Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

styrene

EC number: 202-851-5
CAS number: 100-42-5

ECHA-RAC-CLH-O-0000002714-75-01/A2

Adopted

28 November 2012

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.

Chemical name: Styrene
EC number: 202-851-5
CAS number: 100-42-5

General comments

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
17/10/ 2011	Italy / Individual	*ECHA comment: Replaced I with Y in the word STIRENE.* STYRENE THE MOST REACTIVE SOLVENT FOR POLYESTER PAINT USED IN THE 1950 AND THERE IS NO EVIDENCE THAT SHOW ITS TOXICITY . DURING THE APPLICATION OF POLYESTER PRODUCTS THE STYRENE JOIN THE REACTION WITH THE PAINT AND IS NOT ISSUED BY POLYESTER MADE WITH PAINT By contrast, in the DK items coated with paints acid catalyzed release formaldehyde (toxic) months after the application	Thank you for the comments on the proposed classification. Substance classification is based on the inherent properties of the substance and therefore any considerations about the use or exposure are not included.	Thanks for the information.
03/11/ 2011	United Kingdom / UK CLP CA/ Health and Safety Executive / MSCA	The UK CA remains of the opinion that classification of styrene for developmental toxicity is not warranted on the basis of the available evidence. Please see our specific comments in the section for reproductive toxicity.	Please see our response in this section.	Noted
09/11/ 2011	Poland / Individual	p.5 table 2 There is one mistake in table 2 in classification according to DSD (rows named "Current proposal for consideration by RAC" and "Resulting harmonised classification"). It should be "Repr. Cat. 2; R61" instead of "T; R61", because this is classification not labeling.	Thank you.	Noted

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
11/11/ 2011	Germany / Vosschemie GmbH / Company-Downstream user	Please find attached a statement of a CEFIC sector group, concerning the important role of styrene for unsaturated polyester resins and the lacking of real alternatives. Regarding this, a classification and labelling of styrene with Repr. 1B, H372 / T, R61, especially in consideration of all consequences in other (national) regulations depending on classification (e.g. storage, authorisations etc.), would strongly affect the UPE branch in an alarming way. For many downstream users (mainly SME's) it would be a threat of existence. *ECHA comment: The attached document(1)* "***The European UP Resin Sector Group - Statement concerning styrene-free technologies***" (*Cefic Styrene.pdf) is copied below.* *September 2011* **The European UP Resin Sector Group** **Statement concerning styrene-free technologies** The European UP Resin Sector Group in CEFIC[1] , which is currently composed of Ashland, CCP Composites, Reichhold and Scott Bader, has been and will continue to be deeply committed to innovation and technological development. Over the past decades, it has taken many initiatives towards the continuous improvement of products, equipment, transport, handling, best practices and information for the benefit of its consumers and workers. This has helped to ensure the safe handling of styrene based UP resins and the ever growing success of these resins in numerous applications. Recently, there have been announcements on the development and commercialization of styrene-free UP resins for use in specific applications. The European UP Resin Sector Group believes that such technologies could deliver benefits in the future. The	Thank you for the comments. Substances fulfilling the criteria for reproductive toxicity (or other harmonised endpoints) shall be subject to harmonised classification and labelling according to the CLP Regulation. Based on the available data it is our opinion that Styrene fulfils the criteria for classification with Repr. 1B; H360D and STOT RE 1; H372.	Thanks for the information. Classification should only be based on the inherent properties of the substance.

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		member companies of the Sector Group have not only been committed to the continuous support and development of styrene-based resins, but equally to the development of alternatives resins. However, as we are still in the early stages of the development of these alternatives, styrene-based resins will continue to be the most reliable substance on the market for UP resin applications. Styrene-based resins will also continue to be the most cost-competitive choice for the time being. Equally, styrene monomer as an important base raw material is widely available across the globe from long term manufacturers. As styrene-free resins lack the versatility of styrene containing UP resins and are not available for all applications, styrene remains the preferred monomer for cross linking unsaturated polyester resins. Research into substitutes has been extensive, but it has proven to be very challenging. Current alternatives to styrene in UP resins are less versatile and, in addition, less well-studied from a regulatory perspective. Therefore, it can be concluded that at this stage there is no alternative solution that can match the universal performance of styrene. Already in 2007, the European Union (EU) risk assessment of styrene[2] concluded that it is safe for both the environment and for consumers. The European UP Resin Sector Group is fully committed to developing best practices and has produced extensive safe use guidelines for handling UP resins. In addition, the members have been active in developing effective closed-mold systems that further protect workers' health. It has been demonstrated that workers can safely work with styrene when using recommended protective equipment and by limiting possible exposure to emissions. _____ [1] CEFIC is the European Chemical Industry Council		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		2 The final draft EU risk assessment report was published on the European Chemicals Agency (ECHA) website in December 2008, following nearly 10 years. This was an extensive assessment of the full body of available science. Its conclusions on carcinogenicity can be found on page 271. Conclusions on risk to human health can be found on page 335. http://echa.europa.eu/doc/trd_substances/styrene/rar/trd_rar_uk_styrene.pdf In June 2011, the United States of America Department of Health and Human Services (HSS) included Styrene monomer in the National Toxicology Program's (NTP) 12th Report on Carcinogens (RoC), as a substance that is "*reasonably anticipated to be a human carcinogen".* This conclusion by the NTP is diametrically opposed to the European-wide assessment that styrene does not pose a concern for human carcinogenicity. On the basis of EU risk assessment report and taking into account all available scientific information the Competent Authorities of the EU decided already in 2007 not to classify styrene for carcinogenicity. As a result styrene is not classified for carcinogenicity in the European Union. The US industry association, Styrene Information and Research Center, (SIRC) is actively contesting the listing by the NTP, based on solid scientific arguments. The European UP Resin Sector Group also works closely with and actively supports, EuCIA, the leading Brussels based Association of the European Composites Industry, in sharing best practices of safe handling of UP/VE resins within composites manufacturing. For more information on the **European UP Resin Sector Group** please visit the following website: http://www.upresins.org/ For more information on **EuCIA** please visit the following website: http://www.http://www.eucia.org		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		For more information, please contact: Eric Faes Director Styrenics Chain Email: efa@cefic.be Tel: +32(0)2 676 72 27 Or Philippe Maréchal Manager Styrenics Chain Email: pma@cefic.be Tel: + 32(0)2 676 72 05 *End of attachment(1)*		
21/11/ 2011	Czech Republic / Jana Marelova / Synthos Kralupy a.s. / Company-Manufacturer	page 2 *ECHA comment : The attached document(2)* ***Synthos_final_styrene_document.pdf*** *is copied below.*	Thank you for your comments. Substance classification is based on the inherent properties of the substance and therefore any considerations about the use or exposure are not included. Styrene has been discussed in the previous TC C&L group. However, no final conclusion on the classification for reproductive toxicity was adopted. Substances fulfilling the criteria for reproductive	Thanks for the information.

		Synthos Kralupy a.s. (until 2007 Kaučuk Kralupy a.s.) has been manufacturing products based on styrene since the mid 1960s. Currently its product portfolio includes compact plastics (HIPS, GPPS), EPS, SBR, XPS and styrene monomer. Compact polystyrenes with the trade name Krasten comply with all of the legal standards for materials intended to come into contact with food (Regulation of EP and Council No. 1935/2004, Regulation No. 10/2011). The level of free styrene is from 350 to 450 ppm, which is below 500 ppm, a voluntarily specified level in the EU. Synthos Kralupy also manufactures expandable polystyrene EPS under the trade name Koplen, which complies with the requirements of the building standard EN 13 163 and the level of free styrene is below 1,000 ppm. This material fulfils the hourly concentrations limit of styrene in the indoor environment of buildings according to Act No. 6/2003, item 4, where it is specified that these concentrations must not exceed 40 $\mu g/m^3$. Synthos is certified according to ISO 9001 and ISO 14000 and has obtained all authorisations required by European legislation, in particular by the REACH regulation. As manufacturers, for more than 10 years we have been members of the international organization Plastics Europe established in Brussels. Our company is an active member and regularly takes part in proceedings in its individual committees, in particular PS and EPS EH&S. It also participates in the elaboration of an eco-profile for compact PS and expandable PS within the group of the most significant producers of compact PS and expandable PS, whose activities are ensured by Plastic Europe. Synthos Kralupy manufactures 80,000 t/year of compact PS. Its main clients include companies manufacturing products intended to come into contact with food - about 70%. The production of expandable polystyrene plastics EPS and XPS is currently 120,000 t/year. These materials are used most often in the building (75%) and packing (25%) industries. In Europe there are 22 manufacturers of styrene monomer, 247 manufacturers of granules and 17,629 processors, which together employ 440,000 employees and contribute EUR 5.9 billion to the European economy (without business transactions). In the Czech Republic there is one manufacturer of monomer, one manufacturer of compact and expandable PS, 176 companies processing compact PS and 30 companies processing EPS. Styrene is a basic monomer for the production of polystyrene and it has been produced industrially over 80 years. For example, in 1955 only about 10,000 tons was produced worldwide and 2010 already 25 million tons were produced, which demonstrates the large expansion of processing of this commodity. The low threshold of detection of styrene by smell is a special characteristic of styrene. It is 0.1 ppm (0.43 mg/m^3), which exceeds in many cases the capability of detection even of very sensitive analytical methods – even the smallest release of styrene into the environment becomes obvious immediately. Styrene is also classified as a harmful substance – direct contact with skin – skin corrosion. In the Czech Republic, the personal hygiene exposure limit for styrene is 100 mg/m^3 – it is valid especially for working environments with direct contact with liquid styrene, whereas hygienic limits worldwide vary from 90 mg/m^3 (Germany, ACGIH) to 420 mg/m^3 (Great Britain). According to measurements of the National Institute of Public Health in the Czech Republic, the occurrence of styrene in the working environment in 2010 was comparable to the European average.	toxicity (or other harmonised endpoints) shall be subject to harmonised classification and labelling according to the CLP Regulation. Based on the available data it is our opinion that Styrene fulfils the criteria for classification with Repr. 1B; H360D and STOT RE 1; H372.	

According to recent special studies (2004–2010), styrene is biodegradable and is not carcinogenic. 28 million tons of styrene was produced and processed worldwide in 2009, of which 5.9 million tons was produced in Europe, more than 50% was used for compact polystyrenes, 19% was applied in production expandable polystyrene and XPS, 11% were styrene copolymers, 5% styrene-butadiene latexes and 5% unsaturated polystyrene resins (UP). Styrene is also an ingredient in many foods and beverages. For example, strawberries contain 1.7 ppb of styrene, beef 2 – 6 ppb, beer 10 – 200 ppb and cinnamon 150 – 40,000 ppb of styrene. Since the main applications of polystyrenes are in the field of packaging and direct contact with food (including yogurt cups), extensive studies of the migration of styrene to food were performed. Currently, the valid specific migration limit for styrene is 60 ppm. As a results of these studies, the use of polystyrene packages intended to come into contact with food was allowed – no negative impacts on human health appeared. An EU study (Existing Substances Regulation 793/93) listed styrene among 150 substances where limits for health certification are determined. According to an EU study (HSE Styrene Risk Assessment, 2002), the average exposure of styrene to the human body under normal living conditions is 90 μg/day.

The discussion in the EU has not ended, but within the study for REACH all available data related to scientific research of toxicity, carcinogenity and reprotoxicity of styrene were evaluated and in 2010 the conclusion that there are no basic data for the classification of styrene as a reprotoxic substance, as was proposed, was made within the presented documentation of REACH. Since no new scientific studies which would bring new scientific evidence supporting the proposed classification are known, we recommend **not to change the classification of styrene to 1B** (May damage the unborn child when exposed via inhalation) **according to CLP** (Regulation (EC) No. 1272/2008).

Ing. Jana Marelovám, PhD

Synthos Kralupy , a.s.

O.Wichterleho 810

278 01 Kralupy nad Vltavou

The Czech Republic

Ing. František Svoboda

Synthos Kralupy , a.s.

O.Wichterleho 810

278 01 Kralupy nad Vltavou

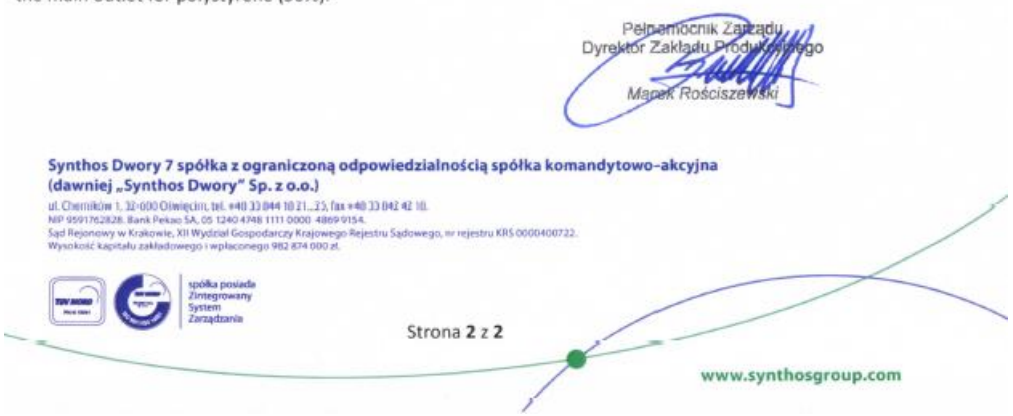
The Czech Republic

End of attachment(2)

21/11/2011	Poland / Synthos Dwory Sp. z o.o. / Company-Manufacturer	Please see the attachement. *ECHA comment : The attached document(3) "**Comment to the Danish proposal concerning the change of classification of styrene"** (komentarz do zmiany klasyfikacji styrenu.pdf) is copied below.* synthos chemical innovations **Comment to the Danish proposal concerning the change of classification of styrene.** Styrene is the main raw material manufactured and used in production processes carried out by Synthos Dwory 7 spółka z ograniczoną odpowiedzialnością S.K.A (dawniej Synthos Dwory Sp. z o.o.) Any proposals to change the styrene classification will significantly affect the activities of our company and are of particular interest to us. We hereby inform, that we do not agree with the change in styrene classification proposed by Denmark. Based on Plastics Europe studies, styrene classification as Repr. 1B, H360D, "May damage the unborn child when exposed via inhalation" is unjustified since no evidence to confirm the classification is available. In 2007, Denmark submitted an application to ECHA, where the same change in classification based on identical data was proposed. Most experts from member states did not agree with its content, 11 member states claimed, that the styrene shall not be classified as: Repr. 1B, H360D, "May damage the unborn child when exposed via inhalation". Also, no new studies are available up to date to justify the change in classification. CLP regulation shall also be considered, since it indicates, that the substance classification must be supported by specific evidence: Annex I CLP, Basis of classification for reproductive toxicity, point 3.7.2.2.1: Classification is made on the basis of the appropriate criteria, outlined above, and an assessment of the total weight of evidence (see 1.1.1). Classification as a reproductive toxicant is intended to be used for substances which have an intrinsic, specific property to produce an adverse effect on reproduction and substances shall not be so classified if such an effect is produced solely as a non-specific secondary consequence of other toxic effects. Annex I CLP, Basis of classification, point 3.7.2.2.2: In the evaluation of toxic effects on the developing offspring, it is important to consider the possible influence of maternal toxicity (see section 3.7.2.4). Annex I CLP Weight of evidence Point 3.7.2.3.1:	Thank you for your comments. Styrene has been discussed in the previous TC C&L group. However, no final conclusion on the classification for reproductive toxicity was adopted, whereas classification as R48/20 was concluded. Substances fulfilling the criteria for reproductive toxicity (or other harmonised endpoints) shall be subject to harmonised classification and labelling according to the CLP Regulation. Based on the available data it is our opinion that Styrene fulfils the criteria for classification with Repr. 1B; H360D and STOT RE 1; H372.	RAC is aware of the history of the substance, and notes that there were indeed disagreements in TC C&L with regard to reproductive toxicity. RAC has to process all CLH-proposals even though there is no new information. In the opinion of RAC, the data do not warrant classification with Repr. 1B.

