Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SALICYLIC ACID

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2014	France		MemberState	1
Comment received				
MS-FR agrees with the proposed classifications for acute toxicity and eye damage. Nevertheless, we have specific comments regarding reproductive toxicity endpoint and environmental hazards (see below). *ECHA note: Please refer to comments 4 and 13.*				
Dossier Submitter's Response				
Environmental hazards were not documented because not requested in the CLH dossier. And, as salicylic acid is a natural substance, environmental assessment is particular, See comment 13.				
RAC's response				
Noted. RAC agrees with the DS in the matter of the environmental assessment.				

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2014	Germany		MemberState	2
Comment received				
The German CA supports the CLH proposal of Salicylic acid. There were differences in self-classification between different notifiers in the C&L Inventory and the registration dossier. The CLH proposal aims to harmonise these endpoints where there was no agreement. In particular, deeper analysis of the reproductive toxicity endpoint, including an epidemiology literature analysis was performed.				

Dossier Submitter's Response
This summarises very concisely our position.
RAC's response
Thank you for the comment.

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2014	Netherlands		MemberState	3
Comment received				
The Netherlands was the rapporteur member state (RMS) for the biocide application of salicylic acid. During the assessment of the provide data a concern regarding the classification for developmental toxicity was identified and discussed with the applicant in several meetings. However, the CAR has not yet been finalised. Therefore, no CLH proposal from the RMS is available. The scope of the CLH proposal submitted by industry was limited to three endpoints (Acute toxicity, serious eye damage/eye irritation and reproductive toxicity). We can support the conclusions on acute toxicity and serious eye damage/ eye irritation. However, we disagree with the absence of a classification proposal for developmental toxicity. Our comments are focused to developmental toxicity.				
Dossier Submitter's Response				
The submitter was not involved in the Biocide submission. The Biocide dossier was prepared in 2007 by a downstream users consortium, on the basis of a previous application in NL by one user. The salicylic acid (SA) REACH registration dossier submitted in 2010 was updated in 2013, then improved in the CLH IUCLID file, by the Submitter, according to other salicylic compounds and particularly acetylsalicylic acid, with new information found in Rainsford book (Aspirin and related drugs, 2004) and the epidemiological analysis done by an expert (Pr Denis Bard, EHESP, France, 2012, report provided as Annex 1 of CLH report, in IUCLID file chapter 13). These documents are provided with the RCOM.				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2014	France		MemberState	4

Comment received

The reproductive endpoint for which the dossier submitter proposes no classification is partially based on data with methylsalicylate. Methylsalicylate has been identified because of concern related to embryofoetotoxicity. Indeed, methylsalicylate is included in the Corap list (FR as e-MSCA; 2015) based on the following concern:
Available data with MeS give hint that it could be embryofoetotoxic. From the tremendous amount of data presented for read-across from aspirin and salicylic acid, the results of the key and supporting studies suggests that salicylic acid has embryofoetotoxic effect in rats at doses not causing clear maternal toxicity, with evidence of malformations at maternally toxic doses (registration data). Therefore this point deserves to be evaluated.
Therefore, after evaluation, FR will gain confidence on this endpoint and might have additional information than those presented in this proposal.

We consider that the level of details of each study presented in the CLH report is not sufficient to assess this concern for salicylic acid and its subsequent classification. For example, the read-across between salicylic acid and methylsalicylate or acetylsalicylic acid is not sufficiently justified, only NOAEL/LOAEL are reported for experimental studies. Indeed, some effects were observed in experimental studies such as reduced pup viability, resorptions and malformations reported in several studies. The CLH report concluded that these effects were not applicable to humans. Some human data with acetylsalicylic acid have shown adverse effects such as increased miscarriage but their relevance has not been discussed in the dossier so far.
However, based on the level of details provided, we cannot conclude on the relevance of these effects in humans and we believe that RAC cannot conclude either. Furthermore, if further justification will be provided during the RCOM period, we cannot judge the reliability of the given information and we consider that this point should not warrant any RAC discussion unless any relevant information has gone through public consultation.

Dossier Submitter's Response

"*this point (developmental toxicity endpoint) deserves to be evaluated*"
The Submitter has registered as Lead Registrant in 2013, acetylsalicylic acid (ASA, initial registration) then has submitted updates of salicylic acid (SA) and methyl salicylate (MeS) initial dossiers on the basis of ASA dossier data analysis. These updates have been made because in the ASA registration dossier, an additional review book (Rainsford, 2004), and a new expert report on epidemiology (Bard, 2012, report provided as Annex 1 of CLH report, in IUCLID file chapter 13).) have been considered, leading to conclusions for ASA that could be applied to salicylic acid and methyl salicylate as well, due to the demonstration of a common metabolic pathway, and therefore a common mechanistic mode of action. The practical consequence is that the "developmental toxicity" chapters in the IUCLID files of all 3 substances are identical.

In the MeS dossier, the endpoint discussion begins with the sentence: "No developmental toxicity studies according to current guidelines are available for MeS itself. Assessment has been made by read-across primarily from studies on SA and ASA". See below the

read-across rationale. After this statement, the chapters in the **CLH report from page 89 to 92** ("**Developmental toxicity, animal data**" and "**Key information on effects on both fertility and development from human information**") were written.

"*the read-across between salicylic acid and methylsalicylate or acetylsalicylic acid is not sufficiently justified*"
The rationale for this read-across is as follows:
Salicylic acid is the common metabolite of salicylates, and all salicylates are "active" through this metabolite, therefore the mode of action is common (except for antithrombogenic effects of ASA). In the organism within a few minutes, methyl salicylate (MeS) and acetyl salicylate are transformed in SA (see for more details Rainsford, 2004, Chapter 4).

Davison et al. (1961) reported that gavage of Methyl salicylate, Sodium salicylate and Acetyl salicylate to Wistar rats at doses equivalent to 500 mg/kg Salicylic acid resulted in the appearance of hydrolyzed free salicylate in both the plasma and brain tissue within 20 min. This study showed rapid hydrolysis to free salicylate from Methyl salicylate, Sodium salicylate and Acetyl salicylate, with comparable plasma concentrations of salicylate at 60 minutes post dosing, with no measurable parent compound. In the same study, the authors demonstrated that the major site of hydrolysis of methyl salicylate in the rat, rabbit, dog and monkey is the liver. These results indicated that following absorption, the initial metabolic step for all these salicylates (MeS, NaS and ASA) is hydrolysis to free salicylate.

Rainsford and his colleagues (1980) compared the distribution of acetylsalicylic acid (ASA), salicylic acid (SA) and the methyl ester of ASA in rats. Salicylic acid was found in the stomach, liver, kidney, lungs, bone marrow, intestine, inflamed paws and spleen. The methyl ester of ASA was distributed in vivo very similarly to that observed with ASA and SA. Tjalve *et al.* (1973) confirmed that there was no difference between the distribution of salicylic acid versus acetylsalicylic acid in mice after injection of these compounds.

