Committee for Risk Assessment

RAC

Annex 3
Records
of the targeted public consultation on the reproductive toxicity of

Salicylic acid

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

CLH-O-0000001412-86-110/F

ANNEX 3 – RECORDS OF THE TARGETED PUBLIC CONSULTATION ON THE REPRODUCTIVE TOXICITY OF SALICYLIC ACID

The proposal for the harmonised classification and labelling (CLH) of salicylic acid was submitted by Novacyl S.A.S. in October 2014; it was subject to public consultation from 28 October until 12 December 2014. The comments received by that date are compiled in Annex 2 to this opinion.

After the closure of the public consultation, the Committee for Risk Assessment (RAC) noted that the data on the reproductive toxicity indicated that classification in this hazard class could be justified. As the CLH report initially did not propose classification for reproductive toxicity, and in order to strengthen the information base, ECHA decided to organise an additional public consultation, giving parties concerned a second opportunity to provide comments on this hazard class. A supplementary publication on developmental toxicity of salicylic acid in monkeys and a summary of the classification for all the substances used for the read-across were submitted for PC. The consultation started on 10 July 2015 and finished on 24 July 2015. The comments received are compiled in this annex.

Substance name: Salicylic acid
EC number: 200-712-3
CAS number: 69-72-7
Dossier submitter: NOVACYL S.A.S.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
24.07.2015	France	NOVACYL S.A.S.	Company-Manufacturer	1

Comment received

- Comment 1: on Page 2
« Reproductive toxicity of salicylic acid was assessed by RAC on the basis of read-across data from studies on structural analogues of salicylic acid, including methylsalicylate and acetylsalicylic acid. ». It should be added « (salicylic acid is the first and common metabolite of both substances as well as other salicylates) »

- Comment 2: on Page 3
« Table 1. Self-classification status for reproductive toxicity of some salicylates »
To be complete, this table should also show numbers of notifiers that have not classified for reproductive toxicity, as following

Chemical	Classification according to CLP regulation	C&L Inventory notifications (number of notifiers)**
Methyl salicylate	Not classified	Repr. 1B (n=3) Repr. 2 (n=55) No classification (n=1507) thereof 1006 on basis of REACH registration dossier
Sodium salicylate	Not classified	Repr.2 (n=1) No classification (n=286) thereof 203 on basis of REACH registration dossier

o-acetyl salicylic acid	Not classified	Repr. 1A (n=1) Repr. 1B (n=4) Repr.2 (n=1) No classification (n=118) thereof 74 on basis of REACH registration dossier
Salicylic acid	Not classified	Repr.2 (n=68) No classification (n=2647) thereof 1051 on basis of REACH registration dossier

It is to be noted that notifications joint with the Registration dossier did not classify any of the substances as toxic for reproduction.
The DS made the attempt to use the C&L platform for salicylic acid (30/05/2013) and methyl salicylate (21/06/2013) to harmonize classifications. No answer from any notifier was obtained on 06/12/2013, and thereafter. This is the reason that lead the DS to submit a CLH dossier.

- Comment 3: on Paragraph: 2.1.2. Read across between selected salicylates: this paragraph should be completed with data supporting the read-across in humans as well: Read across is based on metabolism of salicylates (see Rainsford (2004) Chap.4) and for human it said:
- Humans hydrolyse methyl salicylate more slowly than rats and dogs (Davison et al., 1961).
- Unchanged aspirin can be detected in plasma for about 1 hour after its intravenous or oral administration.
- Following its intravenous administration in man, it has a distribution half-life of about 3 minutes, an elimination half-life of 10 minutes and a clearance of about 800 ml blood/min (Rowland and Riegelman, 1968; Figure 4.4). Aspirin is hydrolysed enzymatically in blood, but its clearance in blood accounts for only about 15 per cent of the total body clearance of the drug and the bulk of the clearance is considered to occur in the liver (Rowland et al., 1972). By contrast, the clearance of aspirin in the rat is dose-dependent and at a low dose (40 mg/kg) is slightly greater than hepatic blood flow, indicating significant extra hepatic hydrolysis (Wientjes and Levy, 1988).
Comparative metabolic pathways of salicylate
The pathways of elimination of salicylate are generally similar in all species examined, although the relative amounts of the metabolites vary. The glucuronide and glycine conjugates of salicylate are found in the rat (Nelson et al., 1966; Patel et al., 1990b), dog (Alpen et al., 1951) and rabbit (Short et al., 1991), but salicylurate is the only conjugate of salicylate detected in the urine of goats and cattle (Short et al.,1990). In all these species, a higher proportion of the dose is excreted in urine as free salicylate than in man. This may possibly be due to the high doses that have often been administered, leading to saturation of the salicylurate pathway, lower maximal velocities of the salicylurate pathway, and/or an alkaline urinary pH, which increases the renal clearance of salicylate.
Cattle and goats show a variable pattern of excretion of salicylate. In both species, more salicylurate and lesser amounts of salicylate are found in urine after oral dosage than after intravenous dosage (Short et al., 1990). This may be due to the saturable conversion of salicylate to salicylurate, because slow absorption after oral dosage should lead to lower initial plasma concentrations than after intravenous dosage, and hence

