Committee for Risk Assessment

RAC

Annex 2
Response to comments document (RCOM) to the Opinion proposing harmonised classification and labelling at EU level of

N-(hydroxymethyl)acrylamide; methylolacrylamide; [NMA]

EC Number: 213-103-2
CAS Number: 924-42-5

CLH-O-0000001412-86-211/F

Adopted

8 June 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON N-(HYDROXYMETHYL) ACRYLAMIDE; METHYLOLACRYLAMIDE; [NMA]

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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

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

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Substance name: N-(hydroxymethyl)acrylamide; methylolacrylamide; [NMA]
EC number: 213-103-2
CAS number: 924-42-5
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
27.07.2017	Germany		MemberState	1
Comment received				
The given information about NMA and its possible metabolite AA was not sufficient. As one of the reasons to classify NMA as Carc. 1B, Muta. 1B and STOT RE1 the structural similarity to AA is given which is classified in the same way for these toxicological endpoints. We think a more detailed explanation of the relationship between both substances is necessary. In our view it is not made clear enough in the dossier, whether a (partly) metabolization of NMA to AA is proven or not. The results of studies in dossier part "Toxicokinetics" are not explicit: "no epoxide was found in the study" (Mathews, 2001) and "NMA… but no evidence found for conversion to AA in vivo. … it is not known whether NMA is converted to an epoxide metabolite" (Edwards, 1975). In addition the mechanism presented in this chapter is only a "potential metabolic pathway for AA and NMA".				
Dossier Submitter's Response				
The data are contradictory among publications in literature. No epoxide was found in the study by Mathews, 2001, in contrast Paulsson *et al*, 2002 stated that NMA is known to convert into acrylamide, and both chemicals have been reported to be capable to acrylamide-hemoglobin (AA Hb) adducts. A OECD QSAR toolbox v3.3.0 analysis supports the hypothesis that NMA is converted into acrylamide or an epoxide. In addition the Hardarian tumors observed with NMA treatment in mice are an indicator of an epoxide effect (Hue-Hua L. Hong,Christopher D. Houle, Thai-Vu T. Ton, and Robert C. Sills. K-*ras* Mutations in Lung Tumors and Tumors from Other Organs are Consistent with a Common Mechanism of Ethylene Oxide Tumorigenesis in the B6C3F1 Mouse. Toxicol Pathol. 2007; 35(1): 81–85). This is thus consistent with the hypothesized mode of action (formation of an epoxide metabolite responsible of the genotoxicity and carcinogenicity of NMA).				

In summary there is no guideline kinetic study demonstrating the conversion of NMA in epoxide however there are some evidence from other types of study.
RAC's response
Noted.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
27.07.2017	Germany		MemberState	2
Comment received				
Classification proposal as Carc. 1B is supported based on statistically increased incidence of tumours (ovary and lung) in both sexes (lung) of a single species (mice) in a well-conducted study under GLP (NTP 1989), which is considered as sufficient evidence of carcinogenicity (CLP Regulation section 3.6.2.2.3.). However, presentation of data should be more precise. Page 25/26, table 15 Historical control data for tumour incidences in all organs described should be provided. Moreover, data for alveolar bronchiolar adenomas and alveolar bronchiolar carcinomas for both sexes are missing (only combined numbers are shown for both sexes). Tumour incidences should be given as %. Page 30, table 16: Please consider changing the point 'Consideration of mutagenicity' based on the information given in the specific comment for 'Mutagenicity below'.				
Dossier Submitter's Response				
The presentation of data of increased incidence of tumors (ovary and lungs) in both sexes on a single species (mouse) are indicated in section 3.2. carcinogenicity pages 57 to 75 in annex 1. Table 32 and Table 33 in annexe 1. Historical control data for tumour incidences in all organs are provided pages 71to 74 table 32 Combined adenomas and carcinomas for both sexes and inciences expressed in % are also indicated. Page 30, table 16 of CLH report : see response to specific comment on mutagenicity.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.08.2017	Netherlands		MemberState	3
Comment received				
There is a clear difference in the carcinogenic response between rats and mice as rats do not develop tumours. The only available mutagenicity test which compares both species				

(Paulsson, 2002) also shows positive results in mice but negative results in rats for the formation of micronuclei. This suggests differences between the two species. The cause of this difference is unclear and the species relevant for humans is unknown. As the suggested classification is based on the combination of carcinogenicity and mutagenicity but both seem to be species specific, classification in category 1B can be questioned.