The pathways of biotransformation of ASA, SA, MeS, NaS and other salicylate esters are considered to be the same following initial hydrolysis to free salicylate. In qualitative terms, types of adverse effects reported from all of these salicylates is predicted to be similar, (except for antithrombogenic effects of ASA) supporting a read-across approach of toxicological data between these substances (see Rainsford, 2004).
A very complete analysis of metabolism data is done in the Rainsford Book (ASPIRIN and related drugs, Chap 4, 2004), used as reference in the IUCLID registration file and provided as attached document.

"*Some human data with acetylsalicylic acid have shown adverse effects such as increased miscarriage but their relevance has not been discussed in the dossier so far. However, based on the level of details provided, we cannot conclude on the relevance of these effects in humans"*
Relevance of human data with acetylsalicylic acid has extensively been reviewed in the report by Pr Denis Bard attached as Annex 1 in the CLH dossier as well as in IUCLID chapter 13 "Assessment reports" and in IUCLID chapter 7.8 "Reproductive toxicity Endpoint summary"). Details have not all been reported as IUCLID summaries, as 90 references have been analysed, among them some meta-analyses, but are discussed in depth in the report of Pr. D. Bard (provided with the RCOM document)

Hereafter, conditions, conclusions, and general comments of the report by Pr. D. Bard are cited (please note it is an extract of a whole document an some parts may not be self-explaining and need to refer to the whole text) :

Conditions

In this review, it is considered that salicylic acid (SA) risk assessment for reproductive outcomes is best approached by studies on the same outcomes associated with acetylsalicylic acid (ASA), since SA is the initial metabolite of ASA. In addition, no epidemiological data seem to be available for exposure to SA.

This work is not intended as an exhaustive review on reproductive and teratogenic risks of SA in humans, since i) the literature available on these topics is very large; ii) some investigations date back to the 1950s, raising questions about the relevance of observations made in the population in these times for the present populations; iii) the literature from this early period up to the year 1989 was reviewed in-depth by Hertz-Picciotto *et al*. (1990)[1].

Rather, a reasoned approach was adopted, considering the most important -or most cited- papers from the pre-1989 period and analyzing comprehensively the literature from 1989 up to the current times. Papers of similar quality leading to discrepant conclusions are specifically discussed. Also, when available, meta-analyses were preferred to the discussion of each paper included in these analyses. Finally, studies considering only non-steroidal anti-inflammatory drugs (NSAIDs) other than aspirin (e.g.[2]) were not discussed in this aspirin-targeted review, although this group is considered to share a common mechanism of action, that is, the inactivation of the cyclooxygenase (COX) enzyme, which is required for prostaglandin synthesis.

Conclusions

Considering the various outcomes, the results of this review are in summary the following:

For *maternal bleeding*, 3 observational studies found an increased risk, whereas only one out of 10 randomized control trials (RCTs) found such an effect.

For *neonatal hemostatic abnormalities*, 3 observational studies found an increased risk; one (the most powerful) did not, whereas two out of 14 RCTs found such an effect.

Pregnancy duration and labor: One observational study and one RCT found an increase in gestation duration, other RCTs showing no such association. For labor duration, only one observational study concluded to such association. The most powerful meta-analysis of available RCTs, as of 2007, did not show any effect of aspirin treatment on both outcomes

Prevention of pre-eclampsia and intra-uterine fetal growth retardation: All the RCTs figured out in this review were conducted to study the effect of aspirin in the prevention of pre-eclampsia. In spite of some inconclusive studies, most concluded to a modest, positive effect of aspirin in the prevention of pre-eclampsia, which was also the conclusion of meta-analyses. However, it appears difficult to conclude on whether this positive effect applies only to high-risk women or are more generally valid. The same statement applies to the optimal timing of treatment, since published results do not allow to concluding.

Stillbirths and infant mortality: RCTs (and all meta-analyses of those) concluded to no

increased risk in aspirin-treated women, as did two powerful observational studies. One large-sized study[89], however, did report such an association, with surprisingly high risk estimates.

Birth weight: Most RCTs concluded to no birth weight differences between infants whose mother was either aspirin-treated or placebo-treated during pregnancy. However, the Cochrane review[16] of these RCTs concluded to a small but significant increase in birth weight in infants born from aspirin- treated women whereas other meta-analyses, less powerful, did not.

Birth defects: Taking into account only the prospective studies of sufficient size,it is concluded to no birth defect excess in women having taken aspirin during the 1st trimester of pregnancy, whereas 2 studies found a significant association. Case-control studies found more frequently an increased risk in exposed women (3/5).
No association was seen between aspirin use and the risk of pre-term constriction of the ductus arteriosus

As regards gastroschisis, the results of case-control studies were inconsistent, the same groups reporting different results from the same database across different papers and time periods. It should be mentioned that a meta-analysis considering the case-control studies conducted before 2005 found an elevated risk. Prospective studies do not report an elevated risk of gastroschisis. Thus, it is not warranted to conclude to an association between aspirin use during the 1st trimester of pregnancy and an increased risk of gastroschisis, although it cannot be completely ruled out, see also below 'general comments'.

Conversely, available good-quality studies essentially do not show an increased risk of cardiac defects in aspirin users, as it appears from a meta-analysis of studies published prior to 2001 and in a more recent one.

For cleft palate, most studies, in particular prospective ones, did not show an association with aspirin taking in pregnancy. Only 2 prospective studies out of 8 and one case-control study out of 6, found such an association.

For central nervous system and neural tube defects, most studies did not found such association.

Some excess risk of specific birth defects were occasionally reported, *e.g.,* pyloric stenosis or hypospadias.

Early childhood development: Children neurodevelopment and intelligence are the results of an extremely complex array of influences, be they proximal (such as *in utero* exposure to aspirin, nature of food, pollutants such as lead) or more distal ("the causes of the causes"). Thus, in the absence of a convincing argument on a mechanism of action, positive associations such as that found by Streissguth *et al.*[87] should be considered with an extreme caution.

General comments

The case-control studies yielded overall inconsistent results, but tended to be more frequently positive than the cohort studies. The possibility of a recall bias, in particular in those studies where exposure was assessed retrospectively, is not supported by all such studies that conclude to no association between aspirin taking and the outcome. The reasons for such discrepancy are all but clear. Publication bias doesn't appear to play a major role in case-control studies, as it appears from meta-analyses. The meta-analyses results are not consistent overall.

Bradford-Hill[90] considerations for causation, that is, the strength of associations, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy are to be put forward here

The above results show no consistency overall, although some associations are found high in several studies for a given endpoint.
Findings are by no means specific: to address this point, it can be said that not only medications studied often included specialties mixing different molecules *(e.g.,* aspirin and dipyridamole) but in many studies the quality of the data doesn't allow a separate analysis of the effects of aspirin alone, i.e. conversely, the possible effects of aspirin may be caused by other agents.