		...The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, the presence of maternal toxicity in experimental animal studies, level of statistical significance for inter-group differences, number of endpoints affected, relevance of route of administration to humans and freedom from bias. Both positive and negative results are assembled together into a weight of evidence determination. Studies of Kishi and Katakura et al. (referred to in Plastic Europe studies) cannot be taken as supportive evidence due to severe deficiencies. Evaluations should only be based on the guideline/GLP studies of Cruzan et al. **Synthos Dwory 7 spółka z ograniczoną odpowiedzialnością spółka komandytowo-akcyjna** **(dawniej „Synthos Dwory" Sp. z o.o.)** ul. Chemików 1, 32-600 Oświęcim, tel. +48 33 844 18 21...25, fax +48 33 842 42 18. NIP 9591762828, Bank Pekao SA, 05 1240 4748 1111 0000 4869 9154, Sąd Rejonowy w Krakowie, XII Wydział Gospodarczy Krajowego Rejestru Sądowego, nr rejestru KRS 0000400722, Wysokość kapitału zakładowego i wpłaconego 982 874 000 zł. spółka posiada Zintegrowany System Zarządzania Strona **1** z **2** www.synthosgroup.com		

		synthos chemical innovations To emphasize the issue, we hereby inform that Synthos Dwory 7 spółka z ograniczoną odpowiedzialnością S.K.A (dawniej Synthos Dwory Sp. z o.o.) is one of the leading manufacturers of styrene-butadiene rubber SBR, polystyrene materials EPS, HIPS, GPPS, XPS and styrene-butadiene latex LBS and styrene-butadiene-carboxylic latex LBSK. We are the only manufacturer of styrene monomer, compact polystyrene, SBR, LBS and LBSK, we are one of the two manufacturers of EPS and one of the three manufacturers of XPS for building applications in Poland. Rubber production capacity is approx. 130 TPA. EPS production capacity is up to 80,000 TPA, and GPPS and HIPS production capacity is up to 50 TPA. XPS sheets production capacity is up to 130,000 m3. Styrene is the main raw material in all production processes. As a manufacturer of styrene and polystyrenes, we are the member of Plastics Europe in Brussels. We are also an active member and we participate in meetings of various committees, PS and EPS committee, EH & S, and Styrene REACH consortium. Styrene is a fundamental material for polystyrene production. In 1955, the production capacity was approx. 10,000 TPA, and the production reached 25 million tonnes and 28 million tonnes in 2006 and 2009, respectively, which indicates constant development. The characteristic feature of styrene is a very low odour detection threshold - 0.1 ppm (0.43 mg/m3), it is not detectable using even the most sensitive analytic methods. The highest threshold limit value (TLV) in Poland is 50 mg/m3, and the TLV-STEL is 200 mg/m3. Currently in Europe, there are 22 styrene monomer manufacturers, 247 polystyrene bead manufacturers and 17,629 styrene processing companies. The styrene chain industry employs 440,000 people. In Poland, 420 companies process compact polystyrene and 150 production plants process EPS. The main use of GPPS and HIPS is the production of packaging intended to come into contact with food (including yoghurt cups). A process of styrene migration into food was widely researched. The study resulted in permission to use polystyrene packaging with food products, since they do not pose a hazard to human health. We also have a confirmation from ITC Zlin Institute, that the GPPS and HIPS meet all the requirements of COMMISSION REGULATION (EU) No. 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. Free styrene level does not exceed 300 ppm for HIPS and GPPS compact styrene. The company also manufactures polystyrene for expansion EPS. EPS production process conforms to EN 13163 requirements, and free styrene level is below 1000 ppm. XPS production process conforms to EN 13164 requirements, and the maximum free styrene level is 300 ppm. The styrene is a strategic raw material for Synthos Dwory 7 spółka z ograniczoną odpowiedzialnością S.K.A (dawniej Synthos Dwory Sp. z o.o.). Based on the data collected by Plastics Europe, styrene is not selectively toxic for reproduction, and the classification of styrene as a substance Repr. 1B, H360D, "May damage the unborn child when exposed via inhalation" is not justified.		

		Incorrect classification of styrene may affect the use of polystyrene packaging intended to come into contact with food. The change in classification may result in ban on use of polystyrene packaging in food industry which is the main outlet for polystyrene (50%).  *End of attachment(3)*		
21/11/ 2011	Czech Republic / Association of Chemical Industry of the Czech Republic	Our Association supports the conclusion of Styrene Producers Association concerning the proposal by the Danish Competent Authority for a revised harmonised classification and labelling for Styrene: we support the proposal to classify Styrene for Specific Target Organ Toxicity folowing repeated exposure (STOT RE 1) and we do not agree with the proposal to classify Styrene as a category 1B for reproductive toxicity, as this proposal is not justified by the available scientific data.	Thank you for your comments. Your comments will be taken into consideration during the forthcoming discussions in the Risk Assessment Committee.	RAC supports STOT RE 1, and share the view that Repr. 1B is not justified.
21/11/ 2011	Belgium / European Trade Union Confederation	The European Trade Union confederation (ETUC) supports the proposed harmonised classification and labelling for Styrene.	Thank you for your support.	The support is noted.
21/11/ 2011	Germany / MSCA	please find our comments in the enclosed document *ECHA comment: The attached document(4)* ***"DE Comments"*** *(DE Comments – CLH-Dossier Styrene.doc) is attached below.*	Please see response to specific comments from the German MSCA under the section "Reproductive	Noted. Thanks for the detailed comments.

		DE Comments Substance name: Styrene CAS Number: 100-42-5 EC Number: 202-851-5 **General Comments:** *It is recognised that the proposal of the Danish Environmental Protection Agency to classify styrene as a reproductive toxicant is based on the database that was available to TC C&L in 2007 and for the preparation of the EU RAR in 2008. Obviously no new data concerning developmental toxicity and/or developmental neurotoxicity properties of styrene have evolved in the meantime.* *It is concluded in the dossier (p. 70) that effects on postnatal growth and developmental (evidenced by decreases in bodyweights, delays in attaining certain pre-weaning developmental landmarks, slight shift in the normal pattern of motor activity and delayed preputial separation) were induced in the high exposure group (500 ppm) F2 offspring in a well-conducted OECD guideline and GLP-compliant two-generation study. Also it is concluded that high exposure group (500 ppm) F2 offspring showed some adverse effects on motor-neurodevelopment during tests on for developmental neurotoxicity subsequent to the two-generation reproduction toxicity test protocol.* *When looking at the available information of the key study (references Cruzan et al., 2005 a, b) we are not in support that the results obtained from the study are appropriate for and sufficient to substantiate a proposal for classifying styrene as a Cat 1B reproductive toxicant.* *If at all only some indication for a substance-related impact in particular on postnatal development can be derived from the results of the two-generation study during which some effects were observed in the 500 ppm exposure group F2-offspring, however not so in the according F1-offspring.* *Effects observed in the concerned F2-offspring were confined to effects on*	toxicity” (page 51)	

pup body weights in both sexes, e.g. slight but statistically significant differences in pup body weights in comparison to controls during PND 7-21 (Cruzan et al., 2005b, table 2) with no differences observed on their pre-culling (PND 1-4) body weight gain (Cruzan et al., 2005a, table 3). Also, there was a tendency for continuously lower post-weaning body weights up to PND 70 in both sexes in the 500 ppm exposure group F2-offspring in comparison to the concurrent controls, which however, did not attain statistical significance. It should be noted that no such pre-weaning body weight effects were observed in the first generation F1-offspring. (Post-weaning body weight development cannot be compared for the two generations, since F1 offspring underwent styrene exposure whereas F2-offspring did not.) A comparison of the body weight performance of F1- and F2-offspring at weaning, - such as in the table below - illustrates the range of body weights on PND 21 across groups and indicates that achievement of statistical significance for the differences in the F2-offspring body weights might have occurred by chance due to the higher values of their according controls.

	Parental styrene exposure level (ppm)			
	0	*50*	*150*	*500*
	PND 21 body weight (g)			
F1-offspring ♂	*38.4+6.3*	*41.4+5.5*	*39.1+5.2*	*38.5+3.8*
F1-offspring ♀	*37.6+5.8*	*40.7+7.1*	*37.1+5.4*	*37.3+3.9*
F2-offspring ♂	*42.6+5.3*	*40.3+5.2*	*38.2+5.1**	*38.0+6.2**
F2-offspring ♀	*40.5+4.7*	*39.1+5.0*	*37.4+4.8*	*35.4+5.7**

** stat. sign. diff. from according controls (p<0.05)*

Indications for a delay in attaining pre-weaning developmental landmarks (note: not observed in the F1-offspring) was also confined to the 500 ppm exposure group F2-offspring and should not be assessed and regarded isolated from offspring body weight. Note: the attainment of several developmental landmarks is clearly linked to growth and body weight development. Thus, any observed small delays are consistent with the small-for-age offspring in the 500 ppm exposure group which is reflected

		in their retardation in body weight development. The same applies for incidental findings of decreased swimming abilities (observed on PND 24 but no longer at the later stages) and of reductions in forelimb grip strength (only observed on PND 60), as these tests demand physical strength which may not be sufficient in small-for-age offspring. No delays in swimming ability were observed in the 50 and 150 ppm exposure group F2-offspring which also did not reveal deficits in their body weight development. More detailed discussions are provided in the Specific comments, Section Reproductive toxicity. *Taken together the observations obtained at certain instances from postnatal neurodevelopmental toxicity testing are not considered as conclusive evidence for selective neurodevelopmental toxicity. Rather they are attributable to the treatment related effects on pre-weaning - and if possible post-weaning - body weight development.* *In summary, from the results of observations of the F1- and F2-offspring development during a high quality OECD guideline and GLP compliant two-generation reproduction toxicity study with styrene there is some evidence of an adverse effect on postnatal body weight development and growth after high parental exposures. Effects were seen on pre-weaning body weights in F2-offspring, however not in F1-offspring, and probably protracted post-weaningly in conjunction with according delays in the acquisition of certain developmental landmarks and weight and age dependent neuromuscular abilities. No significant post-natal functional deficiencies unbiased from body weight gain deficits were revealed. Based on this and with regard to the criteria for classification according to CLP we are not in support of the proposed classification of styrene as a Cat 1B reproductive toxicant.* Furthermore, we would like note that the "Note D" of the current Annex VI entry is missing. *End of attachment(4)*	Thank you for the observation. It has not been our intension to remove note D	RAC shares the view that Repr. 1B is not justified.
22/11/ 2011	Netherlands / RIVM Bereau REACH / RIVM	– Page 10 'Short summary of the justification for the CLH proposal' should– also include the (range of) effect doses/concentrations of styrene that lead to the classification STOT RE1 – Page 11 'Short summary of the justification for– the CLH proposal' should also include the type of animal that was used to study the reprotoxic effects of styrene that lead to the classification Repr. Cat. 1B.	Thank you for the comments. The doses and the types of animals will be indicated.	Noted

22/11/2011	Belgium / SPA (CEFIC) / Industry or trade association	The comment given in the CLH Dossier is: Quote "2.4.1 Current self-classification and labelling based on the CLP Regulation criteria Denmark has investigated a number of product Safety Data Sheets for products currently distributed in the EU containing styrene and none of them use the labelling in line with a STOT RE 1 classification" Unquote The comment listed in point 2.4.1 of the CLH dossier has nothing to do with the decision on styrene CLP. Moreover it is not substantiated as shown in annexed document. It needs to be removed or replaced by "In October 2011 most of the Styrene producers and distributors in Europe have updated their SDS and extended SDS in accordance with the hazard listed in the Styrene Reach registration dossier and thus including self classification STOT RE 1". *ECHA comment: The attached document(5) "**Comment on the section 2.4.1 of the Styrene annexe XV dossier "** (Comment on the section 2 4 1 (SDS aspects).docx) is copied below.* **Comment on the section 2.4.1 of the Styrene annexe XV dossier** **The comment given in the CLH[i] Dossier is:** **"2.4.1 Current self-classification and labelling based on the CLP Regulation criteria** Denmark has investigated a number of product Safety Data Sheets for products currently distributed in the EU containing styrene and none of them use the labelling in line with a STOT RE 1 classification" **Comments** At the date of the submission of the dossier (10 October 2011) Most of the Styrene producers have already updated their extended SDS with registration information. This in accordance with the ECHA guidance on SDS (see extract below) For sure the following Styrene producers SDS were available before	Thank you for the comments. We did find a lack of information regarding classification when examining the SDS during the preparation of the CLH proposal. It is appreciated that producers and distributors of styrene have now updated their SDS and extended SDS in accordance with the hazards listed in the Styrene REACH Registration dossiers, including STOT RE 1. However, it turns out not to be the case when a quick search via Google is performed. 4 out of 4 found safety data sheets still are not updated with STOT RE 1, H372.	Thanks for the information. Whether IND is self-classifying in SDS is of no importance for RAC, but might be useful information for the COM when deciding if a non-harmonised end-point should be classified via Annex VI.

		October 2011 with listing of Hazard H372 - STOT RE 1 in accordance with registration dossier: BASF 21/1/2011, Shell 22/2/2011, Total 18/4/2011, Sabic 17/1/2011, HELM (distributor) 20/4/2011, LyondellBasell 29/10/2010 (as non exhaustive list)[i]. Down stream user industry group are taking this new information into account in their communication to their customers. One of the industry group most concerned by STOT RE 1 classification is the producers of unsaturated polyester resins for, e.g., the composite industry. In that case as there are several hundreds of SDS to update per company, Letters were sent to customers informing them that the process of updating the SDS is starting and that STOT RE 1 will be listed in the new SDS (see Reclassification of Styrene and the Influence on UP/VE resins) . Risk management measure are made available on internet through 14 Safe Handling Guides issued in 6 different languages: http://www.upresins.org/safe-handling-guides Note also that Article 31.9 of the REACH Regulation states that the SDS must be updated without delay as soon as new information affecting the Risk Management Measures is available. However, it is widely recognised that industry needs time to update the SDSs following new information. This is due to - among others - the need to update the relevant software systems. The information needs to be communicated down in the supply chain and it may take time until it reaches all levels of downstream users. In addition, when substances are incorporated into mixtures, this adds additional complexity. This issue has been raised by industry in numerous occasions in the context of discussions with authorities, particularly MS at the Forum who received an open letter from Cefic in October 2010 addressing this issue. **Conclusions** The comment listed in point 2.4.1 of the CLH dossier has nothing to do with the decision on styrene CLP. Moreover it is not substantiated as shown here above. It needs to be removed or replaced by "In October 2011 most of the Styrene producers and distributors in Europe have updated their SDS and extended SDS in accordance with the hazard listed in the Styrene Reach registration dossier and thus including self classification STOT RE 1".		

