occurred throughout pregnancy, and specifically throughout the first trimester, which is critical for organogenesis.

Maternal and cord blood serum salicylate levels were measured at the time of delivery or as soon as possible after delivery while the mother was still in the labour ward. Blood samples were not taken from all women, and results from Groups 1 & 2 were not distinguished. These serum salicylate levels are summarised in the following table.

Serum salicylate levels in mothers and babies

	Number	Serum salicylate (µg/mL)				
		0-10	11-30	31-50	51-70	71-90
Mothers	81	13	60	7	1	0
Babies	76	21	45	5	2	3

It was not possible to make a precise comparison between maternal and cord blood salicylate levels, but where the maternal level was high, so was the cord blood level. Since the mean duration of labour in women of Groups 1 & 2 was approximately 5.5 hours, it is clear that many hours had elapsed since the last ASA dose and that therefore these serum levels do not represent peak values.

A short report on analgesic overdose in pregnancy (McElhatton, 1991) stated that only one of the 31 women who had taken an ASA overdose gave birth to a malformed baby (with no indication that the malformation was due to ASA). This study was cited by the DS in the CLH report with no further description and therefore the magnitude of the dose was not available.

Summary of medical concerns regarding the usage of ASA during pregnancy

According to a literature search performed and results from a written consultation with representatives from the European Medicines Agency (EMA), ASA doses up to 100 mg/d are generally considered safe during pregnancy *(*FASS.se; 25 September 2015*)*. A dose of 100 mg/d corresponds to 1.6 mg/kg bw/d of ASA for a 60 kg woman. For the dose range of 100-500 mg (equiv. to 1.6-8.3 mg/kg bw/d) it seems that "*there is not enough clinical experience*" for specific recommendations to be given, so a precautionary approach has been taken, giving the same warnings as for higher doses (above 500 mg/d). For doses exceeding 500 mg/d the concern is related to effects caused by prostaglandin synthesis inhibition having a negative impact on pregnancy and/or foetal development. The following information was obtained from FASS.se (25 September 2015):

During the third trimester, all prostaglandin synthesis inhibitors can lead to the following in the foetus:

- Heart/lung toxicity (with a premature closure of the Ductus arteriosus and pulmonary hypertension);

- Renal dysfunction, which can lead to renal failure with oligo-hydroamniosis;

In the mother and the new-born baby, at the end of pregnancy, it can lead to the following:

- Possible prolongation of the bleeding time, an anti-coagulant effect that can occur also at very low doses.

- Inhibition of uterus contractions which can lead to delayed or prolonged delivery.

Therefore, acetylsalicylic acid at doses above 100 mg/d is contraindicated during the third trimester.

It should be underlined that this text is precautionary. Prostaglandin inhibitors include many substances and for instance, there is evidence of premature closure of *Ductus arteriosus* and pulmonary hypertension for the specific substance indomethacin but not for other NSAIDs. Also, it should be noted that according to written responses from EMA representatives "*miscarriage is an increased risk with preeclampsia; i.e. the reason for using the aspirin, not aspirin itself (other than if caused by haemorrhage following aspirin overdose)*".

Summary of human data

Aspirin is a widely used medicine and has been used for a long time. Depending on the disease and the degree of severity, several dose regimes are usually employed; general guidance values have been listed in the table "Indicative doses of ASA used in therapy" (above). However, it has to be pointed out that aspirin is a medicine dispensed without prescription and the exact characterization of the exposure is very difficult; exposure during pregnancy being no exception.

Apparently, the severity of effects increases with the dose. The first signs of toxicity are present in the range of 3 g/d (41.7 mg/kg bw/d ASA); the effects are not related to direct effects on the foetus but are described as increased mean gestational length and labour duration. Higher doses (up to 6 g/d, or 77 mg/kg bw/d ASA) show maternal toxicity, labour difficulties, lower birth weight and increased stillbirth. No malformations were identified at any dose. However, the conclusions taken from the studies of Turner and Collins have received criticism over time; although the publications are widely cited, the conclusions are mainly presented as having limited reliability due to the relatively small database and due to lack of consistent support from further studies. In addition, the authors themselves underscored a series of confounding factors such as the concurrent maternal exposure to Phenacetin or the low reliability of the serum levels of salicylic acid.

In medical practice there is a strong concern regarding the toxic effects following the administration of NSAIDs during pregnancy. Therefore, the usage of ASA is subject to precautions; however, the analysis of therapeutic implications of ASA administration during pregnancy is beyond the scope of the RAC opinion on the reproductive toxicity of salicylic acid.

In summary, assessment of the reproductive toxicity of ASA from the human data is difficult due to three main reasons: a) low statistical power of the studies, b) confounding factors are difficult to control and c) it is difficult to distinguish between effects of the drug and effects of the disease for which ASA is used as treatment (written responses from EMA representative).