As regards biological gradient, observational studies never provided accurate dose estimates. The pattern of aspirin taking by the subjects studied (doses and time course) is often self-reported, sometimes a long time after pregnancies, notwithstanding with recall bias, *e.g.,* in case-control studies. In addition, even when drug consumption is recorded during antenatal visits or characterized from prescription data, there is little means to check whether over-the-counter medications were accurately recorded. If such unrecorded consumption is greater in pregnant women who had an abnormal outcome, this may lead to underestimate the true effect of SAL, if any. Low dose testing was in fact addressed only in randomized control trials, *e.g.,* for assessing the efficacy of aspirin low doses in the prevention of pre-eclampsia and IUGR, except in the study by Czeizel *et al.* (2000)[60] where low-dose aspirin was explicitly investigated.

As regards plausibility, much is known on the basic mechanism of action (see introduction). However, addressing coherence (a causal conclusion should not fundamentally contradict present substantive knowledge), either conclusion of the existence or absence of an association between aspirin and a specific outcome would not fundamentally contradict the present state of knowledge. Experimental evidence, in particular in the light of effects observed in the laboratory animal, raises difficult questions, in particular for teratogenicity[91], although this point is not addressed in the present review. Analogy is a very general viewpoint, that is, some drugs are teratogenic in man, so other drugs may be, too. Nevertheless, considerations on plausibility, coherence, experimental evidence and analogy are most useful when an association is convincingly assessed, including consistency across studies.

Some additional considerations should be discussed: It should be kept in mind that the subjects tested in a RCT are usually highly selected through stringent inclusion/exclusion criteria. As a result, a simple extension of RCT conclusions to the general population cannot be straightforward. In addition, these studies were designed to test treatments for specific conditions *(e.g.,* pre- eclampsia)[11], often for high-risk pregnancies. Thus, inferring results for the general population as regards outcomes such as pregnancy duration, not specifically targeted by the study design, is questionable.

For birth defects, not all studies considered mothers' medical conditions during the 1st

trimester, that is, viral fever that could lead to birth defects. In such a case, aspirin taken for treating fever may be seen wrongly as a risk factor. In addition, symptoms produced in the mother by a congenitally abnormal fetus might result in a significant association between any drug used for the treatment of these symptoms and the congenital abnormality. Finally, birth defect studies considered only live births, so birth defects risk may have been underestimated since dead-born infants were not accounted for. Furthermore, a drug inhibiting the spontaneous abortion of already malformed embryos might wrongly appear to be responsible of birth defects.

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. Low-dose aspirin prevention of pre-eclampsia and associated adverse outcome may be modestly effective, although some uncertainties remain on the time window bringing such benefit with respect to possible adverse effects, *e.g.,* mother or infant bleeding.

References cited in above extract:

1. Hertz-Picciotto I, Hopenhayn-Rich C, Golub M, Hooper K. The risks and benefits of taking aspirin during pregnancy. *Epidemiol Rev* 1990; **12**:108-48.

2. Ericson A, Kallen BA. Nonsteroidal anti-inflammatory drugs in early pregnancy. *Reprod Toxicol* 2001; **15**(4):371-5.

11. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. *Lancet* 1994; **343**(8898):619-29.

16. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev* 2007(2):CD004659.

60. Czeizel AE, Rockenbauer M, Mosonyi A. A population-based case-control teratologic study of acetylsalicylic acid treatments during pregnancy. *Pharmacoepidemiol Drug Saf* 2000; **9**(3):193-205.

87. Streissguth AP, Treder RP, Barr HM, Shepard TH, Bleyer WA, Sampson PD, et al. Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements. *Teratology* 1987; **35**(2):211-9.

89. Li DK, Liu L, Odouli R. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ* 2003; **327**(7411):368.

90. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med* 1965; **58**:295-300.

91. Carney EW, Scialli AR, Watson RE, DeSesso JM. Mechanisms regulating toxicant disposition to the embryo during early pregnancy: an interspecies comparison. *Birth Defects Res C Embryo Today* 2004; **72**(4):345-60.

Complete reference of Rainsford Book:
ASPIRIN and related drugs, Chap 4 pp 121: Pharmacokinetics and Metabolism of the Salicylates, G.G. Graham, M.S. Roberts, R.O. Day and K.D. Rainsford
K.D. Rainsford Ed., 2004

RAC's response

The disagreement regarding the justification of the read-across has been noted.
The relevance of the rat developmental toxicity for humans has been considered by RAC.

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2014	Belgium		MemberState	5

Comment received

A quick search on the websites Toxnet (toxicology data network, US) and eMC (electronic Medicines Compendium, UK) clearly indicate some concerns when using salicylic acid/aspirin during the pregnancy and lactation. Here is an example of information found on aspirin and salicylic acid in those database
- Aspirin 300mg Gastro-resistant Tablets:
Pregnancy
Although clinical and epidemiological evidence suggests the safety of aspirin for use in pregnancy, caution should be exercised when administered to pregnant patients. Aspirin has the ability to alter platelet function and, therefore, there may be a risk of haemorrhage in infants whose mothers have consumed aspirin during pregnancy. The onset of labour may be delayed and the duration increased, with an increase in maternal blood loss. Therefore, analgesic doses should be avoided during the last trimester of pregnancy.High doses of aspirin may result in closure of foetal ductus arteriosus in utero and possibly persistent pulmonary hypertension in the new born. Kenicterus may be a consequence of jaundice in neonates. Administration of aspirin at doses greater than 300 mg/day, shortly before birth, can lead to intra-cranial haemorrhage, particularly in premature babies.
Lactation
The intake of aspirin by breast-feeding patients is contraindicated as there is a risk of Reye's syndrome. Regular use of high doses could impair platelet function and produce hypoprothrombinaemia in the infant if neonatal vitamin K stores are low.
https://www.medicines.org.uk/emc/medicine/29215#CONTRAINDICATIONS

- Salicylic Acid
Teratogenicity: 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 mass at birth. In addition, there is an increase in prenatal mortality, anemia, 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.
http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~Om5Vgz:3
Also in the eMC database where salicylic acid is used in some medicines , it is reported that even if there are no kown contra-indications to use of this medicine during pregnancy and lactation, the safety has not been established yet. This medicine should therefore be used with caution or following professional advice.
This quick screening in those databases indicates some concerns mainly related to development and lactation. We consider that this information should be deeply assessed as this could be supportive evidence for classification.