According to the Risk Assessment Report (RAR, 2002) and its registration dossier, AA induces tumors in amongst others thyroid, adrenals, mammary glands, and testis in rats. As both the tumor type and species differ, the role of AA in the carcinogenicity of NMA is questionable. Do you have any information on differences in metabolism or mode of action that may explain these different outcomes between NMA and AA?

Further, an additional carcinogenicity study in transgenic mice is available with N-methylolacrylamide (The Journal of Toxicological Sciences Vol. 40 (2015) No. 6 December p. 685-700).

Dossier Submitter's Response

We consider that category 1B is more justified than category 2 based on the following arguments

1. There are effects in one species and in two sexes. According to CLP guidance, "*an increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites*." Therefore the classification category 1B is fulfilled even if effects are not reported in both rat and mouse species. In the absence of data suggesting that mice are not relevant to humans, this species is judged adequate for concluding on carcinogenicity.

2.Carcinogenic effects are reported in several organs: Hardarian gland, liver, lung and ovary. The occurrence of tumours at multiple sites also support classification as Cat. 1B.

Even if there is no equivalence in Hardarian tumor for human, according to CLP guidance, it is stated that "*tumours occurring in such tissues indicate that the substance has the potential to induce carcinogenic effects in the species tested. It cannot automatically be ruled out that the substance could cause similar tumours of comparable cell/tissue origin (e.g. squamous cell tumours at other epithelial tissues) in humans*." In addition these tumors are an indicator of an epoxide effect (Hue-Hua L. Hong,Christopher D. Houle, Thai-Vu T. Ton, and Robert C. Sills. K-*ras* Mutations in Lung Tumors and Tumors from Other Organs are Consistent with a Common Mechanism of Ethylene Oxide Tumorigenesis in the B6C3F1 Mouse. Toxicol Pathol. 2007; 35(1): 81–85). This is thus consistent with the hypothesized mode of action (formation of an epoxide metabolite responsible of the genotoxicity and carcinogenicity of NMA).

There are also liver tumors observed in mice. According to the CLP guidance, liver tumours present a high spontaneous tumour incidence in B6C3F1 mice. Thus historical control data (HCD) are useful to judge the biological significance of these tumours.

In females combined adenomas/ carcinomas:
Overall rates: 17/49 (35%)
Adjusted rates (relative to mortality): 48.2%
Terminal rates: 15/33(45%)

These incidences are clearly above the NTP HCD:
In water gavage vehicle controls: 22/348 (6%±5%)
In untreated controls: 107/2032 (5%±4%)

In males combined adenomas/ carcinomas
Overall rates: 26/50 (52%)
Adjusted rates (relative to mortality):: 76.8%
Terminal rates: 14/21(67%)
These incidences are clearly above the NTP HCD:
In water gavage vehicle control: 106/347 (31%±6%)
In untreated controls in NTP studies: 609/2032 (30%±8%)

In conclusion despite the high spontaneous incidence of the hepatocellular tumors they highly exceeded HCD. Thus, they should be considered for classification purpose.

Moreover malignant tumours were reported in ovary and lungs which clearly contribute to the weight of evidence of sufficient evidence of carcinogenicity.

3.There are some evidence that NMA is metabolized in AA and in epoxide which support a classification 1B. See also response to comment 1.