Discussion on species differences in the effects seen on development

In general, it appears that two major reasons account for observed species differences in teratogenic response of substances: (a) intrinsic sensitivities of the developing tissues; (b) differences in exposure of the embryo during the sensitive stages of gestation (Nau, 1986).

The traditional endpoint in assessing teratogenic potential is structural malformation.
The recognition or identification of teratogens in humans is difficult for several reasons; for example, therapeutic dosages or exposure levels are generally several orders of magnitude lower than doses purposefully given to animals in experimental studies (Schardein, 1985).

These generalities apply to the present assessment. Apparently, the developmental toxicological profile differs between species: in rats and monkeys the effects are growth delays, malformations and eventually foetal death. In rabbits and humans, malformations could not be identified. Again, the magnitude of exposure appears to be the main drawback for the scope of the present analysis.

<u>Dosages and serum level concentrations</u>

As stated above, the difference in the dose range between the animal studies and the human epidemiology studies is very high. In the following, a common ground of comparison is attempted.

In the study of Wilson *et al.* (1977), when general embryotoxicity of rats and monkeys to ASA was compared at equivalent dosages, some differences were detected. According to the study

author this difference in effects seen can be attributable to the differences in embryonic exposure; since the free (unbound) salicylic acid is responsible for the teratogenic potential and the binding capacity differs between species, the rat embryo is exposed to higher levels and for a longer duration than the monkey embryo.

Also, as the salicylic acid is the prospective teratogen under analysis, the serum concentration of free salicylate appears to be the only metric representative in the present interspecies and inter-compounds comparison. However, this metric is very sensitive to kinetic factors such as decreasing concentration with time and the variation in concentration due to the albumin binding saturation; consequently, the concentration varies depending on the experimental conditions.

To follow a common ground, the data from the Wilson *et al.* (1977) study will be used. This study offers both concentrations of total salicylate in maternal plasma and the corresponding percentage of unbound salicylate associated to the lowest doses at which malformations were induced. The values are measured at intervals of 1, 2, 4, 8 and 17 hours after gavage. In addition, the validity of the comparison was confirmed by the author when performing his own assessment.

When multiplying the total serum concentration with the corresponding percentage the following values of free serum salicylate in pregnant females are obtained:

Serum concentrations of free (unbound) salicylate in the Wilson et al. (1977) study (rounded values)

Species	Dose (mg/kg bw)	Conc. at 1h (µg/mL)	Conc. at 2h (µg/mL)	Conc. at 4h (µg/mL)	Conc. at 8h (µg/mL)	Conc. at 17h (µg/mL)
Rat	150 twice daily	85	84	114	87	15
Monkey	150 twice daily	52	44	41	13	-

When calculating the average values for the interval of measurement, the concentration of free serum salicylate becomes 77 µg/mL in rats and 37.5 µg/mL in monkeys. These values are in line with the conclusions of Wilson *et al.* (1977) and represent the lowest levels of maternal serum concentrations associated with the induction of malformations. The values are in the same order of magnitude and close enough to assume that an average of 50 (57 to be exact) µg/mL represent an indicative serum level for the two species. Moreover, if the serum level in rats is taken from the study of Tanaka (*i.e.* 115 µg/mL total serum salicylate corresponding to a value of 58 µg/mL free serum salicylate) a very similar conclusion is reached.

In humans no malformation could be detected; consequently, there are no comparable associated values of free salicylic acid serum concentrations. However, based on the premises of the read across assessment, there is no plausible reason to assume a different mechanism of action: salicylic acid is the suspected teratogen, it has similar distribution in serum (both free and serum albumin bound), it crosses the placenta and (depending on the degree of albumin binding) may expose the foetus to lower or higher concentrations. Therefore, as a result, toxic potential may be assumed. If a generic value of 25% (Rainsford, 2004) free plasma salicylate in man is assumed (28% in Kucera & Bullock, 1969) then a value around of 200 µg/mL of total salicylate in maternal serum could be expected as a hypothetical human threshold for malformations.

Conclusions

The type and magnitude of the developmental response to exposure to chemicals depends on the intrinsic sensitivities of the developing tissues as well as on the differences in exposure of the embryo during the sensitive stages of gestation. Since the mode of action of the chemicals inside the embryo is not known, the exposure remains the working tool for the assessment.

Acetylsalicylic acid has been used as a medicine for a very long time and consequently, it has been extensively studied. However, older as well as more recent studies have failed to arrive at a strong conclusion on the potential of ASA to induce malformations; the low doses used in therapy and the absence of reliable epidemiological evidence are often invoked as explanations. Still, when it comes to use during pregnancy, a precautionary dose range and duration of medication are recommended, and no robust conclusion can be drawn regarding the developmental potential of salicylates in humans.