		Annexe **The guidance on SDS[ii] indicates:** **Where a Chemical Safety Report (CSR) is required to be prepared for a substance, the information in the SDS for the substance must be consistent with that provided in the CSR as well as with that provided in the registration dossier**. In addition, according to Article 31(7) of REACH, registrants and downstream users that are required to prepare a CSR, must place the relevant exposure scenario(s) (ESs)6 into an annex to the Safety Data Sheet. **Downstream users have to consider relevant exposure information received from suppliers when compiling their safety data sheets.** For mixtures there are several options for placing relevant ESs into an annex or for including relevant exposure information in the core Sections 1 – 16 of the SDS. If however, a Downstream User is required to prepare his own CSR under Article 37 of REACH and this results in the generation of an ES, this ES must be placed in an annex to the SDS. _____ [i] CLH report, Proposal for Harmonised Classification and Labelling, Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 - Substance Name: Styrene (EC Number: 202-851-5 / CAS Number: 100-42-5 / Index Number: 601-026-00-0) - Contact details for dossier submitter: Danish Environmental Protection Agency, Strandgade 29; 1401 Copenhagen K. Phone +457254 4000; Peter Hammer Sørensen, e-mail: phas@mst.dk. - Date: September 2011 (link: [View]) [ii] Dates given are the date of the SDS reviewed. It does not mean that the previous version of the SDS didn't contained yet the hazard listed in the registration dossier. [iii] ECHA Guidance on the compilation of SDS Version 1.0 of September 2011 pg2. *End of attachment(5)*		
22/11/ 2011	Germany / DuPont	The Danish proposal does not look at any new data, however, they reinterpret a known study. This known study had been reviewed in the	Styrene has been discussed in the	RAC is of the view that the data do not fulfil

	Performance Coating GmbH / Company-Downstream user	literature previously by a world leading group of experts in developmental toxicology and their conclusion was that styrene was not a developmental toxicant. ("NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Styrene", Ulrike Luderer et al., 2005.)	previous TC C & L group. However, no final conclusion on the classification for reproductive toxicity was adopted. In the current CLH proposal it is argued that developmental toxicity has been observed in the absence of maternal toxicity in a number of studies with rats. The toxicity is expressed as developmental delay, including delayed neurological development, and developmental neurotoxicity effects on post-weaning behaviour, especially neuromotor function. Substances fulfilling the criteria for reproductive toxicity (or other harmonised endpoints) shall be subject to harmonised classification and labelling according to the CLP Regulation. Based on the available data it is our opinion that Styrene fulfils the criteria for classification with Repr. 1B; H360D and STOT RE 1; H372. So it is now up to the Risk Assessment	the requirements for Repr. 1B.

			Committee to conclude on the proper classification of the substance.	
23/11/ 2011	Czech Republic / MSCA	We support the proposal the classification of styrene for Specific Target Organ Toxicity following repeated exposure (STOT RE 1, H372) because a number of serious health effects after prolonged exposure by inhalation in experimental animals and in humans has been observed. We therefore consider a classification as STOT RE 1, with the hazard statement H372 "Causes damage to the nervous system through prolonged or repeated exposure via inhalation" relevant. On the other side we are not in favor of the proposed classification Repr. Cat 1B, H360D. The dataset used for support of this classification is the same as was used in the TCC&L group during discussions on styrene classification in 2007. The majority of EU Member State authorities agreed that the data was not sufficient for any classification for reproductive toxicity. Lead Registrant in the registration dossier also did not propose any classification for reproductive toxicity. It is there considered that the observed effects are a consequence of maternal toxicity and that there is no indication of developmental toxicity. As no new studies indicating rationale for developmental toxicity are available we are not able to support the proposed classification Repr. Cat 1B, H360D.	Thank you for your comments. It is true that styrene has been discussed in the precious TC C&L group. However, no final conclusion on the classification for reproductive toxicity was adopted. According to the classification proposal, we argue for classification in repr. cat 1b. This has now to be discussed and concluded in the Risk Assessment Committee.	RAC shares the view that STOT RE 1 is warranted. Likewise, RAC is also of the view that the data do not fulfil the requirements for Repr. 1B.
24/11/ 2011	France / MSCA	ANSES is rather in favour of a classification in category 2 for the developmental effects because of the inconsistency of some results, the bad reliability of some studies and the probably influence of the body weight reduction on the toxic effects. Otherwise we agree with the whole proposition of classification for endpoints others than for reproduction.	Thank you for your comments. We still ague for classification with Repr. 1B; H360D, however, discussions regarding fulfilment of the criteria and the possibility for a category 2 claasification is now up to RAC	RAC is also of the view that the data do not fulfil the requirements for Repr.1B, but rather Repr. 2.

Carcinogenicity

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment

22/11/2011	Netherlands / RIVM Bereau REACH / RIVM	Based on standard regulatory tests (in vitro and in vivo) there is no convincing evidence that styrene possesses significant mutagenic/clastogenic potential from the available data. This conclusion is taken from the EU RAR and is also in line with the TCC&L group that agreed in sept 2007 not to classify styrene for carcinogenicity and mutagenicity. We agree with no classification of styrene with respect to mutagenicity/carcinogenicity.	Thank you for your comments.	Noted

Mutagenicity: no comments received

Toxicity to reproduction

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
03/11/ 2011	United Kingdom / UK CLP CA/ Health and Safety Executive / MSCA	Developmental toxicity The UK CA remains of the opinion that classification of styrene for developmental toxicity is not warranted on the basis of the available evidence. Although a pattern of developmental delay was seen in pups from the 500 ppm exposure group in the well-conducted 2-generation study, this was the secondary, unspecific consequence of maternal toxicity. There is no convincing evidence that styrene causes specific developmental neurotoxicity. One of the key observations used to support a proposal for classification for developmental toxicity is a supposed effect on grip strength. However, we do not agree that there is convincing evidence that styrene causes a clear adverse effect on grip strength. We would argue that the findings relating to effects on grip strength are of limited value and do not represent a clear adverse effect for a number of reasons. • The grip strength test is well known to have limitations. In particular, the nature of the test makes it difficult to reliably and reproducibly detect small changes in grip strength (Maurissen et al., 2003 and Frank Sullivan; personal communication).	Grip strength is recognized in the OECD GD 43 as a measure for neuromotor function Peripheral nerve damage after adult exposure can typically affects both hind and forelimb grip strength. However, it is unknown whether the effect after styrene is due to peripheral nerve damage. Central nervous damage may be involved. We find that most weight has to be put on the concurrent control group. Also, we find that 6 of 20 males (30%) with a lower grip strength than any of the controls is a large proportion.	Effects on grip strength can clearly be related to a low body weight, but the effects seem larger than would be expected based on a 13% decrease in body weight. RAC agrees that the pattern of effects seems inconsistent, but also notes that as the mode of action is not known, it is difficult to ignore the findings. The Maurissen *et al*. study (2003) shows that for a clearly neurotoxic substance (doxorubicin),

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		• The apparent effect on grip strength was limited to the fore limbs and was not evident in the hind limbs. Chemicals that cause peripheral nerve damage typically affect both hind limb and fore limb grip strength. Therefore, the findings are not really consistent with a genuine treatment related effect. • The 500 ppm group mean values for fore limb grip strength were within the range of control group means (from 8 subsequent studies) for both male and female SD rats of this age, which suggests that this reduction may actually be an expression of normal variation and have no toxicological significance. It is also noted that only 6/20 male and 3/20 female individual values were outside the range of concurrent controls. • The measured deficits in grip strength were relatively small and occurred in the presence of general toxicity (reduced pup body weight). Grip strength has been correlated with body weight (Maurissen et al., 2003). It is our opinion that the observed decrement in grip strength, if any, was a non-specific secondary consequence of this toxicity. • All other neurotoxicity evaluations, including neuropathology, learning and memory and startle response, did not reveal any adverse effects. Other effects, such as delays in attaining developmental landmarks and in acquiring preputial separation, the slight shift in the normal pattern of motor activity and the decreased swimming ability are also regarded as being secondary to general toxicity (reduced pup body weight). The reduced pup body weight observed at 500 ppm, which was seen in the presence of some maternal toxicity, is rather small (up to 13%) and does not warrant classification for developmental toxicity. Maurissen JPJ, Marable BR, Andrus AK, and Stebbins, KE (2003) Factors affecting grip strength testing. Neurotoxicol Teratol, 25, 543-553.	We find that the reduction of 24-28% is not small. Actually it appears larger than the reduction of 17-18% in Maurissen et al 2003. The evaluations of learning and startle response are on other domains of the nervous systems and lack of effect is therefore not an argument against the effect on grip strength. We do not find a reduction of pup body weight up to 13% small. For comparison, the estimated reduction in human birth weight after smoking is lower, i.e. around 5% (180g/3450g)	causing neurological degeneration, fore and hindlimb grip strengths are decreased much more (30%) than body weight (11%). The effect of diet restriction on grip strength was also studied, clearly showing that a decreased body weight (26%) led to decreased grip strength (18%). However, after body weight correction of the grip strength, no effects on grip strength remained. Thus, when diet restriction is the only cause for the decreased strength there is a close correlation between body weight and grip strength. However, for styrene the decreased grip strength was much larger (24-28%) than the effect on the body weight (13%), and remained after body weight correction,

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
				indicating that the decreased body weight is not the only cause for the decreased grip strength.
11/11/ 2011	Germany / Vosschemie GmbH / Company-Downstream user	The CLH report describes on p. 10 the "history of the previous classification and labelling". Referring to that, there are different interpretations of one specific study (with rats) of Cruzan et.al. (2005) by "EU RAR Styrene" and the registrants on one side (p. 5 : the Lead Registrant agrees only STOT RE. 1) and the CLH report on the other side, regarding maternal effects (p. 69). Since "EU RAR Styrene" there are obviously no new scientific findings to be considered. This is a small basis for a classification and labelling of styrene with Repr. 1B, H372 / T, R61 with its tremendous consequences for the unsaturated polyester (UPE) resin industry and its numerous down stream users, e.g. GRP and putties. Regarding the responsible evaluations of "EU RAR Styrene" and the registrants, there is, to our opinion, a need for more and definite data before harmonizing Repr. 1B, H372 / T, R61. If data were sufficient and stringent, labelling of styrene would have been harmonized with T, R61 by EU since 2008 or 2009**.**	Thank you for your comments, they will be considered during the discussions in the Risk Assessment Committee. It is true that styrene has been discussed in the precious TC C&L group. However, no final conclusion on the classification for reproductive toxicity was adopted. Substances fulfilling the criteria for reproductive toxicity (or other harmonised endpoints) shall be subject to harmonised classification and labelling according to the CLP Regulation. Based on the available data it is our opinion that Styrene fulfils the criteria for classification with Repr. 1B; H360D and STOT RE 1; H372.	RAC has to deal with all CLH-proposal, based on the available data. RAC is of the view that the data do not fulfil the requirements for Repr. 1B.
17/11/ 2011	Belgium / Eric Faes /CEFIC	SUMMARY		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		A CLH dossier prepared by Denmark (DK) proposes a reproductive (developmental) effects classification for styrene. This position paper examines the case given in the CLH report for classification and provides evidence-based responses that the effects proposed for supporting classification are in fact secondary non-specific consequences of exposure to styrene and/or chance variations in data inherent when measuring large numbers of observations in complex studies. This position paper is organized as follows: - In the summary the main arguments are given without details - More details with references are found in the main section - In some cases specific numerical support is given in the annexes The most important arguments provided by the CLH report for Cat. 1B classification are found in measurements of various endpoints in an OECD guideline two generation reproductive toxicity and developmental neurotoxicity study in rats. A short outline of the study design is given in the main section on p.53 .In particular the CLH report refers to (in brackets the pages in the CLH report): - body weight effects (p. 61/61) - delays in attaining some preweaning developmental landmarks and preputial separation (p.61 and 62) - slight shift in the normal pattern of motor activity (p. 63) - decreased swimming ability (pnd 24) (p. 63) - reduction in forelimb grip strength (pnd 60) p.62) - reduced pituitary gland weights (p. 62; but this effect is not mentioned in the summary section 4.11.4 nor in the classification section 4.11.6) As additional information the studies of Kishi et al. (1992, 1995)(p. 65), Katakura et al. (1999, 2001) (p. 66/67), Ninomiya et al.(2000) (p. 67) and Zaidi et al. (1985) (p. 67) are mentioned. General considerations (main section p.20): Classification for developmental effects entails more than a catalogue of changes in isolated or individual endpoints but rather requires a consideration of the influencing parameters affecting such endpoints. These include, but are not restricted to: • the point of life span and generation affected, • severity of effects, and	We do not find that the results show "a catalogue of changes in isolated or individual endpoints", but a pattern of developmental delays both before and after weaning (decreased body weights, delays in attaining some pre-weaning developmental landmarks, slight shift in	Thanks for the detailed comments. RAC believes there is some evidence of developmental toxicity, but agree that Repr. 1 B is not warranted. The criteria says that reproductive toxicity effects should not be secondary non-

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		• maternal toxicity with possible effects on maternal care As the general basis for classification is evidence of developmental toxicity which is not a secondary non-specific consequence of other toxic effects, toxicological effects of styrene not directly related to developmental toxicity are summarized here. In rat studies repeated inhalation exposures to 500 ppm styrene produces degeneration of the olfactory epithelium with more subtle effects at 50 ppm resulting in histopathological alterations after 12 months exposure. In studies with prolonged exposure reduction of body weight is a general observation at exposures of 200 or 500 ppm. Clinical signs of respiratory tract irritation were observed in a 13 week study at exposure of 200 ppm. Mild narcotic effects that may impair maternal care have been described by various authors at exposures ranging from 50 to 300 ppm with a short lasting weight loss during exposure even at 50 ppm. The exposure concentrations used in the OECD guideline two generation reproductive toxicity and developmental neurotoxicity study (i.e. 50, 150 or 500 ppm) are thus within the range known to already lead to toxicological effects. With styrene exposures producing such general toxicological effect the question to be answered in evaluating these points for classification is: - are the findings direct, specific effects on development, or - non-specific delays of development associated with maternal toxicity combined with some "chance" variations in data inherent in the large numbers of observations and measurements responsible for the findings. To help address this question the endpoints suggested in the CLH report as being specific development effects have been analyzed against those influencing parameters which might affect such observations: Body weight effects (main section.p.25 .): The CLH report points to statistically significant reductions in the bodyweights of male F2 offspring born to F1 rats exposed to 150 ppm styrene in the absence of statistically significant effects on body weights of F1 females in the 150 ppm treatment group during premating and gestation. In addition statistically significant reductions in bodyweight of the 500 ppm F2 pups and F1 pups (- pnd 22-28) are mentioned accompanied by reduced bodyweight of maternal animals. General observation: The proposition that this provides evidence of a	the normal pattern of motor activity and delayed preputial separation). In addition, decreased swimming abilities on PND 24 and reductions in forelimb grip strength on PND 60 indicate affected neuromotor functions. This is based on a weight of evidence approach. Thus the many detailed comments below that actually appear to treat the each of the effectss in isolation will only be partly addressed. For the toxicological effects in adult animals mentioned here there are no data showing that they are likely to cause the developmental toxicity effects seen after styrene exposure as a secondary non-specific consequence. Such effects in paternal animals have been seen in many other studies without signs of developmental effects.	specific consequences of other toxic effects. However, it is not clear how olfactory effects, irritation, and transient narcotic effects could explain the observed delayed pup development. Furthermore, the comments suggest that the decreased pup body weight is a chance finding, giving even less reason to believe that the delays are secondary to other toxic effects.