We acknowledge rats and mice are both sensitive to carcinogenicity of AA in contrast to NMA for which only mice develop significantly tumors. However there is a similar response in targeted organs with AA and NMA in particular mice develop tumors in Hardarian gland, liver, lung, ovary, forestomach, spleen (Beland *et al.,* 2013).

4.Based on the publication by Tsuji, 1995 (The Journal of Toxicological Sciences Vol. 40 (2015) No. 6 December p. 685-700) you refer, the authors concluded that significant changes of expression following NMA treatment were all related to inflammation in lung in both the ras H2Transgenic and non transgenic mice. The results suggested that 4-weeks' NMA treatment was too short to detect tumorigenic potential in the rasH2 Tg mice. This study is just a screening and do no replace a good quality of carcinogenicity as NTP study. The authors suggest a threshold carcinogenic effect but the effect on carcinogenicity is not called to be into question. However the study alone is not sufficient to demonstrate an absence of mutagenic effect in regard to results reported in guideline mutagenicity studies described in the CLH report.

We consider that Carc. Cat 1B is still justified.

RAC's response
Noted. RAC concurs with the classification proposed by the DS.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
27.07.2017	Germany		MemberState	4
Comment received				
Classification proposal is not supported. Page: 23, table 14 (Comparison with the CLP criteria): Overall, no in vivo mutation study performed according to an OECD test guideline is available for NMA.				

Results from in vivo micronucleus assays (considered by the DS to be performed similar to OECD TG 474 (Paulsson 2002, Witt 2003)) are contradictory (as also stated in table 14 in the CLH report).
Further, there are two 13-week oral in vivo dominant lethal assays in mice available with positive results. These both studies, according to the DS; were not performed following OECD TG 478 but considered as 'reliable with restriction'. However, the DS stated that no positive controls were included in the tests. According to OECD TG 478 concurrent positive control animals should always be used unless the laboratory has demonstrated proficiency in the conduct of the test and has used the test routinely in the recent past. In table 13 in the CLH dossier no information is provided why concurrent positive controls have not been included. Without positive controls the sensitivity of the given tests cannot be estimated. Thus, based on the information provided in table 13 the tests are not considered to be reliable and a substantiated assessment of the relevance of the test results seems to be impossible.
Thus, classification criteria for classification in Category 1B are not fulfilled (in vivo heritable germ cell mutagenicity tests in mammals are not reliable, contradictory results in in vivo somatic cell mutagenicity tests in mammals).

Page 24, table 14 (Comparison with the CLP criteria)
It is stated by the DS that NMA is a structural analogue of AA which is classified as Muta. 1B. According to CLP regulation (table 3.5.1) substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens. As a reliable positive in vitro mammalian mutagenicity assay is available for NMA (NTP 1989) and the DS postulated structural similarity to acrylamide (AA), classification criteria for classification in Category 2 are considered to be fulfilled.

In conclusion, based on the provided information by the DS, classification rather as mutagen Category 2 than Category 1B seems to be appropriate for NMA.

Page 19-22, table 13
It would be appreciated if important information would be added to table 13, e.g. all dose levels should be provided in mg/kg bw/d; for the dominant lethal assay please indicate total number of implants, for the micronucleus assays please provide: results on positive controls, the number of immature erythrocytes scored per animal and information on sampling times.

Dossier Submitter's Response

Dossier submitter disagrees and maintains classification proposal as Muta. Cat.1B.

We agree that positive controls are missing in both dominant lethal studies (Chapin (1995) and Witt (2003)) however these studies are judged of good quality. Moreover, the lack of positive control is considered as a limitation in particular in case of negative result. Here, the results are positive with NMA showing a sufficient sensitivity of the test. Even if not conducted according to OECD guideline, both *in vivo* dominant lethal assays in mice (Chapin 1995 and Witt 2003) are conducted within the well recognized RACB protocol from the NTP. This design has been used by NTP for 15 years. For example, acrylamide which is classified Muta. Cat.1B was also tested in the same type of protocol. Increased postimplantation loss (dominant lethal effect) was reported.This support the fact this methodology is appropriate.