lesser saturation of the salicylurate pathway.

- Comment 4: on Page 6, para 2.2.3 about Study on Monkey : The conclusion was that 150 mg/kg twice daily is in the teratogenic range. It should be added that daily dose was therefore 300 mg/kg/d.

- Comment 5: on Page 7, third paragraph : Only 22 women out of 1002 reported exposure to Aspirin in the Li-Study which was originally intended to examine the effects of NSAIDS. So though the Li Study was a large sized study (1055 women included on a voluntary basis out of 2799 women eligible) only 22 received ASA and 5 of these females showed miscarriage up to 20 weeks of gestation. The indication for use of ASA (impaired health) might have played a role in the pregnancy outcome. Epidemiological studies prove associations but no causality.
This study has to be put in perspective with the number of Aspirin users in the randomized controlled trials/in the powerful observational studies:

CLASP Study (1994): N = 9364 participants taking 60 mg ASA/day or placebo in pre-eclampsia

Sibai et al. (1993): N = 1570 pregnant women taking 60 mg ASA/day, 1565 took placebo (normotensive women)

Caritis et al (2001): N = 2503 women taking 60 mg ASA/day or placebo (women at high risk for preeclampsia

COCHRANE (meta-analysis) (Duley 2007, updated 2009) : N=37560 women 50-150 mg ASA/day) (pregnant women at risk of developing preeclampsia)

PARIS collaborative group (meta-analysis) (2007); N = 32217 women (50-150 mg ASA/day) (preeclampsia, primary prevention)

Comments on Table 6: Summary of doses vs. effect in the human studies
In this table, figures reported have not the same level of confidence. The case studies are on individual, and epidemiological studies on large numbers. In the following table, number of individuals studied was added for more accuracy:

Total ASA per day (mg)	Dose as ASA (mg/kg bw/day)*	Dose as SA (mg/kg bw/day)**	Effect	Number of cases/comments
150	2,5	1,92	No effect	
3250	54	41,7	Increased gestational length and labour Duration	See comment 6

800 – 6000 (worst case)	13- 100	10 to 77	Stillbirths	See Comment 7
16250	270	208	Newborn in high Distress	Case study, 1 individual (suicide). See Comment 8
10000 (calculated for a 200 mg ASA tablet)***	166	128	Fetal death	Case study, 1 individual (suicide)

Comment 6: This reports use of ASA in 3rd quarter of pregnancy, typical pharmacological effect of a NSAID; no effect on development was observed.
Comment 7: All occurred in older women who had been taken salicylates for many years. Effects observed are probably more a consequence of the general health of the mothers.
Comment 8: These individual cases are not considered reproductive toxicity but salicylate poisoning.

Comment 9: general comment on table 6 : The overall conclusions of the epidemiology study (Bard, 2012) is : « As a final conclusion, no adverse effect of aspirin treatment can be considered as established, either at low (<150 mg daily) or higher, usual dose. ». Therefore it seems inappropriate to raise some effects, as, statistically, they have been demonstrated not to be relevant. Generally the effects described in Table 6 are only seen during the late period of gestation and related to the pharmacological effects of NSAIDS (ASA less potent than other NSAIDS).