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		specific developmental effect is not however supported by the available body weight information which shows: □ There were numerical reductions in body□ weights in F1 and F0 dams at 150 ppm during premating and gestation although not reaching statistical significance. □ While body weights of F2 males at 150□ ppm (pnd 21) were significantly different from F2 controls they were almost identical to F1 controls. □ No statistically significant reductions in the□ bodyweights of F2 exposed to 150 ppm were observed during the post-weaning phase □ A pattern of body weights effects were seen only in F2 but not in F1 offspring. □ The persistence of reduced bodyweight of F2 pups (500 ppm) throughout postweaning may be attributed to the unexceptionally high control F2 weights. □ A recent detailed analysis of a broad data base revealed no critical differences between the F1 and F2 generations and that an evaluation of the F2 offspring will very rarely provide critical information (Piersma et al., 2011). □ As the body weights of control F2 offspring were clearly higher than those of control F1 offspring the body weight effects of exposed F2 pups may be a chance finding. □ Weight reductions observed in parent generations of the 2-generation studies and in various other toxicological investigations indicate that body weight effects noted in offspring may rather be a general toxicological consequence of styrene exposure of parents, not being a specific developmental effect. Point of life span and generation affected: Significantly reduced body weight was only observed in F2 but not in F1 preweaning offspring. If the effects are regarded as exposure related, the different findings in both generations can only be explained by different exposure scenarios of the F0 and F1 parents. In contrast to F0 animals (exposure only after puberty), F1 parents were exposed during pregnancy, lactation, and also after weaning up to puberty. Severity of effects: A pattern of body weight reductions only occurred in F2 (in the range of about 10%) but not in F1 offspring and body weights in exposed F2 offspring were very similar to those of F1 offspring. Therefore, this effect can by no means be regarded as severe and is best explained by the high F2 control body weights. Although reductions in	See our response to the German MSCA page 52	

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		body weight of 500 ppm F2 pups continued throughout postweaning without exposure, this effect may similarly be attributed to the high control F2 weights persisting into the postweaning phase. In addition, in relative terms the 500 ppm F2 pups gained more weight compared to the 0 ppm pups. Maternal toxicity with possible effects on maternal care: Maternal toxicity must not only be defined by significantly reduced body weight but, as body weight effects in preweaning F2 offspring are mainly discussed here, any possible influence on maternal care must also be considered like olfactory effects, irritation and transient narcotic effects that are already to be expected at 150 ppm. Assessment in the UK RAR (p. 292): in the summary discussion it is concluded: "… - Although at 150 ppm there was a decrease in pup body weight, since this was small (up to 10%), limited to the pre-weaning period of the F2 generation only and not accompanied by other related effects…" Delays in attaining some developmental landmarks (main section p.31.): The CLH report points to delays in developmental landmarks (pinna detachment, surface righting response, incisor eruption, preputial separation and hair growth) in 500 ppm F2 pups. General observation: The CLH document concedes these effects may be due to the delay in growth and thereby may indirectly be related to developmental toxicity. These developmental landmarks were not affected in F1 pups. In F2 pups the mean ages for pinna detachment, surface righting response, preputial separation and hair growth were not statistically significantly increased. Only incisor eruption was statistically significantly delayed in F2 500 ppm animals. Point of life span and generation affected: As the effects were only observed in F2 offspring at 500 ppm the same considerations apply to the delay in developmental landmarks as for the body weight effects. In this respect the findings of Piersma et al. (2011) have to be taken into account that an evaluation of the F2 offspring will very rarely provide critical information. Severity of effect: As the mean ages for acquisition of developmental landmarks were generally not statistically significantly increased, the relevance of this effect is questionable. Only for incisor eruption in F2 500		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		ppm rats a statistically significant delay was observed. But for F2 male controls the time until incisor eruption was extremely short (9.3 d) in comparison to F1 male controls (10.0 d). Thus, time until incisor eruption for F2 500 ppm males was just the same as for the control F1 males. Maternal toxicity with possible effects on maternal care: The delay of pre-weaning developmental landmarks occurred only in offspring of dams exposed to 500 ppm with statistically reduced maternal body weights. All other effects that may affect maternal care should also be taken into consideration. Assessment in the UK RAR (p. 278/279): "The attainment of the pre-weaning developmental landmarks (pinnal detachment, surface righting response, incisor eruption and hair growth) and the acquisition of the preputial separation were also slightly delayed in the high-exposure F2 pups. It is considered that these effects were probably due to the slight delay in growth (reduced body weights) observed in these pups." Shift in pattern of motor activity (main section.34.): The CLH report points to the age-related pattern of motor activity being slightly shifted in the 500 ppm pups: the activities were lower (not statistically significant) at PND 13, then rose and were similar to control by PND 61. According to the CLH report this effect may be related to the growth delay in the pre-weaning stage. General observation: There were no statistically significant differences between all exposure groups at all time points. While at PND 13 motor activity was slightly decreased at 500 ppm, a high activity was found in females at 150 ppm as an indication for inherent variability. The only effects, if related to exposure at all, were found in the preweaning phase. Point of life span and generation affected: As motor activity was only measured in F2 offspring, a comparison to F1 offspring as e.g. for body weight is not possible. Severity of effects: The effects at 500 ppm never attained statistical significance. The measurements show a high variability and no clear dose relationship. Maternal toxicity with possible effects on maternal care: Motor activity was only affected at 500 ppm during the preweaning phase. This exposure level led to significantly reduced maternal body weights and all other effects that might affect maternal care have also to be taken into	Swim time as a measure for swim speed is assessed best in the straight channel as swim speed in the learning part of the test is confounded by other factors such as trying to solve the learning task. The most	RAC also finds the lack of effects in the other swimming exercises as surprising, suggesting that it is not a motor effect. RAC also notes the very nice dose-response relationship for the effect in the first

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		consideration. Assessment in the UK RAR (p. 279): "Therefore, the slight shift in the age-related pattern of motor activity observed in the high-exposure group was considered to be related to the growth delay evident in this group of animals particularly in the pre-weaning stage." Decreased swimming ability (PND 24) (main section p.36.): The CLH report points to an increased straight channel swimming time at PND 24 for the 500 ppm offspring. Point of life span and generation affected: As straight swimming time was only measured in F2 offspring, a comparison to F1 offspring is not possible. Severity of effects: A "real" increase of straight channel swimming time would mean a generalised impairment of swimming performance that should also affect the total swimming times in the part for learning and memory in the maze test. But this was not the case. The mean swimming times of the contemporary control animals were low compared to historical control data while at 500 ppm the values were within the historical control range. The mean swimming times are derived from 4 consecutive trials. The most prominent difference was obtained in trial 1, while swimming times in trials 2-4 were similar over all treatment groups. Therefore, the difference in group mean swimming time reflects the unusual contemporary control value and a chance finding. Maternal toxicity with possible effects on maternal care: Straight channel swimming time was only increased in offspring of dams exposed to 500 ppm 3 days after weaning. This exposure level led to statistically reduced maternal body weights and all other effects that might affect maternal care should also be taken into consideration. Assessment in the UK RAR (p. 280): "Therefore, the effect on swimming ability observed at PND 24 did not represent an effect on learning and memory but it was just an indication of general malaise. Historical control data … show that the swimming time values … were within the historical control ranges and that the observed increase was due to an unusually low value in the concurrent controls. This suggests that this increase in swimming time may actually be an expression of normal variation and have no toxicological significance."	relevant group to compare with is the concurrent control instead of historical controls as the concurrent controls are tested under exactly the same conditions as the exposed animals. It is agreed that the effect on swimming ability does not represent an effect on learning. However, we find that the effect suggest effect on neuromotor ability. Concerning grip strength, see also response to UK. This argumentation on the alleged relationship between body weight and grip strength is difficult to follow. It seems to be argued that there were	trial, suggesting the effect to be substance-related.

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Reduction in forelimb grip strength (PND 60) (main section p.42): The CLH report points to statistically significant reductions in the forelimb grip strength in both sexes of the 500 ppm group on PND 60. Hindlimb grip strength was reduced in males on PND 45. After correction of grip strength for body weight on the basis of proportionality this effect is considered to be a direct consequence of the styrene exposure. Point of life span and generation affected: As grip strength was only measured in F2 offspring, a comparison to F1 offspring is not possible. Severity of effects: Grip-strength shows considerable variation. Of the 500 ppm offspring only 6 of 20 males and 3 of 20 females fell outside the range of concurrent controls and the majority were within normal range. Grip-strength is influenced by body weight and body weights of 500 ppm animals were lower than controls. But a simple proportional correlation as applied in the CLH report is misleading. Although reductions in body weights on PND 63 were only moderate, during preweaning weight reductions were much more pronounced, resulting in continued reductions until measurement of grip-strength. There were no statistically significant effects on fore-limb grip strength on either PND 22 and 45. There was no statistically significant difference in hind-limb grip-strength although peripheral nerve damage typically leads to more pronounced effects on hind-limb grip-strength. A significant increase in fore-limb grip strength in females at PND 45 in the 150 ppm group indicated to variability of the effect. The group mean values for fore-limb grip-strength are within the historical control range supporting the conclusion that the findings reflect normal variability. There was no underlying histopathology and therefore the difference in grip-strength is unlikely to represent a specific neurological effect. Maternal toxicity with possible effects on maternal care: Forelimb grip strength on PND 60 was only reduced at 500 ppm with significantly reduced maternal body weight Assessment in the UK RAR (p. 280): "the reduction in forelimb grip strength observed on PND 60 only is considered to be the consequence of the reduced body weight seen in these pups. Furthermore, as there was no similar difference in hindlimb grip strength at the same time point and no underlying histopathology, it is unlikely that the reduced forelimb grip strength represents a specific neurological effect of styrene".	reductions in body weight until measurement of grip strength on PND 60 (although not on PND 60) and that this should be related to the effect on grip strength on PND 60. However, it is also recognized that there were no effect on grip strength on PND 22 and 45, where there was effect on body weight. To us, this shows that there is not a relationship between the effect on body weight before PND 60 and the effect on grip strength on PND 60.	The very big variability in pituitary weights at PND 21 may make this effect difficult to evaluate. However, it is also difficult to ignore it.

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Reduced weight of the pituitary gland (main section p.47.): The CLH report points to statistically significant reductions of absolute pituitary gland weights for female F2 pups at 150 and 500 ppm, for males at 500 ppm and especially to the reduced relative weights for male F2 pups at 500 ppm. It is concluded in the CLH report that in the absence of information on the normal growth rate of the pituitary gland in fast-developing organisms the reduced pituitary weight may represent an adverse developmental effect. General observation: As determination of pituitary weights in pnd 21 F2 pups is not required by the test guidelines. Historical control data are not available. The high variability of pituitary weights in conjunction with the very low absolute weights (between 0.6 and 10.9 mg for F2 pups) at pnd 21 requires great caution when assessing weight differences of this tiny organ to avoid misinterpretations caused by chance variation. Point of life span and generation affected: Significantly reduced absolute or relative pituitary gland weights were only observed in pnd 21 F2 pups but not in pnd 21 or adult F1 pups. In this respect the findings of Piersma et al. (2011) have also to be taken into account that an evaluation of the F2 offspring will very rarely provide critical information. Severity of effect: No histopathological alterations were noted in the pituitary of 500 ppm exposed male or female F1 adult animals. Furthermore only a few exposed F2 pups fell below the range of the F2 controls. In addition the absolute and relative weights of the exposed F2 groups with statistically significant reductions were comparable to those of F1 control pups of the same age. Maternal toxicity with possible effects on maternal care: Reduced relative pituitary gland weights were only observed at 500 ppm with significantly reduced maternal body weight. Assessment in the UK RAR (p. 278): "given the lack of any associated histopathology, it is reasonable to assume that these pup organ weight reductions (including pituitary weight - added) are unlikely to represent adverse developmental effects" Effects on F2 pups secondary to body weight (main section p.52): The bodyweight of F2 control pups is much higher than that of the F1 control pups and apparently there is no dose response relationship for the F2 pups at 150 and 500 ppm. Thus the high bodyweight of F2 control pups may have occurred by chance. Several effects noted in F2 pups have a	We find that there are signs of a consistent pattern for effects on the functional domain neuromotor abilitiy due to the increased swim time and decreased grip strength.	

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		direct relationship with body weight (developmental landmarks, motor activity, swimming ability, grip strength). Under such circumstances the alterations of these parameters are not exposure related but a secondary consequence of the incidentally high control bodyweights. General considerations regarding DNT studies (main section p.53): statistically significant alterations can be expected as chance findings when conducting complex investigations such as DNT studies which include measurements of 143 endpoints in 2 genders resulting in a total of 286 datasets to be statistically analysed. These datasets do not include the histopathological investigations, organ weight determinations and interval/trial data. Statistical analyses of all parameters at $p<0.05$ will lead inevitably to a substantial number of positive findings. Therefore it is necessary to consider functional domains for inter-correlated endpoints. Evaluation of such domains in 500 ppm F2 offspring does not show a consistent pattern that would indicate a direct impairment of development of the nervous system as displayed in the tables below: Neuromuscular domain PND 20-28 PND 60-74 Grip Strength None Decrease (M, F) Mobility None None Gait None None Motor activity None None Swim Time – Biel Straight Channel Increase time None Neuropathology Not evaluated None Activity and excitability domains PND 20-28 PND60-72 Ease Removal No effect No effect Ease Handling No effect No effect Arousal No effect No effect Home cage-posture No effect No effect Motor Activity (Increase activity?) n.s. No effect Swim Time – Biel Increase time No effect Startle (Vmax) No effect No effect	The studies have been included as part of the weight of evidence including due considerations of their limitations and their strengths (i.e. lack of effect on maternal body weight). We find that the Kishi and Katakura studies –	RAC notes the limitations of these studies, but agree that they should be part of a WoE analysis.

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		CNS Neuropath None None Comments on the studies of Kishi, Katakura and Zaidi (main section p.57): Six studies are mentioned in the CLH dossier (Zaidi et al., 1985; Ninomiya et al., 2000; Kishi et al., 1992; 1995; Katakura et al., 1999; 2001). It is unclear how much weight is given to the studies of Kishi et al. (1992, 1995) and Katakura et al. (1999, 2001) for the proposal of cat. 1B. But in several sections the results of these studies are mentioned stating that delayed neurological development and behavioral effects have been reported at 300 ppm styrene in the absence of maternal toxicity. When comparing the CLH report and the UK RAR, the CLH report is identical or closely follows the UK RAR in the description of the methods and the results, but often major deviations are found in the overall assessment. We are of the opinion that the assessments in the UK RAR are scientifically by far more robust than those given in the CLH report. In the study of Zaidi et al. (1985) only used 3-4 female rats/dose and investigated receptors in the brain that are not contained in any regulatory guideline. Because of the very limited number of animals, the questionable toxicological significance of the observations, and the missing historical data, this study must not be used for an assessment of styrene. The studies of Kishi et al. (1992, 1995) and Katakura et al. (1999, 2001 were carried out by the same group of investigators. Both publications of Kishi are derived from the same experimental setup. In the first report of Kishi et al. (1992) the number of pregnant animals was 14, 3, and 7 at 0, 50, and 300 ppm, respectively. In the 1995 publication it was mentioned that "due to the limited number of inhalation chambers available only 12 litters exposed at the same period were evaluated" (5, 2, and 5 litters at 0, 50, and 300 ppm). If different subgroups were treated at different times under not exactly the same conditions, a statistical analysis of all the subgroups in combination may not be appropriate. Many of the findings reported by Kishi et al. (1995) were not observed in	although limited – are important for the evaluation of developmental toxicity. A major reason for that is that these studies include a dose level of 300 ppm with no effects on the dams. The Cruzan study use dose levels of 50, 150 and 500 ppm. As the Cruzan study is performed several years after the Kishi studies, it is surprising and unfortunate that the Cruzan does not include 300 ppm as one of the dose levels. There are signs of consistency on the functional domaine	RAC is also of the view that the data do not fulfil the requirements for Repr. 1B.