The micronucleus test on somatic cells gave positive results in mice in guideline study with positive control (Paulsson, 2002).

The kinetic study by Edwards (1975) showed a distribution of NMA in blood following iv administration of NMA (see table 3 of Edwards (1975) publication). Distribution and reactivity of acrylamide and NMA were very similar. Both compounds distribute very rapidly throughout the total body water and are then removed with a half life of under 2 hours. Witt (2003) study reported some levels of radioactivity (even if low) in testis (Table VIII, Witt 2003)) that underscores the sensitivity of germ cells to genetic damage from NMA".

In summary, positive results were both found in dominant lethal studies and in one guideline micronucleus assay. Distribution data from Matthews (2001) study show that NMA is well absorbed and thus systemically available. Since germ cell such as the spermatogonia are generally not protected from substance exposure by the blood-testes barrier formed by the Sertoli cells, it is considered that germ cells will be exposed to the substance. This is supported by distribution data in testis from Witt (2003) study.

Page 24, table 14
Structural similarity with AA is an additional argument to support classification as Muta. Cat.1B. This information should be taken into account in a weight of evidence approach integrating the positive results reported with NMA in the mutagenicity studies in germ and somatic cells.

Page 19-22, table 13: the equivalent doses estimated are around 13, 37 and 68 mg/kg bw/d for males and 17,47 and 101 mg/kg bw/d for females: see page 40 annexe 1 for details

Dominant lethal assay:
Chapin (1995): for total number of implants: see table 13 p 42 annexe 1; Witt (2003) : see table 14 p46 annexe 1 for details.

Micronucleus assay:
NTP 1989: see p50 annexe 1 for details
Results of positive control: positive (see table 19 p50 annexe 1); no data on number of immature erythrocytes scored per animal, in the study 2,000 polychromatic erythrocytes were scored for the incidence of micronucleated cells in each of five animals per dose group. Sampling times information : 24 hr after the second injection.

Paulsson *et al*., 2002: see p51 annexe 1 for details
Results of positive control: positive with MMC, no data on number of immature erythrocytes scored per animal; sampling information: blood collected 24 and 48h for rats and 48h for mice.

Witt *et al.,* 2003: see p 54 annexe 1 for details
Results of positive control : positive with DMBA (dimethylbenzantracene) for acute study and with urethane for subchronic study (see p 55 annexe 1); no data on number of immature erythrocytes scored per animal.
Acute study: scoring *:* Two thousand PCE were scored per animal for the frequency of MN. In addition, 1,000 total erythrocytes were analyzed to determine the percent PCE (%PCE), as a measure of toxicity to the bone marrow from NMA.
Subchronic studies (31 day gavage and 13 week drinking water)*:* scoring*:* Bone marrow samples from five mice per treatment group were scored for MN-PCE and %PCE. Blood

smears from the same five animals were scored for the frequency of micronucleated normochromatic erythrocytes (MN-NCE). sampling times information available: acute study : 2 treatments separated by 24hr, bone marrow obtained 24 hr after the second treatment (p54 annexe 1); subchronic study: 31-day and 13 week after administration.
RAC's response
Noted. RAC concurs with the classification proposed by the DS.