Dossier Submitter's Response

This type of statements is at first a general precaution for drugs during pregnancy. For Acetyl Salicylic Acid (ASA) it is said "to avoid during the 3d trimester" due to effects on coagulation (except when mothers have such problems and are followed by physician) and due to the action on prostaglandins (i.e. the mode of action) like other Non Steroidal

Anti Inflammatory drugs (NSAID). The recommended subacute high dose is 3000 mg/d (60 mg/kg). The usual dose for cardiovascular-antitrhombotic effets is 100-200 mg/day. Teratogenic effects of salicylic acid were analysed in the Pr Denis Bard Epidemiology report provided as Annex 1 of CLH report, in IUCLID file chapter 13). (Bard, 2012) and " no evidence of effects due to aspirin in pregnancy" was concluded (see comment 4 and report provided with the RCOM document).
The following reference has been analysed in (Bard, 2012):

EPIDEMIOLOGIC REVIEWS Vol. 12, 1990

Printed in U.S.A.

THE RISKS AND BENEFITS OF TAKING ASPIRIN DURING PREGNANCY

IRVA HERTZ-PICCIOTTO,[1] CLAUDIA HOPENHAYN-RICH,[2] MARI GOLUB,[3] AND KIM HOOPER[4]

In

nancy (21). In 1988, the US Food and Drug Administration proposed the following warning label for products containing aspirin: "IMPORTANT: Do not take this product during the last three months of pregnancy unless directed by a doctor. Aspirin taken near the time of delivery may cause bleeding problems in both mother and child" (123). On April 6, 1990, the

123. US Department of Health and Human Services, Food and Drug Administration. Internal analgesic, antipyretic, and antirheumatic drug products for over-the-counter human use: tentative final monograph; notice of proposed rulemaking. Federal Register 46256. Vol 53, no. 221, 21 CFR parts 310, 343, and 369. Washington, DC: US GPO, 1988.

RAC's response

The quantitative ranges of the doses for the onset of the emphasized effects are not mentioned; therefore, it is difficult to use the information for regulatory purposes. RAC agrees that the teratogenicity aspects have been analysed according to the DS's response.

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2014	Germany		MemberState	6

Comment received

The conclusion that salicylic acid does not present a developmental toxicity hazard for humans and that classification as such is therefore not appropriate is supported.

Results from developmental toxicity studies with salicylic acid in rats have shown reduced fetal viability and delayed development at doses below those causing evident maternal toxicity and with malformations at maternally toxic dose levels. Results from developmental toxicity studies with acetylsalicylic acid (aspirin, its metabolite being salicylic acid) in rats, mice and rabbits have led to the conclusion that there are considerable species differences in sensitivity, with the rat being a particularly sensitive species.
Human epidemiological data on aspirin have clearly demonstrated the absence of developmental toxicity in pregnant women at dose levels toxic to the mothers and delivering salicylic acid serum concentrations at least equal to those where rat studies demonstrate clear teratogenic effects. The human epidemiological studies are therefore considered fully representative of human exposure.

Dossier Submitter's Response

In accordance with the Submitters assessment.

RAC's response

The support and comment have been noted and considered for assessment.

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2014	Netherlands		MemberState	7

Comment received

Please add the page number in front of your comment e.g. p.12 the conclusion on ...
Pages 13-14, pages 74-94. It is concluded by the dossier submitter that, based on the available data from human (epidemiological) and animal studies no classification for effects on reproduction (development) is necessary according to CLP criteria.

The Netherlands notes the following:
Salicylates have a long history of use and are still used to date in human medicine, food products and cosmetics. Epidemiological studies on the effects of acetylsalicylic acid on the development of the unborn child do not show consistent results. It seems reasonable to conclude that at low exposure levels of humans salicylates are likely to be safe. However, a number of guideline or similar studies on salicylates including salicylic acid (SAL) (Tanaka, 1973a, 1973b, 1974), sodium salicylate (Fritz, 1990) and acetylsalicylic acid (ASA) (Gupta, 2003) report developmental toxicity in rats. Dose levels not clearly maternally toxic have shown reduced pup viability, while studies at higher, maternally toxic, dose levels have shown delayed development, variants and/or malformations. In addition in a limited study with ASA in rats and rhesus monkeys malformations were reported (Wilson et al., 1977). In the monkeys, 3 out of 15 fetuses at 300 mg/kg bw/d had malformations. At 200 mg/kg bw/d no malformations were observed. The results

indicate that ASA may induce teratogenic effects in monkeys. This is in line with the findings in rats, although malformations occur in rats at lower doses. Although the study in monkeys has its limitations, it can be considered supportive of the classification of salicylic acid for developmental effects. It is noted that the fact that treatment of the monkeys covered only a part of the organogenesis does not disqualify the findings. No developmental toxicity was observed in studies with ASA in rabbits. No developmental toxicity studies in mice were available. The reproductive toxicity studies in mice that are referenced in the CLH proposal are not appropriate to conclude on the teratogenic effects of ASA and SAL in mice, although the studies do show developmental toxicity (e.g. decreased number of live pups, decreased pup weight. It is further noted that in the NOVACYL position paper it is stated that ASA and SAL do not induce developmental toxicity in the mouse. However, in the referenced study (Takahashi, 1985) the developmental toxicity of ASA and SAL was not investigated.
In the C&L proposal a number of arguments are put forward in favour of the applicant's conclusion that no classification for developmental toxicity is required.
• In the NOVACYL position paper it is suggested that rats may be not an appropriate species to study the effects of salicylates on the developing embryo since the placental disposition in the rat may lead to higher fetal salicilate levels in the rat.
Although this may be the case, no data are provided to support this suggestion. It is also not indicated how much higher the fetal salicylate levels would be as compared to the human fetus at equimolar maternal plasma concentrations. Furthermore, the Netherlands recognizes that rats may be more susceptible than humans to developmental toxicity induced by salicylates, although the experimental evidence for this supposition is limited. But even if rats are more susceptible than humans, effects observed in this species can still be considered relevant for humans.
• It is also suggested that lower doses of salicylates in humans (on a mg/kg bw basis) lead to similar plasma levels as in rats treated with higher doses. This assumption is based on kinetic studies in males and non-pregnant female patients (Bochner et al., 1987 and Gibson et al., 1975). These studies indicate a peak plasma concentration of around 180 ug/ml at an external ASA dose of 60 – 65 mg /kg bw/day and around 340 ug/ml at 100 mg ASA/kg bw/day. The peak plasma levels did not vary strongly between exposures (twice daily) especially for the high exposure level (Bochner et al, 1987). The lower plasma concentration is within the therapeutic concentration range of 150 – 300 ug/ml required for optimal anti-inflammatory activity and the higher is above the concentration of 300 ug/ml where more serious adverse effects occur (Martindale, The complete drug reference on line, third quarter 2012). There are only two rat studies in which SA levels were determined at the LOAEL for developmental effects. In the dietary developmental study by Tanaka et al (1973), serum levels were determined after 7 days of feeding 0.2% SA (equivalent with approximately 165 mg/kg bw/day) at an unknown point in time during feeding. The serum SA level was 116±9 ug/ml. However, it is unclear whether this value is representative of the steady state level of SA in the serum of rats. Rats normally eat in the evening and morning and when the blood is sampled during the day, there is a period over which the SA concentration may decline. This decline depends on the time between feeding and blood sampling and the kinetics in rats. In the gavage developmental study by Tanaka et al (1973), the blood was sampled at 3 hours after the last of 7 daily gavage treatments with 150 mg/kg bw/day. The average SA serum value was 247±21 ug/ml. However, it is unclear whether the value after 3 hours is a value that can be compared to the values observed for humans.
As this comparison is based on pregnant rats versus non-pregnant humans and it is known that pregnancy can affect the plasma protein concentration, the relevancy of this comparison can be doubted.
Therefore, as there is no information provided on the kinetics of SA in rats, it cannot be excluded that the measurement in rats was performed well before or after the Tmax and that the peak value is much higher. Also there is no information from pregnant women.