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		the Cruzan studies even under continuous exposure conditions. The findings of Kishi et al. (1995) are difficult to evaluate because of the small number of litters (5, 2, 5 at 0, 50, 300 ppm) in combination with the missing historical database for the highly variable endpoints. Kishi et al. (1995) themselves caution that "the findings of this study should be regarded as preliminary". Therefore the assessment of neurobehavioral development should rely on the Cruzan data. The data of both Katakura et al. (1999, 2001) studies refer to the same basic experiment. As the same equipment was used as for the Kishi studies, there is uncertainty whether all animals exposed at the same time. In addition, the following shortcomings in the Katakura studies must be taken into account: - The lower number of pregnant rats as compared to the Cruzan study - No comparison is possible with historical control data - Alterations in neurotransmittors are not mirrored by histopathological findings - The toxicological significance of the neurochemical findings is unclear because of the large number of measurements with only a few significant differences to controls. Overall, these limited studies must not be considered as key or supportive in the evaluation and have no impact on the interpretation of the Cruzan et al. (2005a, b) studies given above. Conclusion. The observations mentioned in the CLH dossier do not provide sufficient evidence to cause a strong suspicion that styrene exposure produces specific developmental toxic effects: All the effects mentioned in CLH dossier can by no means be considered as being severe. Whenever a comparison between F1 and F2 generation was possible (body weight, developmental landmarks, pituitary weight, time to incisor eruption), the findings only occurred in F2. It has recently been shown that there are no critical differences in sensitivity between F1 and F2 offspring. Therefore, these effects most probably are a chance finding. As all effects (apart from offspring body weight) were only noted for the high exposure group (500 ppm), maternal toxicity and impairment of	neuromotor function, i.e. increased swim time and decreased grip strength We do not find that there are "severe deficiencies" in the Kishi and Katakura studies, but recognize that there are limitations in these studies.	Thanks for the

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		maternal care have to be taken into account. If histopathology was done on corresponding tissues, there was no correlate to the effects observed (forelimb grip strength, pituitary weight). There was no consistency when the same endpoint was determined at different ages (motor activity, swimming ability, forelimb grip strength). Some effects observed have a high inherent variability that may lead just by chance to a statistical significance (forelimb grip strength, pituitary weight). If a comparison with historical data was possible, the effects at 500 ppm were within the historical range (swimming ability, forelimb grip strength). Studies of Kishi et al. and Katakura et al. cannot be taken as supportive evidence due to severe deficiencies. Evaluations should only be based on the guideline/GLP studies of Cruzan et al. The large amount of datasets in the DNT study should be evaluated according to patterns of effects. Thereby, no functional domains could be identified that were consistently affected. The weight of evidence indicates that the endpoints highlighted in the CLH report in addition to being of minor toxicological relevance are not specific developmental effects but rather non-specific findings associated with maternal toxicity or reduced maternal care in combination with some "chance" variation in data. Therefore based on the evaluation provided in this document, classification for developmental toxicity is not warranted for styrene. Please refer to attached pdf document *ECHA comment: The attached document(6)* ***"Response of the Styrene Producers Association (*) to the CLH proposal (Sept. 2011) for the classification of styrene as a Cat. 1B reproductive toxicant (developmental effects) according to Regulation (EC) No 1272/2008 (CLP)"*** (*COMMENTS RELATED TO REPROTOX _ Nov 15 2011_FINAL EDITION.pdf) is attached separately.*		detailed comments and information on relevant publications not being covered by the CLH proposal. RAC has considered the detailed comments, and also consulted the EU RAR when preparing the RAC opinion. Many of the comments below have been considered and led to the conclusion that classification with Repr. 1B is not warranted. *ECHA comment: The rapporteurs' responses to these comments from IND are located in the Appendix to the Opinion and in the Background Document.*

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON STYRENE

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Copy19 first pages below:		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Nov. 14, 2011 **Response of the Styrene Producers Association (*) to the CLH proposal (Sept. 2011) for the classification of styrene as a Cat. 1B reproductive toxicant (developmental effects) according to Regulation (EC) No 1272/2008 (CLP)** TABLE OF CONTENTS **SUMMARY** *p.3* *General considerations p.4* *Body weight effects p.5* *Delays in attaining some developmental landmarks p.7* *Shift in pattern of motor activity p.9* *Decreased swimming ability (PND 24) p.10* *Reduction in forelimb grip strength (PND 60) p.11* *Reduced weight of the pituitary gland p.12* *Effects on F2 pups secondary to body weight p.13* *General considerations regarding DNT studies p.14* *Comments on the studies of Kishi, Katakura and Zaidi p.15* *Conclusion p.17* **MAIN SECTION** *Introduction p.20* *Assessment of the proposal of the CLH report to classify styrene as a Cat. 1B developmental toxicant p.22* *Design of the Cruzan et al. (2005 a, b) studies p.23* *Body weight effects p.25* *Delays in attaining some developmental landmarks p.31*		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		  (*) The Styrene Producers Association, SPA, is a Sector Group of CEFIC, the European Chemical Industry Council. The members of the SPA are BASF SE, Bayer Material Industries, LyondellBasell Industries, Polimeri Europe, Repsol-YPF, Sabic, Shell Chemicals, Styrolution, Styron, and Total Petrochemicals		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		SUMMARY A CLH dossier prepared by Denmark (DK) proposes a reproductive (developmental) effects classification for styrene. This position paper examines the case given in the CLH report for classification and provides evidence-based responses that the effects proposed for supporting classification are in fact secondary non-specific consequences of exposure to styrene and/or chance variations in data inherent when measuring large numbers of observations in complex studies. This position paper is organized as follows: - In the **summary** the main arguments are given without details - More details with references are found in the **main section** - In some cases specific numerical support is given in the **annexes** The most important arguments provided by the CLH report for Cat. 1B classification are found in measurements of various endpoints in an OECD guideline two generation reproductive toxicity and developmental neurotoxicity study in rats. A short outline of the study design is given in the main section on p.53 .In particular the CLH report refers to (in brackets the pages in the CLH report): - body weight effects (p. 61/61) - delays in attaining some preweaning developmental landmarks and preputial separation (p.61 and 62) - slight shift in the normal pattern of motor activity (p. 63) - decreased swimming ability (pnd 24) (p. 63)		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		- reduction in forelimb grip strength (pnd 60) p.62) - reduced pituitary gland weights (p. 62; but this effect is not mentioned in the summary section 4.11.4 nor in the classification section 4.11.6) As additional information the studies of Kishi et al. (1992, 1995)(p. 65), Katakura et al. (1999, 2001) (p. 66/67), Ninomiya et al.(2000) (p. 67) and Zaidi et al. (1985) (p. 67) are mentioned. *General considerations (main section p.20)*: Classification for developmental effects entails more than a catalogue of changes in isolated or individual endpoints but rather requires a consideration of the influencing parameters affecting such endpoints. These include, but are not restricted to: • the point of life span and generation affected, • severity of effects, and • maternal toxicity with possible effects on maternal care As the general basis for classification is evidence of developmental toxicity which is not a secondary non-specific consequence of other toxic effects, toxicological effects of styrene not directly related to developmental toxicity are summarized here. In rat studies repeated inhalation exposures to 500 ppm styrene produces degeneration of the olfactory epithelium with more subtle effects at 50 ppm resulting in histopathological alterations after 12 months exposure. In studies with prolonged exposure reduction of body weight is a general observation at exposures of 200 or 500 ppm. Clinical signs of respiratory tract irritation were observed in a 13 week study at exposure of 200 ppm. Mild narcotic effects that may impair maternal care have been described by various authors at exposures ranging from 50 to 300 ppm with a short lasting weight loss during exposure even at 50 ppm. The		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		exposure concentrations used in the OECD guideline two generation reproductive toxicity and developmental neurotoxicity study (i.e. 50, 150 or 500 ppm) are thus within the range known to already lead to toxicological effects. With styrene exposures producing such general toxicological effect the question to be answered in evaluating these points for classification is: - are the findings direct, specific effects on development, or - non-specific delays of development associated with maternal toxicity combined with some "chance" variations in data inherent in the large numbers of observations and measurements responsible for the findings. To help address this question the endpoints suggested in the CLH report as being specific development effects have been analyzed against those influencing parameters which might affect such observations: ***Body weight effects*** *(main section.p.25 .):* The CLH report points to statistically significant reductions in the bodyweights of male F2 offspring born to F1 rats exposed to 150 ppm styrene in the absence of statistically significant effects on body weights of F1 females in the 150 ppm treatment group during premating and gestation. In addition statistically significant reductions in bodyweight of the 500 ppm F2 pups and F1 pups (- pnd 22-28) are mentioned accompanied by reduced bodyweight of maternal animals. *General observation*: The proposition that this provides evidence of a specific developmental effect is not however supported by the available body weight information which shows:		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		• There were numerical reductions in body weights in F1 and F0 dams at 150 ppm during premating and gestation although not reaching statistical significance. • While body weights of F2 males at 150 ppm (pnd 21) were significantly different from F2 controls they were almost identical to F1 controls. • No statistically significant reductions in the bodyweights of F2 exposed to 150 ppm were observed during the post-weaning phase • A pattern of body weights effects were seen only in F2 but not in F1 offspring. • The persistence of reduced bodyweight of F2 pups (500 ppm) throughout postweaning may be attributed to the unexceptionally high control F2 weights. • A recent detailed analysis of a broad data base revealed no critical differences between the F1 and F2 generations and that an evaluation of the F2 offspring will very rarely provide critical information (Piersma et al., 2011). • As the body weights of control F2 offspring were clearly higher than those of control F1 offspring the body weight effects of exposed F2 pups may be a chance finding. • Weight reductions observed in parent generations of the 2-generation studies and in various other toxicological investigations indicate that body weight effects noted in offspring may rather be a general toxicological consequence of styrene exposure of parents, not being a specific developmental effect. *Point of life span and generation affected:* Significantly reduced body weight was only observed in F2 but not in F1 preweaning offspring. If the effects are regarded as exposure related, the different findings in both generations can only be explained by different exposure scenarios		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		of the F0 and F1 parents. In contrast to F0 animals (exposure only after puberty), F1 parents were exposed during pregnancy, lactation, and also after weaning up to puberty. *Severity of effects:* A pattern of body weight reductions only occurred in F2 (in the range of about 10%) but not in F1 offspring and body weights in exposed F2 offspring were very similar to those of F1 offspring. Therefore, this effect can by no means be regarded as severe and is best explained by the high F2 control body weights. Although reductions in body weight of 500 ppm F_2 pups continued throughout postweaning without exposure, this effect may similarly be attributed to the high control F2 weights persisting into the postweaning phase. In addition, in relative terms the 500 ppm F2 pups gained more weight compared to the 0 ppm pups. *Maternal toxicity with possible effects on maternal care:* Maternal toxicity must not only be defined by significantly reduced body weight but, as body weight effects in preweaning F2 offspring are mainly discussed here, any possible influence on maternal care must also be considered like olfactory effects, irritation and transient narcotic effects that are already to be expected at 150 ppm. *Assessment in the UK RAR (p. 292):* in the summary discussion it is concluded: "… - Although at 150 ppm there was a decrease in pup body weight, since this was small (up to 10%), limited to the pre-weaning period of the F_2 generation only and not accompanied by other related effects…" ***Delays in attaining some developmental landmarks*** *(main section p.31.):* The CLH report points to delays in developmental landmarks (pinna detachment, surface righting response, incisor eruption, preputial separation and hair growth) in 500 ppm F_2 pups.		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		General observation: The CLH document concedes these effects may be due to the delay in growth and thereby may indirectly be related to developmental toxicity. These developmental landmarks were not affected in F1 pups. In F2 pups the mean ages for pinna detachment, surface righting response, preputial separation and hair growth were not statistically significantly increased. Only incisor eruption was statistically significantly delayed in F2 500 ppm animals. *Point of life span and generation affected:* As the effects were only observed in F2 offspring at 500 ppm the same considerations apply to the delay in developmental landmarks as for the body weight effects. In this respect the findings of Piersma et al. (2011) have to be taken into account that an evaluation of the F2 offspring will very rarely provide critical information. *Severity of effect:* As the mean ages for acquisition of developmental landmarks were generally not statistically significantly increased, the relevance of this effect is questionable. Only for incisor eruption in F2 500 ppm rats a statistically significant delay was observed. But for F2 male controls the time until incisor eruption was extremely short (9.3 d) in comparison to F1 male controls (10.0 d). Thus, time until incisor eruption for F2 500 ppm males was just the same as for the control F1 males. *Maternal toxicity with possible effects on maternal care:* The delay of pre-weaning developmental landmarks occurred only in offspring of dams exposed to 500 ppm with statistically reduced maternal body weights. All other effects that may affect maternal care should also be taken into consideration. *Assessment in the UK RAR (p. 278/279):* "The attainment of the pre-weaning developmental landmarks (pinnal detachment, surface righting response, incisor eruption and hair growth) and the acquisition of the preputial separation were also slightly delayed in the high-exposure F_2		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		pups. It is considered that these effects were probably due to the slight delay in growth (reduced body weights) observed in these pups." ***Shift in pattern of motor activity*** *(main section.34.):* The CLH report points to the age-related pattern of motor activity being slightly shifted in the 500 ppm pups: the activities were lower (not statistically significant) at PND 13, then rose and were similar to control by PND 61. According to the CLH report this effect may be related to the growth delay in the pre-weaning stage. *General observation:* There were no statistically significant differences between all exposure groups at all time points. While at PND 13 motor activity was slightly decreased at 500 ppm, a high activity was found in females at 150 ppm as an indication for inherent variability. The only effects, if related to exposure at all, were found in the preweaning phase. *Point of life span and generation affected:* As motor activity was only measured in F2 offspring, a comparison to F1 offspring as e.g. for body weight is not possible. *Severity of effects:* The effects at 500 ppm never attained statistical significance. The measurements show a high variability and no clear dose relationship. *Maternal toxicity with possible effects on maternal care:* Motor activity was only affected at 500 ppm during the preweaning phase. This exposure level led to significantly reduced maternal body weights and all other effects that might affect maternal care have also to be taken into consideration. *Assessment in the UK RAR (p. 279):* "Therefore, the slight shift in the age-related pattern of motor activity observed in the high-exposure		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		group was considered to be related to the growth delay evident in this group of animals particularly in the pre-weaning stage." ***Decreased swimming ability (PND 24)*** *(main section p.36.):* The CLH report points to an increased straight channel swimming time at PND 24 for the 500 ppm offspring. *Point of life span and generation affected*: As straight swimming time was only measured in F2 offspring, a comparison to F1 offspring is not possible. *Severity of effects*: A "real" increase of straight channel swimming time would mean a generalised impairment of swimming performance that should also affect the total swimming times in the part for learning and memory in the maze test. But this was not the case. The mean swimming times of the contemporary control animals were low compared to historical control data while at 500 ppm the values were within the historical control range. The mean swimming times are derived from 4 consecutive trials. The most prominent difference was obtained in trial 1, while swimming times in trials 2-4 were similar over all treatment groups. Therefore, the difference in group mean swimming time reflects the unusual contemporary control value and a chance finding. *Maternal toxicity with possible effects on maternal care*: Straight channel swimming time was only increased in offspring of dams exposed to 500 ppm 3 days after weaning. This exposure level led to statistically reduced maternal body weights and all other effects that might affect maternal care should also be taken into consideration. *Assessment in the UK RAR (p. 280):* "Therefore, the effect on swimming ability observed at PND 24 did not represent an effect on learning and memory but it was just an indication of general malaise.		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Historical control data … show that the swimming time values … were within the historical control ranges and that the observed increase was due to an unusually low value in the concurrent controls. This suggests that this increase in swimming time may actually be an expression of normal variation and have no toxicological significance." ***Reduction in forelimb grip strength (PND 60)*** *(main section p.42)***:** The CLH report points to statistically significant reductions in the forelimb grip strength in both sexes of the 500 ppm group on PND 60. Hindlimb grip strength was reduced in males on PND 45. After correction of grip strength for body weight on the basis of proportionality this effect is considered to be a direct consequence of the styrene exposure. *Point of life span and generation affected*: As grip strength was only measured in F2 offspring, a comparison to F1 offspring is not possible. *Severity of effects*: Grip-strength shows considerable variation. Of the 500 ppm offspring only 6 of 20 males and 3 of 20 females fell outside the range of concurrent controls and the majority were within normal range. Grip-strength is influenced by body weight and body weights of 500 ppm animals were lower than controls. But a simple proportional correlation as applied in the CLH report is misleading. Although reductions in body weights on PND 63 were only moderate, during preweaning weight reductions were much more pronounced, resulting in continued reductions until measurement of grip-strength. There were no statistically significant effects on fore-limb grip strength on either PND 22 and 45. There was no statistically significant difference in hind-limb grip-strength although peripheral nerve damage typically leads to more pronounced effects on hind-limb grip-strength. A significant increase in fore-limb grip strength in females at PND 45 in the 150 ppm		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		group indicated to variability of the effect. The group mean values for fore-limb grip-strength are within the historical control range supporting the conclusion that the findings reflect normal variability. There was no underlying histopathology and therefore the difference in grip-strength is unlikely to represent a specific neurological effect. *Maternal toxicity with possible effects on maternal care:* Forelimb grip strength on PND 60 was only reduced at 500 ppm with significantly reduced maternal body weight *Assessment in the UK RAR (p. 280):* "the reduction in forelimb grip strength observed on PND 60 only is considered to be the consequence of the reduced body weight seen in these pups. Furthermore, as there was no similar difference in hindlimb grip strength at the same time point and no underlying histopathology, it is unlikely that the reduced forelimb grip strength represents a specific neurological effect of styrene". ***Reduced weight of the pituitary gland*** *(main section p.47.):* The CLH report points to statistically significant reductions of absolute pituitary gland weights for female F2 pups at 150 and 500 ppm, for males at 500 ppm and especially to the reduced relative weights for male F2 pups at 500 ppm. It is concluded in the CLH report that in the absence of information on the normal growth rate of the pituitary gland in fast-developing organisms the reduced pituitary weight may represent an adverse developmental effect. *General observation*: As determination of pituitary weights in pnd 21 F2 pups is not required by the test guidelines. Historical control data are not available. The high variability of pituitary weights in conjunction with the very low absolute weights (between 0.6 and 10.9 mg for F2 pups) at pnd 21 requires great caution when assessing weight differences of this tiny organ to avoid misinterpretations caused by chance variation.		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Point of life span and generation affected: Significantly reduced absolute or relative pituitary gland weights were only observed in pnd 21 F2 pups but not in pnd 21 or adult F1 pups. In this respect the findings of Piersma et al. (2011) have also to be taken into account that an evaluation of the F2 offspring will very rarely provide critical information. *Severity of effect*: No histopathological alterations were noted in the pituitary of 500 ppm exposed male or female F1 adult animals. Furthermore only a few exposed F2 pups fell below the range of the F2 controls. In addition the absolute and relative weights of the exposed F2 groups with statistically significant reductions were comparable to those of F1 control pups of the same age. *Maternal toxicity with possible effects on maternal care:* Reduced relative pituitary gland weights were only observed at 500 ppm with significantly reduced maternal body weight. *Assessment in the UK RAR (p. 278):* "given the lack of any associated histopathology, it is reasonable to assume that these pup organ weight reductions (including pituitary weight - added) are unlikely to represent adverse developmental effects" ***Effects on F2 pups secondary to body weight*** *(main section p.52):* The bodyweight of F2 control pups is much higher than that of the F1 control pups and apparently there is no dose response relationship for the F2 pups at 150 and 500 ppm. Thus the high bodyweight of F2 control pups may have occurred by chance. Several effects noted in F2 pups have a direct relationship with body weight (developmental landmarks, motor activity, swimming ability, grip strength). Under such circumstances the alterations of these parameters are not exposure related but a secondary consequence of the incidentally high control bodyweights.		