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2017	Finland		MemberState	5
Comment received				
Two dominant lethal tests in mice conducted with N-(hydroxymethyl)acrylamide showed positive results. Classification criteria for Muta. 1B; H340 H is met. FI CA supports the proposed classification of Muta. 1B; H340 May cause genetic defects for N-(hydroxymethyl)acrylamide.				
Dossier Submitter's Response				
Dossier Submitter thanks Finland for their support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.08.2017	Netherlands		MemberState	6
Comment received				
We agree that the increase in dominant lethalities in the oral and ip studies warrant classification in category 1B. With regard to the possibility that the observed mutagenicity is due to the presence of AA as an impurity it is suggested to check the dose of AA required to induce such effects and compare this to maximum theoretical amount of AA in the dominant lethal studies with NMA.				
Dossier Submitter's Response				
. Acrylamide is carcinogenic to experimental mice. Based on publication by Beland *et al.,* in 2013, (Carcinogenicity of acrylamide in B6C3F(1) mice and F344/N rats from a 2-year drinking water exposure. Food Chem Toxicol. 2013 Jan;51:149-59. doi: 10.1016/j.fct.2012.09.017. Epub 2012 Sep 23) the carcinogenicity of AA was assessed in male and female B6C3F(1) mice administered 0, 0.0875, 0.175, 0.35, or 0.70 mM acrylamide (equivalent to 0, 6.25, 12.5, 25, and 50 ppm acrylamide or 1.04, 2.20, 4.11, and 8.93 mg AA /kg/d) in the drinking water ad libitum for 2 years. Histopathological analyses indicated significant dose-related increases in Harderian gland and lung tumors in male and female B6C3F(1) mice. In male and female B6C3F1 mice administered acrylamide in the drinking water, there was a dose-related increase in Harderian gland adenoma, with the incidence being significant at all doses of acrylamide. Harderian gland adenocarcinoma also was observed in 1 male mouse administered 0.35 mM (4.11 mg AA /kg/d) acrylamide and 1 male mouse administered 0.70 mM (8.93 mg AA /kg/d) acrylamide. Dose-related increases in alveolar/bronchiolar adenoma of the lung occurred in both sexes of B6C3F1 mice, with the incidence being significant at 0.175 (2.20 mg/kg /d) and 0.70 mM (8.93 mg				

AA /kg/d) acrylamide in male mice and at 0.35 (2.20 mg AA /kg/d) and 0.70 mM (8.93 mg AA /kg/d) acrylamide in female mice. Low incidences of alveolar/bronchiolar carcinoma (0–8%) were also observed in both sexes, but these were not considered to be related to treatment. Male B6C3F(1) mice also had a significantly increased incidence of forestomach tumors, while female B6C3F(1) mice had significant dose-related increases in mammary gland, ovary, and skin tumors. In particular compared to NMA, acrylamide dosing resulted in an increasing dose-related trend in benign granulosa cell tumors of the ovary in female B6C3F1 mice, with the increase being significant at 0.70 mM (8.93 mg AA /kg/d) acrylamide

For NMA, in the two-year mice gavage study, the doses tested by gavage are 25 and 50 mg/kg bw/d. The incidences of Harderian gland adenomas were increased in males given both doses tested (low and high): control, 1/48 (2%); low-dose, 14/49 (29%); and high dose 29/50 (58%) ($p < 0.001$) and in females given the high-dose: control, 5/47; low-dose, 8/45; and high-dose, 20/48 ($p < 0.001$). The values of incidences of adenomas exceeded the historical data. The incidences of carcinomas of the Harderian gland were not significantly increased by NMA administration (male: 1/48 (2%); 0/49 (0%); 2/50 (4%); female: 0/47 (0%); 3/45 (7%); 2/48 (4%)). The incidence of adenomas and carcinomas (combined) was increased in both sexes and exceeded the historical control values. In high-dose males only, the incidences of alveolar bronchiolar adenomas (control, 3/49 (6%); low-dose, 6/50 (12%); and high-dose, 11/50 (22%); $p < 0.05$) and carcinomas were increased (control, 2/49 (4%); low-dose, 4/50 (8%); and high-dose, 10/50 (20%); $p < 0.05$). The incidence of alveolar-bronchiolar adenomas and carcinomas (combined) showed a positive trend in male mice and was statistically significant at the highest dose (control, 5/49 (10%); low-dose, 10/50 (20%); and high-dose, 18/50 (36%); $p < 0.001$). The incidence of alveolar-bronchiolar adenomas and carcinomas (combined) was increased in high-dose females (control, 6/50 (12%); low-dose, 8/50 (16%); and high-dose, 13/49 (27%); $p < 0.05$). All these incidences were outside the ranges of historical control values. The incidences of benign ovarian granulosa-cell tumours of the ovary were increased in treated groups (control, 0/50 (0%); low-dose, 5/45 (11%); and high-dose, 5/47 (11%); $p < 0.05$). These incidences exceeded the historical control values.