Comment 10: on Table 7: For avoiding misinterpretations , the phrase before the table should be « A summary of salicylate plasma levels in the 2 attempted suicide cases is presented in Table 7 » and the title : Table 7 : Plasma levels in human from 2 attempted suicide cases »

RAC's response

Thank you for the comments. Our responses follow below:

Comment 1 The statement is only introductory; the fact that the salicylic acid is the first and common metabolite is detailed in the paragraph "2.1.2. Read across between selected salicylates".

Comment 2
The RAC fully agrees with the statement that "notifications joint with the Registration dossier did not classify any of the substances as toxic for reproduction". The number of notifications for reprotoxicity was includedsimply to indicate that there was support for the classification conclusion.

Comment 3
The information referred to was considered by RAC. The (final) opinion includes discussion of the human data as well.

Comment 4
The dose in the Wilson *et al.* (1977) study is expressed as it was in the original publication for reasons of accuracy. It is also consistent with the SCCNFP opinion. RAC does not see any good reason for the dose to be additionally presented as the total daily dose.

Comment 5
The observation regarding the Li *et al.* (2003) study is an exact citation from the conclusions of the Bard study; therefore, it is expected that the particularities detailed in the comment have been taken into account. Moreover, RAC emphasizes that the study did not mention the dose; that also means that RAC has considered it in perspective since the other studies show the dose or the dose range. The fact that the studies that have mentioned the dose are in line with the general conclusion but the Li study is an exception raised concern.

In general, RAC agrees with the observation that "epidemiological studies prove associations but not causality". This is one of the reasons why case control reports were additionally taken into the analysis.

Comments 6,7,8
Table 6 is a summary of data; the drawbacks of each category of studies, including the aspects mentioned in the comments, have been addressed in detail in the paragraphs describing the studies.
The individual cases were treated as salicylate poisoning as the title of the paragraph clearly shows. However, they were brought into the discussion due to some valuable information:

- The effects were in line with the overdose studies but the causality is straightforward and thus more reliable than in the epidemiologic studies;
- The salicylic poisoning general symptoms may not be present in the mother but the baby may still be affected;
- The serum concentration of the baby might be significantly higher than of the mother. Note: The values of the serum levels obtained in emergency services of the hospitals are values as representative as practically achievable.

Comment 9
The conclusions of the Bard study were cited exactly and interpreted as such. The statement that "no adverse effect of aspirin *treatment* can be considered as established" reinforces the well-known fact that the administration of aspirin under medical guidance and/or surveillance is beneficial. But the goal of the present analysis is to investigate the reproductive toxic potential of the salicylic acid; therefore we do not consider it inappropriate to seek information in dose ranges other than the therapeutic range of ASA.

The statement that "statistically, they have been demonstrated not to be relevant" is inaccurate. In the Collins & Turner studies it is clearly stated that "mean birth weights of live-born Group 1 babies were significantly lower than controls and correlated with the duration of maternal ASA consumption (years)". Moreover, even if the effects cannot be clearly attributed to ASA consumption, the contribution cannot be neglected either ("Effects observed are probably more a consequence of the general health of the mothers").

RAC agrees that the effects seen in the Table 6 are only seen during the late period of gestation; nevertheless, it is a period relevant for the analysis of the developmental effects. The third trimester is particularly sensitive to ASA usage. Also, in line with this, in 1990 the US FDA issued a warning that it is especially important not to use aspirin during the last trimester of pregnancy, unless specifically directed to do so by a physician, because it may cause problems in the unborn child or complications during delivery.

Comment 10
RAC does not agree, since Table 7 does not refer exclusively to the two case reports of salicylate poisoning; the first row summarises the values detailed in the Collins & Turner studies (Table 5).

Date	Country	Organisation	Type of Organisation	Comment number
23.07.2015	France		Member State	2
Comment received				
Thanks for this additional information, nevertheless the toxicokinetics data does not allow us to have a real good estimation of the percent of ASA converted into salicylic acid. Therefore it is not possible to easily compare the plasma levels between ASA and SA in animals and humans. Then, to our point of view there no enough evidence to not consider the important effects seen in animals. Consequently we do support a classification of salicylic acid for development.				
RAC's response				
Thank you for the comment. Your position has been noted.				