<table>
<tr><th>Date</th><th>Country / Organisation / MSCA</th><th>Comment</th><th>Dossier submitter's response to comment</th><th>RAC's response to comment</th></tr>
<tr><td></td><td></td><td>
General considerations regarding DNT studies (main section p.53): statistically significant alterations can be expected as chance findings when conducting complex investigations such as DNT studies which include measurements of 143 endpoints in 2 genders resulting in a total of 286 datasets to be statistically analysed. These datasets do not include the histopathological investigations, organ weight determinations and interval/trial data. Statistical analyses of all parameters at $p<0.05$ will lead inevitably to a substantial number of positive findings. Therefore it is necessary to consider functional domains for inter-correlated endpoints. Evaluation of such domains in 500 ppm F2 offspring does not show a consistent pattern that would indicate a direct impairment of development of the nervous system as displayed in the tables below:

Neuromuscular domain
<table>
<tr><th></th><th>PND 20-28</th><th>PND 60-74</th></tr>
<tr><td>Grip Strength</td><td>None</td><td>Decrease (M, F)</td></tr>
<tr><td>Mobility</td><td>None</td><td>None</td></tr>
<tr><td>Gait</td><td>None</td><td>None</td></tr>
<tr><td>Motor activity</td><td>None</td><td>None</td></tr>
<tr><td>Swim Time – Biel Straight Channel</td><td>Increase time</td><td>None</td></tr>
<tr><td>Neuropathology</td><td>Not evaluated</td><td>None</td></tr>
</table>
</td><td></td><td></td></tr>
</table>

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Activity and excitability domains PND 20-28 / PND60-72 Ease Removal: No effect / No effect Ease Handling: No effect / No effect Arousal: No effect / No effect Home cage-posture: No effect / No effect Motor Activity: (Increase activity?) n.s. / No effect Swim Time – Biel: Increase time / No effect Startle (Vmax): No effect / No effect CNS Neuropath: None / None ***Comments on the studies of Kishi, Katakura and Zaidi*** *(main section p.57):* Six studies are mentioned in the CLH dossier (Zaidi et al., 1985; Ninomiya et al., 2000; Kishi et al., 1992; 1995; Katakura et al., 1999; 2001). It is unclear how much weight is given to the studies of Kishi et al. (1992, 1995) and Katakura et al. (1999, 2001) for the proposal of cat. 1B. But in several sections the results of these studies are mentioned stating that delayed neurological development and behavioral effects have been reported at 300 ppm styrene in the absence of maternal toxicity. When comparing the CLH report and the UK RAR, the CLH report is identical or closely follows the UK RAR in the description of the methods and the results, but often major deviations are found in the overall assessment. We are of the opinion that the assessments in the		

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON STYRENE

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		UK RAR are scientifically by far more robust than those given in the CLH report. In the study of Zaidi et al. (1985) only used 3-4 female rats/dose and investigated receptors in the brain that are not contained in any regulatory guideline. Because of the very limited number of animals, the questionable toxicological significance of the observations, and the missing historical data, this study must not be used for an assessment of styrene. The studies of Kishi et al. (1992, 1995) and Katakura et al. (1999, 2001 were carried out by the same group of investigators. Both publications of Kishi are derived from the same experimental setup. In the first report of Kishi et al. (1992) the number of pregnant animals was 14, 3, and 7 at 0, 50, and 300 ppm, respectively. In the 1995 publication it was mentioned that "due to the limited number of inhalation chambers available only 12 litters exposed at the same period were evaluated" (5, 2, and 5 litters at 0, 50, and 300 ppm). If different subgroups were treated at different times under not exactly the same conditions, a statistical analysis of all the subgroups in combination may not be appropriate. Many of the findings reported by Kishi et al. (1995) were not observed in the Cruzan studies even under continuous exposure conditions. The findings of Kishi et al. (1995) are difficult to evaluate because of the small number of litters (5, 2, 5 at 0, 50, 300 ppm) in combination with the missing historical database for the highly variable endpoints. Kishi et al. (1995) themselves caution that "the findings of this study should be regarded as preliminary". Therefore the assessment of neurobehavioral development should rely on the Cruzan data.		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		The data of both Katakura et al. (1999, 2001) studies refer to the same basic experiment. As the same equipment was used as for the Kishi studies, there is uncertainty whether all animals exposed at the same time. In addition, the following shortcomings in the Katakura studies must be taken into account: - The lower number of pregnant rats as compared to the Cruzan study - No comparison is possible with historical control data - Alterations in neurotransmittors are not mirrored by histopathological findings - The toxicological significance of the neurochemical findings is unclear because of the large number of measurements with only a few significant differences to controls. Overall, these limited studies must not be considered as key or supportive in the evaluation and have no impact on the interpretation of the Cruzan et al. (2005a, b) studies given above. ***Conclusion.*** The observations mentioned in the CLH dossier do not provide sufficient evidence to cause a strong suspicion that styrene exposure produces specific developmental toxic effects: All the effects mentioned in CLH dossier can by no means be considered as being severe. Whenever a comparison between F1 and F2 generation was possible (body weight, developmental landmarks, pituitary weight, time to incisor eruption), the findings only occurred in F2. It has recently been shown		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		that there are no critical differences in sensitivity between F1 and F2 offspring. Therefore, these effects most probably are a chance finding. As all effects (apart from offspring body weight) were only noted for the high exposure group (500 ppm), maternal toxicity and impairment of maternal care have to be taken into account. If histopathology was done on corresponding tissues, there was no correlate to the effects observed (forelimb grip strength, pituitary weight). There was no consistency when the same endpoint was determined at different ages (motor activity, swimming ability, forelimb grip strength). Some effects observed have a high inherent variability that may lead just by chance to a statistical significance (forelimb grip strength, pituitary weight). If a comparison with historical data was possible, the effects at 500 ppm were within the historical range (swimming ability, forelimb grip strength). Studies of Kishi et al. and Katakura et al. cannot be taken as supportive evidence due to severe deficiencies. Evaluations should only be based on the guideline/GLP studies of Cruzan et al. The large amount of datasets in the DNT study should be evaluated according to patterns of effects. Thereby, no functional domains could be identified that were consistently affected. The weight of evidence indicates that the endpoints highlighted in the CLH report in addition to being of minor toxicological relevance are not specific developmental effects but rather non-specific findings associated with maternal toxicity or reduced maternal care in combination with some "chance" variation in data.		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Therefore based on the evaluation provided in this document, classification for developmental toxicity is not warranted for styrene. *End of first 19 pages of attachment (6)*		
21/11/ 2011	Czech Republic / Association of Chemical Industry of the Czech Republic	The Styrene Producers Association undertook a careful assessment of the available scientific information and concluded that the weight of the available evidence demonstrates that styrene is not selectively toxic to development and hence classification is not waranted. *ECHA comment: The attached document(7) "**Denmark proposes unjustified reprotoxicity classification for Styrene"** (Statement on CLP submisssion Oct 19 2011 Final.pdf) is copied below.*	Thank you for your comments. Your comments will be taken into consideration during the forthcoming discussions in the Risk Assessment Committee.	Thank you for your comments.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON STYRENE

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		cefic PlasticsEurope Association of Plastics Manufacturers 18 October 2011 **Denmark proposes unjustified reprotoxicity classification for Styrene** On Monday 10 October 2011, the European Chemicals Agency (ECHA) opened a 45 day public consultation on the proposal by the Danish Competent Authority (CA) for a revised harmonised classification and labelling for Styrene. The public consultation is the first step in the development of a scientific opinion from ECHA's Risk Assessment Committee (RAC) on this draft proposal. It will close on 24 November 2011. The Danish CA has proposed two new classifications[I] for Styrene under the EU's Classification, Labelling and Packaging (CLP) Regulation[II]. 1. The Styrenics industry fully supports the proposal to classify Styrene for Specific Target Organ Toxicity following repeated exposure (STOT RE 1). Indeed, the Styrene Consortium proposed this classification as *"a substance causing damage to the nervous system through prolonged or repeated exposure via inhalation"* in the Styrene REACH registration dossier submitted in October 2010[II]. 2. The Styrenics industry believes, however, that the Danish proposal to classify Styrene as a category 1B for reproductive toxicity, *"a presumed human reproductive toxicant"* is not justified by the available scientific data. The Styrene Producers Association undertook a careful assessment of the available scientific information and concluded that the weight of the available evidence demonstrates that styrene is not selectively toxic to development and hence classification is not warranted. The Styrene Producers Association will submit this position, and the supporting analysis, to the RAC via the current public consultation. Equally during discussions based on the same scientific datasets, held under the former EU classification system in 2007, the majority of EU Member State authorities agreed with the styrenics industry that the data was not sufficient for any classification for reproductive toxicity.		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Following the consultation, the Danish proposal and the comments of interested stakeholders will be reviewed by the RAC, who have a maximum of 18 months to form an opinion. The RAC opinion on Styrene will have no regulatory impact but will be forwarded by ECHA to the European Commission as a recommendation. The European Commission may then decide to propose an amendment to the classification, labelling and packaging requirements for Styrene as listed in the CLP Regulation. The estimated earliest possible adoption of such a change to the legal classification would be late 2013[iv]. The European Styrenics industry is working closely with all the relevant authorities to provide information in support of a "no classification" for reproductive toxicity for Styrene, and will continue to engage constructively throughout the process. For more information, please contact: Mr. Eric Faes Director, Styrenics Chain Email: efa@cefic.be; eric.faes@plasticseurope.org Tel.: +32 2 676 7227 [i] Link to AnnexXV from the Danish Competent Authority: [ii] CLP Regulation, 1272/2008: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:en:PDF [iii] Link to Styrene REACH Registration: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9dab35db-27e6-3e7a-e044-00144f67d249/DISS-9dab35db-27e6-3e7a-e044-00144f67d249_DISS-9dab35db-27e6-3e7a-e044-00144f67d249.html [iv] This timing assumes that the RAC will adopt its opinion during 2012 and that the European Commission would therefore include Styrene in the 2013 Adaptation for Technical Progress of the CLP. Styrene Producers Association Avenue E. van Nieuwenhuyse 4 B - 1160 Brussels Belgium Tel: +32 2 676 72 05 Fax: +32 2 676 7432 Email efa@cefic.be www.styrenemonomer.org www.plasticseurope.org *End of attachment (7)*		
21/11/ 2011	Belgium / European Trade Union Confederation	Styrene is included in the Trade Union priority List for REACH authorisation (http://www.etuc.org/a/6023)as a Repr. 1B	Thank you for the information.	Thank you for the information.
21/11/ 2011	Germany / MSCA	please find our comments in the enclosed document *ECHA comment: The attached document(4)* ***"DE Comments"*** *(DE Comments – CLH-Dossier Styrene.doc) is attached below.* **Reproductive toxicity:** 1) Decreased body weights:	If the significantly decreased pup body weight should be due to	1) RAC finds the reasoning of the DS