Thus, it cannot be concluded on the basis of the available data that therapeutic doses in humans lead to plasma levels similar to those in rat studies in which teratogenic effects of ASA and SAL are observed.
• Further, it is argued that, although no maternal toxicity was observed in the developmental study in rats at dose levels inducing developmental toxicity, maternal toxicity should be expected at these dose levels. The absence of maternal toxicity was argued to be due to the limited number of parameters that was measured.
Assessment of the possible effect of maternal toxicity on the developmental toxicity should focus on SA and should not use ASA as ASA has additional toxicodynamic effects via acetylation of COX. Also the comparison as provided in Annex 5 of the Annex on plasma levels is inconsistent as the available study on MeAS with a high dose of 2% (= 1000 mg/kg bw/day) showed no haemorrhagic effects whereas a reduced prothrombin index was observed with SAL at 204 mg/kg bw (Takahashi, 1985). Therefore, it cannot be concluded that ASA and SA have similar haemorrhagic potential. In addition it is more relevant to compare the 7-day exposure study than the 28-day exposure study with the developmental study with exposure from day 8 to 14 (Tanaka, 1973 and Tanaka, 1974). In the 7-day study with ASA by Takahashi (1985), the NOAEL for haemorrhagic effects was 150 mg/kg bw/day and the LOAEL of 300 mg/kg bw/day.

The Netherlands recognizes that it is possible that developmental toxicity may have occurred in concomitant with maternal toxicity. However, the Netherlands notes that the presence of maternal toxicity is not determinative for the classification for reproductive toxicity. The relevant question is whether the developmental effects are secondary to maternal toxicity. It cannot be concluded from the limited available data that there was marked maternal toxicity at the relevant dose levels in the developmental rat study and furthermore there is no evidence that the developmental effects were secondary to those maternal toxic effects (if present) that, even if developmental effects are induced at high doses only, i.e. doses that would be considerably higher than those to which humans are likely to be exposed to, classification of salicylic acid is warranted, since classification of substances is based on hazard rather than potency/risk.
• The dossier submitter states that there is a difference in plasma binding between humans and rats however this is based on information from non-pregnant rats and humans. According to Rainsford (2004, page 126)

Conclusion
In conclusion, there are clear developmental effects in the rat. These effects are not considered secondary to the maternal toxicity. Systemic exposure of humans to SA due to intake of ASA seems not to clearly result in comparable developmental effects but does result in comparable effects during parturition. Based on all available information it is considered that the use of low doses of salicylates during pregnancy is safe. However, the epidemiologic database on highly exposed pregnant females is too small to conclude on the absence of developmental effects in humans. In addition, too little information is available on kinetic or dynamic differences in rats and humans that could justify why the effect in rats would not be relevant to humans. In view of this, based on the teratogenic effects of salicylates in rats and limited evidence in monkeys, but not in rabbits, the Netherlands proposes that salicylate should be classified with Repr 1B, H360D/May damage the unborn child.

Dossier Submitter's Response

"*Epidemiological studies on the effects of acetylsalicylic acid on the development of the unborn child do not show consistent results. It seems reasonable to conclude that at low exposure levels of humans salicylates are likely to be safe.*"

This has been analysed in D. Bard, 2012 (Annex 1 in chapters 13 and attached in 7.8 in the IUCLID file and provided here with the RCOM document). The overall conclusion (see comment 4 for detailed conclusions) 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. Low-dose aspirin prevention of pre-eclampsia and associated adverse outcome may be modestly effective, although some uncertainties remain on the time window bringing such benefit with respect to possible adverse effects, e.g., mother or infant bleeding.

"*Although the study in monkeys has its limitations, it can be considered supportive of the classification of salicylic acid for developmental effects*"
The monkey study had been assessed but rated as reliability 3 (invalid) e.g. due to lack of controls. Considering the large human database, and its analysis (Bard, 2012), it seems inappropriate to use animal study results of low reliability.

"*The reproductive toxicity studies in mice that are referenced in the CLH proposal are not appropriate to conclude on the teratogenic effects of ASA and SAL in mice*"
The submitters agrees with this comment. The NTP (1984a, b) studies in mice have indeed been referenced for effects in fertility, but not for developmental effects. However, some parameters of development have been observed, and they were negative, while the same parameters were positive in studies in rats.

"*in the referenced study (Takahashi, 1985) the developmental toxicity of ASA and SAL was not investigated*"
The submitter agrees with this comment. Takahashi (1985) reports on bleeding effects in rats and mice, not directly on developmental effect as was erroneously written in the document. It was intended to push forward that the bleeding effects induced by ASA (and SA) are at lower doses in rats than mice, and associated with gut ulcerogenic activity, typical toxicological effects in rats not reported in reprotoxicological studies, and below the official criterion of maternal toxicity "Body weight gain" (see Rainsford, 2004, Chap. 8, Table 8.12 and 8.14). Therefore one should read in NOVACYL ASA reprotox position paper provided as Annex 2 in IUCLID chapter 13, page 2 the following amended (underlined) text:

"**Species differences**
- The mouse did not showed <u>the bleeding effects/gut ulcerogenic activity</u> seen in the rat for ASA and SA (ulcerogenic), even at higher doses (Takahashi 1985).
- Similarly the NTP for Mouse / MeSal (NTP, 1984 a, b): the developmental effects seen in rats are not <u>retrieved in parameters observed</u> in mice.
- For ASA, the Rat (Gupta, 2003) showed effects at high doses (NOAEL maternal and fetal : 50 mg/kg), not seen in rabbits (Cappon, 2003) at 350 mg/kg with a lower maternal toxicity.
…"

Comments on rationale used for concluding that the Rat is not an appropriate species for assessing Human developmental toxicity
As developed in the CLH report p. 90, and more in-depth in the IUCLID file, the arguments are the following ones:

1. In reliable studies on developmental effects of salicylates performed in different species (rat (Tanaka 1973a, 1973b, 1074, Gupta 2003), rabbit (Cappon, 2003), mice (MeSA, NTP, 1984), there are differences in sensitivity in these species.