In contrast to humans, salicylate teratogenicity has been seen in both rats and monkeys. In these species, a wide range of malformations was induced at higher doses, at which the malformations occurred together with developmental retardation or death. At lower doses, foetal retardation was not associated with malformations and in rats, growth retardation was seen in the absence of the maternal toxicity.

Based on the assumption of a similar teratogenic potency in all species, a hypothetical human threshold for malformations around of 200 µg/mL of total salicylate in maternal serum was calculated. When compared to the toxic levels given in the literature, this value falls below the value of 300 µg/mL given as an indicative concentration associated with clinical manifestations of acute salicylate intoxication (Pearlman 2009). Consequently, it may be assumed that foetal exposure to such a high concentration of salicylate in maternal blood could go undetected since the mother can be asymptomatic. In terms of classification and labelling this would mean that foetal toxicity could occur in the absence of maternal toxicity. However, this assumption needs to be treated with caution since "it is important to emphasize that serum salicylate levels cannot be used strictly to determine the severity of intoxication" (Pearlman, 2009). Medical practice precludes high exposures to ASA and the overdose cases are subject to emergency treatment. In summary, the assumption appears plausible based on a toxicological approach but is not confirmed by the ASA usage even in cases with "high doses".

Overall, the available evidence from studies in rats and monkeys (but not from rabbits) indicate potential for developmental toxicity. The data from humans are considered inconclusive.

Opinions by other bodies

The Scientific Committee on Cosmetic Products and Non-Food Products intended for consumers (SCCNFP) adopted an opinion on Salicylic acid in 2002 (http://ec.europa.eu/health/archive/ph_risk/committees/sccp/documents/out170_en.pdf).

The reproductive toxicity evaluation concluded that: *"A NOAEL of sodium salicylate administered orally to mated rats has been established to 80 mg/kg bw/d corresponding to 69 mg/kg bw/d of salicylic acid. The results also showed that following oral administration salicylic acid is neither teratogenic nor embryotoxic up to 75 mg/kg bw/d in rodents and up to 100 mg/kg bw/d in monkey. Above these dose levels, foetal malformations (skeletal malformations, cleft lip, and growth retardation), resorptions and perinatal death were recorded with the compounds salicylic acid or acetylsalicylic acid."*

The Scientific Committee on Consumer Products (SCCP) in the opinion on homosalate in 2007 (http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_097.pdf stated that: *"based on the suggested metabolic fate of Homosalate as pointed out by Roberts (2005) and following his conclusions, it can be stated that the metabolite salicylic acid is comprehensively investigated in respect to teratogenicity".*

Salicylates which are naturally present in our alimentary tract were approved as flavouring ingredients *quantum satis* (EU Regulation No 872/2012 of 1 October 2012).

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

RAC concludes that there is insufficient evidence that salicylic acid exhibits adverse effects on sexual function and fertility. Consequently, for this endpoint RAC supports the proposal of the DS and concludes that no classification for salicylic acid for adverse effects on sexual function and fertility is justified.

Adverse effects on development

In the assessment and comparison with the criteria for the development of the offspring endpoint, RAC took into consideration the following:

- There is robust evidence of developmental effects in animals which justifies classification. In animals, the developmental toxicity was clearly shown in two out of three species. The pattern and magnitude of the effects shown in rats but also in monkeys are sufficient to presume that salicylic acid is a developmental toxicant and to justify classification in Category 1B;
- According to experts in the field of pharmaceuticals, ASA is not considered as being a major teratogen, but may have some potential for teratogenic effects, and it should be noted that prostaglandin inhibitors in general, including ASA, could have other adverse effects on foetuses, especially on their renal development and during the third trimester on the development of the circulatory system;
- However, neither ASA nor salicylic acid are proven human developmental toxicants. There is a lack of evidence to support an increased risk of birth defects following exposure to ASA. Also, the evidence for other developmental effects has uncertainties. Taking that into account, classification in Category 1A is not justified.
- Although the information on effects of ASA on development in humans at "high doses" is marginal, it should be acknowledged and cannot be discarded when discussing classification in Category 1B versus Category 2.
- It is noted that the available human epidemiological data on ASA was rather contradictory and with only a few reported exposures at higher doses, nevertheless demonstrated no clear evidence of malformations in humans. Hence, the RAC concluded that Category 1B may not be justified.

Taking into account the available data, including pharmacokinetics, *in vitro* tests with ASA and salicylic acid, developmental studies in animals (positive findings in rat and monkey studies and a negative rabbit study), human epidemiology and medical experience, the RAC considered classification of salicylic acid as **Repr. 2; H361d** (Suspected of damaging the unborn child) to be justified

Additional references

Additional references not included in the CLH report

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ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and by RAC (excluding confidential information).

Annex 3 Comments and RAC's response to comments received during the targeted public consultation on the reproductive toxicity of salicylic acid.