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		It is pointed out that in the treated groups the mean absolute pup body weights (bw) on PND 21 were similar between F1 and F2 pups. When comparing these absolute bw against each other, F2 pups had only minor decreases ranging from 0-5%. However, in the F2 control group the mean absolute pup bw on PND 21 was 9-10% higher compared to the F1 control group. This considerable disparity in mean absolute body weights between the F1 and F2 control animals may explain why in the treated groups of the F2 pups statistically significant decreases in mean relative pup body weights (i. e. mean absolute bw of the F2 treated groups compared to the mean absolute bw of the F2 control group) were observed on PND 21 ranging from 10-13%. Our conclusion: The partially statistically significant decreases in bw of F2-pups during the pre-weaning and post-weaning period are likely to be incidental findings due to the relatively high mean absolute body weights of the F2 control animals. Moreover, if these effects were considered as being treatment-related, it would need to be discussed whether the extent of bw reduction was really a specific reproductive toxic effect. 2) Decreased swimming ability: F2-pups were tested in the Biel Maze, *inter alia*, starting from PND 24 and over a period of seven consecutive days. Only on the first day of trail a significant increase in mean time to escape in the straight channel swimming trial was observed in male F2-pups of the high-dose group. However, if this effect was indeed related to styrene exposure, one would expect that the swimming ability during the immediately consecutive swimming trials in the maze was also markedly affected leading to a significant increase in swimming time. But this was not the case. In this context it is noted that, according to Cruzan et al. (2005), the number of errors occurring during the animals' search for the correct path in the Biel maze did not differ between the control and treatment groups. This means that the total swimming times between the groups were not biased by this factor. Our conclusion: The decreased swimming ability in male F2-pups of the high-dose group on PND 24 is likely to be an incidental finding. 3) Reduction in forelimb grip strength: We have no access to the original study report in order to check for results in single animals concerning forelimb grip strength testing.	high body weight in the control group it should have been seen in all exposed groups as they are all compared to the control group. This is not the case as the decreased pup body weight was seen mainly in the highest exposure group, i.e. the effect is treatment-related. Consequently, we find it unlikely that this finding is incidental. The extent of this decrease together with the other findings forms a pattern of developmental delays both before and after weaning (delays in attaining some pre-weaning developmental landmarks, slight shift in the normal pattern of motor activity and delayed preputial separation). Developmental retardation is in the criteria for classification one of the recognized four manifestations of developmental toxicity. Thus, such a long-lasting developmental retardation, i.e. up to and including sexual maturation, is considered	plausible and that there is an effect on the body weight of the F2 pups, in the range of 10%. The lack of effect on F1 is, however, noteworthy. 2) RAC acknowledges the comments as plausible, but also notes the very nice dose-response in the F2 males for this effect. The finding should be included in a WoE analysis. 3) RAC does not

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		However, we have access to document ECBI/19/06 Add 7 which was submitted for discussion to the TCC&L by industry in 2007. It contains data on grip strength testing in terms of single measurements for male and female animals of the control and high-dose group each. Based on this information, it is noted that there is a relatively large range of overlap between the measurements (see table below). Our conclusion: We question if the observed reduction in forelimb grip strength can be regarded as evidence for developmental toxicity. Not only is there a large range of overlap between the measurements but also the variability within each group (controls included) is quite considerable. Moreover, based on Cruzan et al. (2005) there is no consistent dose-response relationship for this endpoint.	as a specific developmental toxicity effect. Swim time as a measure for swim speed is assessed best in the straight channel as swim speed in the learning part of the test is confounded by other factors such as trying to solve the learning task. Thus, we do not find that the decreased swimming ability is an incidental finding. Grip strength: see response to UK from page 26	have access to all data either, and although there are clearly inconsistencies in the effects (forelimb vs. hindlimb, time points) there are not sufficient reasons for ignoring them.

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment

Mean grip strength (g) in forelimbs on PND 60

MALE			FEMALE	
Control	500 ppm		Control	500 ppm
	197			**127**
	217			**133**
	283			**160**
	323		183	183
	367			247
	377			267
417	417			280
	425		333	333
433			333	
	437		367	
443				383
	457			392
	460			393
467	467		425	
470				442
473			450	
475				458
483		**Range**	463	
	490	**of**		477
	500	**overlap**	483	
	500		493	
517				517
525			520	520
527				520
	533		525	
	580		558	
	583		577	
625				603
630			608	
643	643		617	
653			633	
675				677
	758		**693**	
783			**792**	
803			**867**	
870				
903				

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		4) Reduced weight of the pituitary gland: We are aware that the relative pituitary gland weight was reduced by 22% in males of the high-dose group (sacrificed on PND 21). However, since this organ is quite tiny and very light and thus possibly prone to high variability through the trimming process , it would be helpful to provide data on absolute pituitary gland weights and body weights of individual animals for a more detailed interpretation. Denmark states in the CLH-report: "Information on the normal growth rate of the pituitary gland in fast-developing organisms and especially its relationship to body weight development would be useful for evaluating this effect. However, in the absence of such information it is assumed that the reduced pituitary weight may represent adverse developmental effects of styrene exposure." (see p. 62, second paragraph). In this context, we question whether this effect shall be considered as evidence for developmental toxicity. 5) Delays in attaining developmental landmarks and shift in motor activity: Since these effects were not statistically significant (except for incisor eruption in the high-dose group), we conclude that these effects are not relevant for classification but are most probably due to decreased body weights in the F2 treated groups compared to the F2 control group. *End of attachment(4)*		RAC would welcome more data, but notes the very high variability among the PND21 pups. This variability could make the analysis more uncertain, but just as well indicate that the development of the pituitary is affected by the treatment. However, the lack of effects on females and in F1 clearly decreases the value of this observation.
22/11/ 2011	Netherlands / RIVM Bereau REACH / RIVM	The following effects were observed: Effects on fertility: o In an OECD/GLP compliant two-generation reprotoxicity study (unpublished, Stomp et al., 2003, Cruzan et al., 2005), the effects of styrene on fertility were evaluated. In this study, Sprague-Dawley rats (25/sex/group) were exposed via inhalation to 0 (clean air) or 50, 150 or		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		500 ppm styrene vapour for 6 hours/day. F0 animals were exposed for 10 weeks prior to mating and throughout 2-week mating period. Females were exposed during gestation/lactation, except for GD21-PND 4 when styrene was administered via oral gavage. F1 was treated from PND 22 and followed F0 protocol. F2 was not exposed directly but was potentially exposed in utero and throughout nursing during PND 0-21. Reproductive performance (i.e. mating behaviour and fertility), gestation length, litter data (number of pups, sex ratio), postnatal survival, sperm evaluations and primordial follicle counts were not adversely affected by styrene exposure across the generations. The mean length of the estrous cycle was shorter in the females exposed to 500 ppm compared to the controls, but this was within the historical control range and not considered exposure related. o In a 3-generation study in conjunction with a 2-year continuous exposure study Sprague-Dawley rats (Beliles et al., 1985) were exposed to 0, 125 and 250 ppm styrene via drinking water. F0 females showed significant reduction in body weight after 2 years of exposure and F2 females producing litters was (not significantly) reduced compared to 125ppm and control group. o In a study by Srivastava et al.,1989 adult (age not specified) Wistar rats were orally dosed with different concentrations of styrene (0, 200 and 400 mg/kg/day) for 60 days. Adult rats exposed to 400 mg/kg/day showed a significant decrease in epididymal sperm count, marked changes in histopathology and enzyme activity in the testes. The same authors also conducted a study with 1-day old male Wistar rats (7 males/group) which were orally dosed with 0, 100 or 200 mg/kg/day styrene for 60 days. Throughout the dosing period there were no clinical signs of toxicity. At termination of this study (PND61), the 200 mg/kg/day exposure has resulted in a significant decrease in testis weight and spermatozoa count and testicular enzyme activity was statistically changed. In conclusion: the only effects on fertility (decreased testis weight and spermatozoa count and altered testicular enzyme activity) were observed in the Srivastava-studies. Other repeated dose studies do not underline these findings.	We agree with the NL evaluation, i.e.: "Styrene exposure, mainly in the F2 at 500 ppm, resulted in exposure specific developmental effects (reduced weight of pituitary gland, decreased swimming activity,	

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Effects on development: o In the OECD/GLP compliant two-generation reprotoxicity study (unpublished, Stomp et al., 2003, Cruzan et al., 2005, the study design is described above), body weights were significantly reduced in the 150 ppm F1 males and in the 500 ppm F0 and F1 generation males and females. Styrene exposure also caused a statistically significant decrease in body weight gain of the 500 ppm F1 pups and in body weight of the 150 ppm and 500 ppm F2 pups. Reductions in body weight of F2 pups continued throughout post-weaning period. Delayed (approx 2 days) preputial separation was observed in the 500 ppm F1 males. Styrene exposure, mainly in the F2 at 500 ppm, resulted in exposure specific developmental effects (reduced weight of pituitary gland, decreased swimming activity, reduction in forelimb grip strength). o In a developmental toxicity study (Kishi et al., 1992/1995) Wistar rats (14, 3, 7/dose group) were exposed to 0, 50 and 300 ppm styrene via inhalation for 6 hr/day during GD 7-21. Pup body weights were significantly reduced in all exposure groups at PND 1 and PND 21 (both sexes) and at PND 77 (females only). Delayed pup (neuro)development (e.g. decreases in neurotransmitter levels) and behavioral effects were observed in the pre-weaning and post-weaning period following prenatal exposure to 300 ppm. No adverse were reported at the age of 3 months (>PND 120). o In another study (Katakura et al., 1999/2001), pregnant female rats (9-14/group) were exposed to 0, 50 or 300 ppm styrene via inhalation for 6 hr/day during GD 6-20. Food consumption and body weight gain were (not significantly) reduced in the 300 ppm group. Neonatal death was significantly increased in the 300 ppm group, but predominantly caused by a high death rate in one or a few litters. At PND21, body weight of male pups exposed to 300ppm was significantly reduced. Significant decrease of neurotransmitters at PND 21 (compared to PND0) and delayed behavioral effects at 300 ppm compared to control were observed. o In a mice study (Ninomiya et al., 2000), ICR female mice (18 or 19 per dose group) were exposed via whole body inhalation to 0, 2, 20 and 100 ppm during GD 0-15. No adverse effects were observed in non-pregnant females. At 100 ppm, dams showed signs of hyperactivity and reduced body weight gain. No mortalities were observed and the number of implantations, resorptions or live fetuses was not affected. At 100 ppm,	reduction in forelimb grip strength)." We agree that the reduced body weight may have influenced the other results (e.g. attainment of pre-weaning developmental landmarks, reduction in forelimb grip strength, increase in swim time in the straight swimming	RAC finds that this study gives some evidence of developmental effects, and although a borderline case, warranting

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		placental weight and foetal weight was reduced associated with impairment of maternal growth during pregnancy. o In an oral exposure study (Zaidi et al. 1985) rats (~12/group) were administered 0 or 200 mg styrene (in oil) by gavage from GD1until parturition. F1 litters (8 pups/litter) were divided into 4 groups each containing 3 litters: group A (controls), group B (styrene-exposed dams and their pups), group C (control dams and fostered in utero exposed pups) and group D (styrene-exposed dams and fostered unexposed pups). Exposure continued until week 3. In pups exposed during gestation and lactation or during lactation only, brain dopamine receptor levels and amphetamine-induced locomotor activity were significantly affected. In conclusion: it was shown that styrene exposure resulted in reduced body weight and body weight gain, developmental effects including neurological effects and some indications of behavioral effects, especially neuromotor functioning. Maternal toxicity may partly but not completely explain these effects. Based on these findings, we do agree that styrene exposure may be associated with developmental toxicity. However, the type of effects (reduced bodyweight and developmenatal delays) observed are considered of limited changes. According to DSD small changes including small differences in postnatal development may warrant classification with R63 or no classification. According to CLP (3.7.2.3.3), small changes in foetal bodyweight and small differences in postnatal development may not necessarily result in classification. Some observed effects as changes in neurotransmitters are more difficult to judge regarding their adversity. Further, there was limited maternal toxicity in some of the developmental studies. reduced maternal weight may result in lower pup weights and subsequently in developmental delays. In our opinion most effects are small and reversible and could possibly be secondary to the maternal toxicity. Classification in Repro cat 2 (DSD), equivalent to repro 1B (CLP) is considered incorrect. However, as for some effects the severity is unclear as is their relation with the maternal toxicity, classification with DSD Repr. Cat 3; R63 (=CLP Cat 2) and H361 is warranted. As fertility is sufficiently tested and seen the total data set, no classification for fertility is needed and a D can be added to H361.	trial at PND 24) and that this is difficult to disregard. Overall, however, we find that this pattern with effects seen up to young adulthood including also the effect on grip strength support classification as Repr. 1B or at least as Repr. 2. We agree that as fertility is sufficiently tested, no classification for fertility is needed and a D can be added to H361.	classification in category 2 (CLP). Agreed.

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
22/11/ 2011	Ireland / Health & Safety Authority / MSCA	The Irish CA is of the opinion that the available data is not sufficient to support a classification of Repr. 1B H360D. While we agree that it is difficult to quantify the impact of the reduced F2 pup weight on the effects observed in the high dose group in the 2-generation study (e.g. attainment of pre-weaning developmental landmarks, reduction in forelimb grip strength, increase in swim time in the straight swimming trial at PND 24), it is not possible to completely disregard the influence of the reduced body weight on these effects. The reduction in absolute pituitary weight in mid and high dose F2 females and high dose males may in part also be linked to the decreased body weight. The effect on the degeneration of the olfactory epithelium of the nasal cavity in parental F0 and F1 animals at the high dose may also have had some impact on maternal care of pups, although again this is difficult to quantify. The other studies presented have limitations, either in number of animals used or in the numbers of parameters tested, and thus are difficult to evaluate. Overall, given the uncertainties in the effects observed in the 2-generation study and the influence of reduced pup weight, we are of the opinion that the available data is not sufficient to support Repr. 1B H360D and that this could be considered a borderline case for Repr. 2 H361d/ no classification.	We agree that the reduced body weight may have influenced the other results (e.g. attainment of pre-weaning developmental landmarks, reduction in forelimb grip strength, increase in swim time in the straight swimming trial at PND 24) and that this is difficult to disregard. Overall, however, we find that this pattern with effects seen up to young adulthood support classification as Repr. 1B or at least as Repr. 2.	RAC shares the view of the Irish CA.
22/11/ 2011	Germany / DuPont Performance Coating GmbH / Company-Downstream user	Denmark (by the Danish Environmental Protection Agency) has provided a proposal for Harmonised Classification and Labelling (CLH Report) for styrene (CAS 100-42-5). The authors of the CLH Report propose to classify the substances for developmental and reproductive toxicity as follows: DSD Cat 2; R61 May cause harm to the unborn child CLP Cat 1B Justification for these proposed classifications begins on page 68 of the CLH dossier. Briefly, the authors of the dossier cite that there was no conventional evidence of developmental toxicity at inhalation exposures up to 600 ppm but that postnatal delays including delayed neurological development and		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		behavioral effects occur at 300 ppm in the absence of maternal toxicity. Additionally, the authors cite that a recent inhalation DNT study, revealed a pattern of delays both before and after weaning (decreased body weights, delays in pre-weaning developmental landmarks, slight alterations in motor activity, and delayed preputial separation) at 500 ppm. It is also noted that reduced offspring weights during lactation occur at 150 ppm in the absence of maternal toxicity. It is concluded by the dossier authors that exposure to 500 ppm causes a pattern of developmental delays, delayed neurological development, and behavioral effects. It is noted that maternal toxicity (body weight reductions and degeneration of the nasal olfactory epithelium) was produced at 500 ppm. In contrast to the proposed classifications provided above, we feel that styrene is clearly not classified for developmental and reproductive toxicity endpoints using the approach and arguments outlined below: a) A critical review of the studies that are driving the proposed Danish classification revealed that the Danish proposal appears to rely upon interpretations of data provided from the relevant studies that draw different or less definitive conclusions that either the original study authors or an Expert Panel convened by the NTP. There is a mention of this difference of opinion on page 11 of the CLH dossier. b) A review of all relevant developmental and reproductive toxicity data for styrene was provided by the "NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Styrene", Ulrike Luderer et al., 2005. The expert panel concluded that the data from experimental animals are sufficient to conclude that styrene is neither a selective developmental nor a reproductive toxicant. The effects of styrene exposure via oral gavage and/or inhalation during pregnancy were studied in mice, rats, and/or rabbits (as summarized in the NTP report). Taken together, the expert panel concluded that the developmental toxicity of styrene is minimal and only observed in the presence of maternal toxicity. When comparing the expert panel report and the original studies with the justification for classification in the CLH dossier, it is apparent that in some cases, the Danish authors are in disagreement with both the original study authors as well as the expert panel conclusions. c) The critical study in question is the DNT study reported by Cruzan et	The Cruzan study was most likely not included in this evaluation. We agree that the Cruzan study is very important for the evaluation. However, we disagree with the argument used for disregarding "the exposure-related developmental and neuromotor changes identified in F2", i.e. that these endpoints are known to be "age- and weight-sensitive parameters". Obviously, endpoints for developmental toxicity	