2. Several mechanistic possibilities as the underlying reason for species specific sensitivity were assessed and the metabolic one could explain simply the situation (see Rainsford Chapter 4 summary). In man, like in rabbit, there is a strong binding of SA to plasma proteins. When comparing SA binding in rabbits and rats, it is observed that it is significantly lower in rat. So, as only free SA could be transfered through placenta to embryos, this explains the effects in rats, which were "illustrated" by different blood levels in human and rat adults and embryos. Note also that the visceral yolk sac placenta in rats as an ion trapping environment for weak acids (another difference between rats and rabbits) resulting in higher embryonal levels of SA in rat foetuses than in rabbit foetuses. See hereafter:

Birth Defects Research (Part C) 72:345–360 (2004)

REVIEW

Mechanisms Regulating Toxicant Disposition to the Embryo during Early Pregnancy: An Interspecies Comparison

Edward W. Carney,* Anthony R. Scialli, Rebecca E. Watson, and John M. DeSesso

The dose of toxicant reaching the embryo is a critical determinant of developmental toxicity, and is likely to be a key factor responsible for interspecies variability in response to many test agents. This review compares the mechanisms regulating disposition of toxicants from the maternal circulation to the embryo during organogenesis in humans and the two species used predominantly in regulatory developmental toxicity testing, rats and rabbits. These three species utilize fundamentally different strategies for maternal-embryonic exchange during early pregnancy. Early postimplantation rat embryos rely on the inverted visceral yolk sac placenta, which is in intimate contact with the uterine epithelium and is equipped with an extensive repertoire of transport mechanisms, such as pinocytosis, endocytosis, and specific transporter proteins. Also, the rat yolk sac completely surrounds the embryo, such that the fluid-filled exocoelom survives through most of the period of organogenesis, and can concentrate compounds such as certain weak acids due to pH differences between maternal blood and exocelomic fluid. The early postimplantation rabbit conceptus differs from the rat in that the yolk sac is not closely apposed to the uterus during early organogenesis and does not completely enclose the embryo until relatively later in development (~GD13). This suggests that the early rabbit yolk sac might be a relatively inefficient transporter, a conclusion supported by limited data with ethylene glycol and one of its predominant metabolites, glycolic acid, given to GD9 rabbits. In humans, maternal-embryo exchange is thought to occur via the chorioallantoic placenta, although it has recently been conjectured that a supplemental route of transfer could occur via absorption into the yolk sac. Knowledge of the mechanisms underlying species-specific embryonic disposition, factored together with other pharmacokinetic characteristics of the test compound and knowledge of critical periods of susceptibility, can be used on a case-by-case basis to make more accurate extrapolations of test animal data to the human. **Birth Defects Research (Part C) 72:345–360, 2004.**

as well as in susceptibility to test agents, such that no individual species accurately predicts the human response (Schardein et al., 1985; Schardein, 1993). Because of the inherent uncertainty of relying on any solitary species, testing in two species has become standard practice. In fact, the major government agencies charged with the regulation of industrial chemicals, pharmaceuticals and other agents typically require testing in one rodent and one nonrodent species (Christian and Hoberman, 1997). The rat and rabbit are most frequently chosen as the respective rodent and nonrodent test species based on physiological characteristics, convenience (e.g., relatively small size and short gestation lengths), and the accumulation of historical data on spontaneous malformation rates.

While developmental toxicity testing in rats and rabbits has become the norm, there are some limitations to this approach. For instance, testing in two species obvi-

TABLE 2. Summary of Case Study Data

Compound	pK_a	Species	Gestational age	Fetal/maternal protein binding	Fetal/maternal concentration	Reference
Salicylic acid	2.97	Rat	GD 12.5	Not reported, but maternal protein binding decreases near term	~0.2	
			Term		~0.5	
		Human	Term	Fetus > mother	1.6	

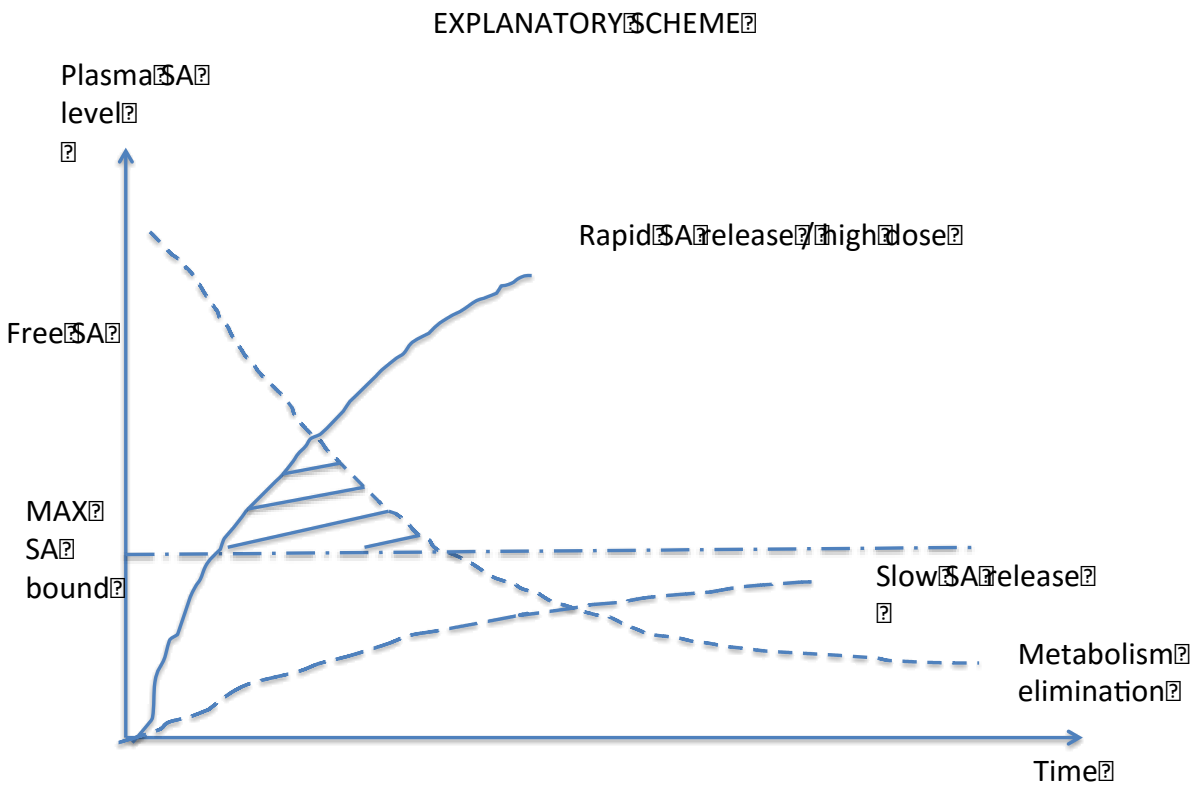
Salicylic Acid

In rats, salicylic acid transfer across the placenta appears to be influenced both by ion trapping and protein binding. Clearance of salicylate from the near-term fetus across the placenta to the more alkaline maternal compartment is greater than maternal transfer to the fetus. This phenomenon can be augmented by alkalinization of maternal blood (Varma, 1988). Administration of salicylate to pregnant rats by intravenous infusion (to maintain constant maternal blood levels) was associated with five-fold higher concentrations of total salicylate in maternal plasma than in the embryo, visceral yolk sac, or extraembryonic fluid on GD12.5 (Daston et al., 1990). However, the proportion of free salicylate was slightly higher in the embryo than in maternal blood, consistent with ion trapping. By contrast, at term, total maternal plasma salicylate was only about twice the level of fetal blood salicylate. The authors attributed the lower maternal:fetal salicylate ratio at term to decreased maternal protein binding closer to term, with free salicylate levels increasing from 14 to 27% between GD12.5 and GD20.5.

The distribution of salicylate in near-term human pregnancy favors the fetus, with neonatal:maternal salicylate concentration ratios of about 1.6 (Garrettson et al., 1975; Levy et al., 1975). The concentration gradient of high concentrations in the fetus relative to the mother was attributed to greater protein binding in the term fetus, with comparable concentrations of free salicylate in the two compartments (Levy et al., 1975).

Furthermore it has been observed in developmental toxicities studies with SA esters in rats, that, according to the length of ester chain, the SA is released less quickly in longer chain salicylates. For example, SA release in blood from hexyl salicylate (IUCLID registration dossier, 2010) is slower than from methylsalicylate (see Rainsford, 2004). Release being slower, there is a balance between this SA release in blood and its degradation, leading to negative results on development even at high doses of hexyl

salicylate (up to 350 mg/kg/ d oral). The fraction unbound in plasma (which exerts the pharmacological effect) is lower and does not reach embryotoxic concentrations .
This supports the essential role of free salicylate in blood in salicylates, including salicylic acid, mode of action. The following scheme is a simplified explanatory one:



Finally a recent paper was published (Daston P.G., Beyer B.K., Carney E.W., Chapin R.E., Friedman J.M., Piersma A.H., Rogers J.M. and Scialli A.R., Exposure-based validation list for developmental toxicity screening assays, Birth Defects Res B Dev Reprod Toxicol. 2014 Dec;101(6):423-8. doi: 10.1002/bdrb.21132. Epub 2014 Dec 4) to define doses which could lead to developmental effects in vitro. They concluded that a minimum of 494 mg/L (3 mM) salicylic acid level was necessary to get some developmental effects in vitro. This is even more (if we use the approximation L = kg) than doses able to have these effects in vivo, with clear maternal toxicity.
This author (Daston et al., cited in the IUCLID file, chapter 7.8.3. were referred to a figure provided in conclusion of the report provided as Annex 2 in the CLH IUCLID file chapter 13 (Relevance of plasma levels in humans and rats to establish equivalence of exposure levels).

"*The dossier submitter states that there is a difference in plasma binding between humans and rats*"
It was effectively written in Rainsford (2004, page 126) "while the lower binding of salicylate in pregnancy is associated with a lower concentration of plasma albumin (Yoshikawa et al., 1984a) ».

Plasma levels were indeed assessed in pregnant rats (It is easier to compare fœtus and

mother plama level) in GEORGE P. DASTON, Embryonal Disposition of Salicylate: In Vivo-In Vitro Comparisons, TERATOLOGY 42:225-232 (1990) :
"Salicylate exposure *in vivo :* Pregnant animals were exposed to salicylic acid via i.v. infusion for 24 hr, from gestation day 11.5 to 12.5. »

The observation that the free fraction of salicylate increases in pregnant woman due to a reduction of plasma proteins was not confirmed in a more recent publication, and variability is such high that there is no significant variation between pregnant and no pregnant women
(M Imoru, A Emeribe. Changes In Plasma Proteins And Fibrinolytic Activity In Pregnant Women In Calabar, Nigeria. The Internet Journal of Gynecology and Obstetrics. 2009 Volume 12 Number 2.)
Hereafter a Table extracted from this publication:
PLASMA PROTEINS AND FIBRINOLYTIC PARAMETERS OF PREGNANT AND NONPREGNANT WOMEN WITH REGARD TO AGE

Parameter	19-25 years		26-32 years		33-39 years	
	Pregnant	Non- pregnant	Pregnant	Non- pregnant	Pregnant	Non- pregnant
Number	27	60	57	34	16	6
PFC (g/l)	3.22 ± 0.73	2.48 ± 0.67*	3.18 ± 0.89	2.41± 0.5*	3.44 ± 0.63	2.5 ± 0.45**
ELT (mins)	351.9 ± 99.6	261.5 ± 92.6*	358.3 ± 81.7	290.8 ± 108.2*	369.2 ± 57.0	245 ± 76.6*
Total proteins (g/l)	61.2 ± 10.9	61.7 ± 11.9 ns	61.6 ± 8.9	62.1± 6.4 ns	60.3 ± 14.4	63.7 ± 8.2 ns
Albumin (g/l)	37.6 ± 6.9	37.5 ± 9.0 ns	38.1 ± 7.4	39.4 ± 6.6 ns	39.2 ± 8.8	40.1 ± 3.3 ns
Globulin (g/l)	20.4 ± 8.4	21.8 ± 8.8 ns	20.3 ± 9.1	20.2 ± 6.1 ns	17.7 ± 10.1	21.1 ± 6.7 ns

This table shows changes in plasma proteins and fibrinolytic parameters with age during pregnancy. The differences in the values of PFC (Plasma Fibrinogen Concentration), ELT (Euglobulins Lysis Time), total proteins, albumin and globulin in the three age groups (19-25 years, 26-32 years and 33-39 years) were not statistically significant (P>0.05).

So, the final comment "Therefore, a comparison between non-pregnant rats and humans is not relevant for developmental effects." does not apply.

General comment on use of animal vs Human data
As developmental effects of salicylic acid (SA), acetylsalicylic acid (ASA) or methyl salicylate (MeS) were only seen in rats but not in other species (rabbit, mouse) which implies a rat specific high sensitivity for salicylates, and findings - at high maternally toxic doses in low reliability studies - in monkeys, are overruled by human epidemiological data, classification for reproductive toxicity isn't warranted.
The CLP regulation has the aim of assigning Hazard categories for Human reproductive toxicants.
Therefore, when doses applied in Humans are representative of actual Human exposure (medical treatment at least, at doses higher than the rat NOAELs) and lead to no classification, no classification has to apply.

In Summary,
There is no effect on fertility in the animal studies with salicylates and particularly ASA, the main metabolite of which is SA.