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		al., 2005c. The DNT study was a component of a multigeneration reproduction study (Cruzan, 2005b) which evaluated inhalation exposure levels of 0, 50, 150, and 500 ppm. In the Cruzan DNT paper, the authors conclude that "the exposure-related developmental and neuromotor changes identified in F2 pups from dams exposed to 500 ppm occurred in endpoints known to be both age- and weight-sensitive parameters, and were observed in the absence of any other remarkable indicators of neurobehavioral toxicity. Based on the results of the study, an exposure level of 50 ppm was considered to be the NOAEL for growth of F2 offspring; an exposure level of 500 ppm was considered to be the NOAEL for F2 developmental neurotoxicity." In the multigeneration reproduction study, Cruzan et al., identified NOAELs of 50 ppm for parental toxicity and 500 ppm for reproductive toxicity. The NTP expert panel also reviewed the Cruzan studies and factored these data into the conclusion that styrene is neither a developmental nor a reproductive toxicant based on data from experimental animals. d) In the CLH justification summarized above, the dossier author also cites effects at 300 ppm in the absence of maternal toxicity. The studies that appear to be driving this justification are studies that include unconventional endpoints with varying experimental design attributes and appear to be investigative studies. Therefore, the studies are not required to include all of the endpoints deemed relevant to safety and hazard assessment exercises. Given that there is a database of available guideline-compliant safety assessment studies, the investigative studies can be considered informative but should not outweigh the conclusions from the guideline-compliant safety assessment studies. These investigative studies were also reviewed by the Expert Panel who concluded that "although these studies do indicate some effects of styrene at high dose levels, it is unclear whether these effects represent adverse changes. Because they were measured at a limited number of time points, it is possible that changes represent developmental delays or transitory changes and not permanent functional deficits."	and especially developmental retardation are age-sensitive – if not they would not be relevant for assessing developmental delays. These studies have been included as part of the weight of evidence including due considerations of their limitations and their strengths i.e. lack of effect on maternal body weight at 300 ppm.	RAC has noted the limitations, but finds that the studies should be considered in a WoE analysis.
24/11/ 2011	Sweden / MSCA	SE supports classification of styrene (Cas No 100-42-5) as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard classes and differentiations.	Thank you for your support.	Noted
24/11/ 2011	France / MSCA	We have some uncertainties as for the classification of styrene in category 1B because of the inconsistency of some results of tests. In particular, the	The apparent discrepancy between the increased	RAC also finds that Repr. 1B cannot be

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		rotarod performance is affected on day 30 and 60 but not on day 120 (showing probably the reversibility of the effects), idem for the spontaneous activity which is increased on days 30-31 and 60-61 but not on days 127-128 (Kishi 1992, 1995). Moreover, in the Biel Maze swimming trials, the results show discrepancies between PND24 (increase of the mean time to escape in straight channel in 500 ppm male offspring) and PND62 (no increase of the mean time). Otherwise, the reliability of the studies is questionable more particular for Kishi and Katakura studies (not enough animals used). In addition, we wonder in which proportion the reduction of body weight may influence some toxic effects as the delayed preputial separation, or in the increased then return to normal mean time to escape in straight channel swimming trial (Stump and Cruzan). However, on the basis of the OECD- and GLP-compliant two generation reproduction toxicity study of Stump and Cruzan, several effects consolidate us in the choice of the category 2 classification. Decreased absolute and relative pituitary weight and decreased grip strength are effects which are directly attributable to the styrene exposure. Moreover, Katakura demonstrates that some effects as the delayed developmental landmarks were not due to decreased body weight, suggesting that the effect was directly related to styrene exposure.	swim time on PND 24, but not on PND 62 is not evaluated as a discrepancy by us. The reason for that is that the testing on PN 62 may not be nearly as sensitive as the one on PND 24, because there is a big difference in body weight, brain development and muscular strength between rather young pups and adult animals. This is actually supported by the positive control data, where effects of the positive controls were seen on PND 24, but not PND 62. Overall, we find that the pattern of effects seen up to young adulthood support classification as Repr. 1B or at least Repr. 2 as proposed by you.	supported, and finds Repr. 2 as a more adequate classification.

Respiratory sensitisation: no comments received

Other hazards and endpoints

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
17/11/ 2011	Belgium / Eric Faes /CEFIC	Summary We agree that the proposed classification (STOT RE) is justified based on ototoxicity. We do not agree that the data on color vision are sufficient to justify such a classification. From the data presented it is	We note that you agree that STOT RE 1 is justified based on ototoxicity. Regarding the effect of	RAC supports STOT RE 1 based on the ototoxicity. Regarding effects on colour vision,

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		completely unclear what other neurotoxic effects are deemed sufficient for this classification. The most relevant studies must be given and evaluated in a scientifically robust manner before such effects can be used for classification. Our comments on the interpretation of the various single studies referenced in the CLH report point to differences in the evaluations by the CLH report and the UK RAR. We are of the opinion that that the assessments in the UK RAR are scientifically by far more robust than those given in the CLH report. In addition various neurotoxic effects are mentioned, but references are missing to support these claims. Such effects relate to unspecific neurotoxicity, nerve conduction velocity, EEG effects, permanent changes in neurotransmitter concentrations and the sense of smell. Finally, there are some recent relevant publications not mentioned in the CLH report, but which may be essential for a scientifically robust assessment. Please refer for full details to attached PDF document *ECHA comment: The attached document(8)* ***"Response of the Styrene Producers Association (*) to the CLH proposal (Sept. 2011) for the classification of styrene for Specific Target Organ Toxicity as a STOT RE 1 toxicant according to Regulation (EC) No 1272/2008 (CLP)"*** *(COMMENTS RELATED TO NEUROTOX _ Nov 15 2011_FINAL EDITION.pdf" is provided separately. Copy 3 first pages below:*	styrene on colour vision we still find that the many human data, as well as the results of the single animal study, support the classification of styrene as STOT RE 1. In our opinion discrimination of colour vision is an adverse and serious effect. This view is in agreement with the fact that ACGIH as well as several other Occupational TLV-authorities have reduced the TLV of styrene to 20 ppm because loss of colour discrimination is considered as a serious effect. It is now up to the Risk Assessment Committee to conclude on the specific target organ(s) toxicity.	RAC finds these effects being well documented (e.g in the meta analysis by Paramei *et al*. (2004)). However, because of the difficulty to evaluate the adversity of these effects we agree that this effect as such do not justify classification, even though it supports STOT RE 1 based on the ototoxicity. Thanks for the information and the publications (Nichols, J. J., Good, G. W. (2006). Quality of life and color vision: the significance of acquired dyschromatopsias. SIRC Review, Nov. 2006: 146-152 -Paramei, G. V., Meyer-Baron, M., Seeber, A. (2004). Impairments of color vision induced by organic solvents: a meta-analysis study. Neurotoxicol. 25: 803-816 -Seeber, A., Bruckner, T., Triebig, G. (2009). Occupational styrene exposure, color vision and contrast sensitivity: a cohort study with repeated measurements. Int. Arch. Occup. Environ. Health 82:

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Response of the *Styrene Producers Association (*)* to the CLH proposal (Sept. 2011) for the classification of styrene for Specific Target Organ Toxicity as a STOT RE 1 toxicant according to Regulation (EC) No 1272/2008 (CLP) **Table of contents** Summary p 3. Introduction p.4 Comments related to section 2: "BACKGROUND OF THE CLH PROPOSAL" p.4 4.7.1: "Non-human information;studies investigating specific organ toxicity: auditory system" p.5 4.7.1: "Non-human information; study investigating the relative ototoxicity of styrene" p.5 4.7.1: "Non-human information; studies investigating specific organ toxicity: ocular system" p,5 4.7.1: "Non-human information; studies investigating specific organ toxicity: the nervous system" p.6 4.7.1.5: "Human information; otoneurological and audiometric studies" p.6 4.7.1.5: "Human information; studies on color vision" p.9 4.7.1.6: "Other relevant information" p.13 4.7.1.8: "summary and discussion of repeated dose toxicity....; dose response estimation including weight of evidence consideration" p.15		757-770 -Triebig, G., Bruckner, T., Seeber, A. (2009).Occupational styrene exposure and hearing loss: a cohort study with repeated measurements. Int. Arch. Occup. Environ. Health 82: 463-480). The publications add useful information that was missing in the CLH dossier, but do not really change the interpretation of the overall database. RAC has considered the detailed comments, and also consulted the EU RAR, when preparing the RAC opinion.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON STYRENE

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		4.7.1.9: "comparison with criteria of repeated dose toxicity findings...." p.16 4.7.1.10: "conclusions on classification and labelling of repeated dose toxicity .... according to DSD" p.19 4.8.2: "comparison with criteria of repeated dose toxicity .... for classification as STOT RE" p.19 4.8.3: "conclusions on classification and labelling of repeated dose toxicity .... for classification as STOT RE" p.20 References p.21 Annex: Comparison of the studies of Gong et al. (2002) and Seeber et al. (2009) p.22 (*) The Styrene Producers Association, SPA, is a Sector Group of CEFIC, the European Chemical Industry Council. The members of the SPA are BASF SE, Bayer Material Industries, LyondellBasell Industries, Polimeri Europe, Repsol-YPF, Sabic, Shell Chemicals, Styrolution , Styron, and Total Petrochemicals		

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Summary We agree that the proposed classification (STOT RE) is justified based on ototoxicity. We do not agree that the data on color vision are sufficient to justify such a classification. From the data presented it is completely unclear what other neurotoxic effects are deemed sufficient for this classification. The most relevant studies must be given and evaluated in a scientifically robust manner before such effects can be used for classification. Our comments on the interpretation of the various single studies referenced in the CLH report point to differences in the evaluations by the CLH report and the UK RAR. We are of the opinion that that the assessments in the UK RAR are scientifically by far more robust than those given in the CLH report. In addition various neurotoxic effects are mentioned, but references are missing to support these claims. Such effects relate to unspecific neurotoxicity, nerve conduction velocity, EEG effects, permanent changes in neurotransmitter concentrations and the sense of smell. Finally, there are some recent relevant publications not mentioned in the CLH report, but which may be essential for a scientifically robust assessment. *End of 3 first pages of attachment (8).*		
21/11/ 2011	Belgium / European Trade Union Confederation	Styrene is included in the Trade Union priority List for REACH authorisation(http://www.etuc.org/a/6023)as a neurotoxicant. Styrene is also known to be endocrine disrupters according to the Community Strategy for Endocrine Disrupters (COM(1999)706; COM(2001)262; SEC (2004) 1372; SEC(2007)1635)	Thank you for your comments	Noted
22/11/ 2011	Netherlands / RIVM Bereau REACH / RIVM	Repeated dose toxicity After prolonged exposure by inhalation, styrene causes a number of neurotoxic effects, including a chronic impairment of auditory function and colour vision. We agree with a classification of styrene with STOT RE1 and Xn, R48/20. This classification is also in accordance with discussions and conclusions of the TCC&L group.	Thank you for your support.	Noted
22/11/ 2011	Ireland / Health & Safety	The Irish CA is in agreement with the proposal to classify styrene as STOT RE1 H372 (R48/20).	Thank you for your support.	Noted

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON STYRENE

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
	Authority/ MSCA			
24/11/ 2011	Sweden / MSCA	Specific target organ toxicity- repeated exposure SE supports classification of styrene (Cas No 100-42-5) as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard classes and differentiations.	Thank you for your support.	Noted

ATTACHMENTS RECEIVED: 8

1. **The European UP Resin Sector Group - Statement concerning styrene-free technologies** (Cefic Styrene.pdf). Submitted by Germany/ Vosschemie GmbH / Company-Downstream user. ***Comment is copied into the table.***

2. **Synthos_final_styrene_document.pdf.** Submitted by Czech Republic /Synthos Kralupy a.s./ Company-Manufacturer. ***Comment is copied into the table.***

3. **komentarz do zmiany klasyfikacji styrenu.pdf.** Submitted by Poland / Synthos Dwory Sp. z o.o. / Company-Manufacturer. ***Comment is copied into the table.***

4. **DE Comments – CLH-Dossier Styrene.doc.** Submitted by Germany /MSCA. ***Comment is copied into the table.***

5. **Comment on the section 2.4.1 of the Styrene annexe XV dossier** (Comment on the section 2 4 1 (SDS aspects).docx). Submitted by Belgium / SPA(CEFIC)/ Industry or trade association. ***Comment is copied into the table.***

6. **Response of the Styrene Producers Association (*) to the CLH proposal (Sept. 2011) for the classification of styrene as a Cat. 1B reproductive toxicant (developmental effects) according to Regulation (EC) No 1272/2008 (CLP)** (COMMENTS RELATED TO REPROTOX _ Nov 15 2011_FINAL EDITION.pdf). Submitted by Belgium / CEFIC. ***Copied the first 19 pages into the table. The full document of 83 pages is not copied here.***

7. **Denmark proposes unjustified reprotoxicity classification for Styrene** (Statement on CLP submission Oct 19 2011 Final.pdf). Submitted by Czech Republic /Association of Chemical Industry of the Czech Republic. ***Comment is copied into the table.***

8. **Response of the Styrene Producers Association (*) to the CLH proposal (Sept. 2011) for the classification of styrene for Specific Target Organ Toxicity as a STOT RE 1 toxicant according to Regulation (EC) No 1272/2008 (CLP)** (COMMENTS RELATED TO NEUROTOX _ Nov 15 2011_FINAL EDITION.pdf). Submitted by Belgium / CEFIC. ***Copied the first 3 pages into the table. The full document of 25 pages is not copied here.***