When analysing the ASA data, it was evident from the metabolism (Rainsford, 2004) that the rabbit is more like humans with high protein binding capacity on the contrary to rats with a low one. In fact, in the rabbit (Cappon, 2003), there is no teratogenic effect at 350 mg/kg/d, a maternal toxic dose. In humans, an epidemiologist expert reviewed the data (Bard, 2012), and concluded to no link with ASA medication.
This made our weight of evidence that the rat is not a relevant species to extrapolate developmental effects to humans.
As further example, as reported in IUCLID, bone effects were observed in rat, while ASA was used for juvenile arthritis treatment in Human without such effects (Abbott and Harrisson, 1978).

Even the human subacute high dose of ASA (3000 mg/d or 60mg/kg for 50 kg) which corresponds to an allometric rat dose of 240 mg/kg, is higher than the rat NOAELS and far higher than DNELs. Note than in other regions the subacute human dose could be higher.

Several Competent Authorities had similar conclusions:
- With respect to developmental toxicity, SCCNFP published an opinion on SA in 2003, after the approval of SA as biocide by NL, giving a threshold of 75 mg/kg/d in rats.
- In a further opinion on homosalate (a salicylic acid ester), SCCP (2005) indicated no teratogenic effect of SA, based on a report (Roberts, 2005, ref. 55).
- Salicylates which are naturally present in our alimentation, were approved as flavouring ingredients quantum satis (Regulation EU No 872/2012 of 1 October 2012).

RAC's response

Both the argumentation and the proposal for new classification have been considered by RAC in their assessment.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2014	Belgium		MemberState	8

Comment received

The key study (1971) indeed presents a dose-response relationships that allows to determine a LD50 within the range of Acute Tox 4 via oral route. However, we question the reliability of this old study chosen as a key study for classification. Only males have been dosed and no information are provided related to the strain of the species, the purity of the substance. we consider that without this crucial information in a very old study (with no reference) the study can't be considered as supportive of classification. We then recommend no classification.

Dossier Submitter's Response

The Submitter agrees that based on the key study classification may be considered inappropriate.

However, other studies (supporting studies in the IUCLID file) support classification as Acute Toxic category 4 after oral intake. Overall and considering the mode of action as cyclooxygenase inhibitor, classification as acute toxic category 4 is still supported.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2014	Germany		MemberState	9
Comment received				
The criteria for classification of salicylic acid as Acute Tox. 4 - H302: 'Harmful if swallowed' are met. Thus the classification proposal is supported.				
Dossier Submitter's Response				
In accordance with the Submitter#s assessment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2014	Netherlands		MemberState	10
Comment received				
Please add the page number in front of your comment e.g. p.12 the conclusion on ... Page 6, page 12. The Netherlands agrees with the proposed classification for acute toxicity (Acute Tox. 4-H302: Harmful if swallowed) and eye damage (Eye Damage 1-H318: causes serious eye damage.				
Dossier Submitter's Response				
In accordance with the Submitters assessment.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2014	Belgium		MemberState	11

Comment received

We support the classification for Eye damage cat.1 based on the severity and irreversibility of the substance after 21 days. The Sugai et al. (1991) study clearly indicates a severe irritation with cornea score of 54.1 and a conjunctivae score of 10.3 that are not recovered within 21days. Those findings are also supported by the study report (Biofax, 1971), although of short duration, where the 6 rabbits exposed present high cornea, iris and conjunctivae score (mean scores of 51.5, 40.3 and 38.7 at 24h, 48h and 72h). We however recommend the DS to complete the dossier by providing the tables showing all the findings of the studies.

Dossier Submitter's Response

In the key study (Sugai et al., 1991), only the following details are available:
SCORING SYSTEM: Draize method (Maximum value of Draize score for cornea, conjunctiva and iris was 80, 20 and 5, respectively)
The raw data for each individual animal at each observation time up to removal of each animal from the test were not available. Iris score was not evaluted due to corneal opacity.
Summary: 100 mg of salicylic acid were placed into the conjunctival sac of the left eye of female white rabbits, the right one being kept as control. The eyes were examined and the grade of ocular reaction was recorded at 1, 4, 24, 48, 72, 96 hr and 7, 14 and 21 days after administration. Corneal opacity, erythema, chemosis, secreta and iritis were classified according to the Draize method. The sum of values, recorded for cornea, conjunctiva and iris, was divided by the number of observation times and the average scores were used as the grade of eye irritation potential. Results showed that salicylic acid induced severe irritation not recovering within 21 days of treatment.

In the study report (Biofax, 1971), the tables were available, and provided in the IUCLID file, as Draize scores:

Time of reading	Structure	scores						mean score(x/110)
Hours		rabbit number						
		1	2	3	4	5	6	
24	cornea	60	15	15	40	15	40	51.5/110
	iris	10	10	10	10	10	10	
	conjunctivae	14	10	8	12	10	10	
48	cornea	40	0	0	40	10	40	40.3/110
	iris	10	10	10	10	10	10	
	conjunctivae	14	8	4	10	8	8	
72	cornea	40	0	0	40	10	30	38.7/110
	iris	10	10	10	10	10	10	
	conjunctivae	14	8	4	10	8	8	

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2014	Germany		MemberState	12
Comment received				
The criteria for classification of salicylic acid as Eye Damage 1 – H318: 'Causes serious eye damage' are met. Thus the classification proposal is supported.				
Dossier Submitter's Response				
In accordance with the Submitters assessment.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2014	France		MemberState	13
Comment received				
Information dealing with environmental fate and ecotoxicity of salicylic acid should be provided to state on the environmental classification of this substance. As at present no information are available for the environmental section, environmental classification has not been reviewed.				
Dossier Submitter's Response				
Information is in the IUCLID registration dossier and did not raise need for Classification . We were also requested by ECHA to only report the information related to the CLH proposal, based on the CLP notifications. Note that salicylic acid is an important molecule in the plant defence system (Delaney et al., A Central Role of Salicylic Acid in Plant Disease Resistance, Science 18 November 1994:Vol. 266 no. 5188 pp. 1247-1250) and its internal level is increased by plant infection. It is proposed to be sprayed, by USDA, in order to increase this internal level. Furthermore, in case of infection, Methyl salicylate, more volatile, can be also released from plants. The usal content in food is shown in a table in Food Info net (http://www.food-info.net/uk/qa/qa-fi27.htm), and salicylates are approved as flavouring ingredients quantum satis (Regulation (EU) No 872/2012 of 1 October 2012).				
RAC's response				
The same as to comment 1.				

Confidential attachments provided with the RCOM by the Dossier Submitter:

1. Bard, D (2012). Reproductive and teratogenic risks of low salicylic acid doses in humans. Owner company: NOVACYL. Report date: 2012-10-30.

2. Aspirin and Related Drugs, Ed Rainsford KD, Taylor & Francis, London (2004)