In conclusion the results of carcinogenicity on the both substances AA and NMA show that AA induces lung and ovary tumors at doses which are lower than for NMA. The similarity in target organs and the fact that AA seems more potent than NMA are in favour of a metabolization of NMA into AA.

RAC's response

In the REACH registration data for acrylamide, one dominant lethal assay was included. In this study (Sublet *et al.*, 1989) male Long-Evans rats were dosed with acrylamide monomer at 0, 5, 15, 30, 45 or 60 mg/kg bw/day for five days, then serially mated to naive females for 10 weeks beginning on study day 8. Effects included reduced fertility and increased pre- and post-implantation losses starting from 15 mg/kg bw/day, primarily over the first three weeks post-treatment. This is in approximately the same dose range as effects seen in the dominant lethal assays for NMA.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
27.07.2017	Germany		MemberState	7

Comment received

Regarding the proposed classification of NMA as STOT RE1 (peripheral nervous system) we could not come to an informed decision. The studies in the dossier and their data were

not presented sufficiently detailed and deepened to come to an assessment. For instance for the study Bucher, 1990; NTP, 1989 only a qualitative and not a quantitative evaluation of the data is given: “decreased forelimb and hind limb grip strength”. But for a complete analysis and assessment of the effects and their severity data in form of numbers are needed.

Moreover, effects described in human studies by Goffeng 2008a and 2008b which are considered with ‘definitively or probably low risk of bias’ by the DS are not considered to be unambiguously related to NMA due to coexposure of AA and NMA.

Dossier Submitter’s Response

For more details, the data and the result in tables of Bucher, 1990; NTP, 1989 study are presented in Annex 1.
We agree that this a coexposure of AA and NMA however the mixture of both compounds contains more NMA than AA. Both compounds have neurological effects somewhat with difference in potency. See comment below.

RAC’s response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
01.08.2017	Netherlands		MemberState	8

Comment received

We agree with the proposal to classify NMA as STOT RE but have some doubt regarding category 1 or 2. The animal data do show at least Cat 2 is justified and the rat data do not exclude effects below 10 mg/kg bw/day in the 90-day study but levels at or below 10 mg/kg bw/day were not tested in the 90-day study. However, as the hind limp grip strength was 82% of the control group in male rats after 13-weeks and considering the shape of the dose response curve it is considered likely that such effect will also occur at 10 mg/kg bw/day.
The value of the human data is difficult to assess due to the co-exposure with AA. The much higher NMA content of the grouting agent compared to AA suggests that NMA had an important contribution. However to make this conclusion clearer, information on the difference in potency between AA and NMA for neurotoxicity is needed. Are there animal data in which the potency can be compared? Also could you elaborate on the relation between Hb adducts and PNS as the current text is somewhat difficult to follow.

Dossier Submitter’s Response

QSAR analysis using DEREK modelisation concluded that neurotoxicity of NMA in mammal is plausible.

In the monography of IARC in 1994 it is concluded that NMA has neurotoxic properties like AA. However its potency for neurotoxicity compared to AA is of about 20-30% that of AA.

The hind limp grip strength was 82% of the control group in male rats after 13-weeks and considering the shape of the dose response curve it is considered likely that such effect will also occur at 10 mg/kg bw/day.Therefore event if dose below 10 mg/kg bw/d was not tested, it is anticipated that effects would also occur at doses below 10 mg/kg bw/d.This justifies the proposal for STOT RE1.

Hb adducts are used as markers of exposure to NMA in order to link the observed neurotoxic effects with Rhoca-Gil solution containing NMA. see section 3.3.2 human data pages 96 to 98 and the results pages 99 and 100 in annexe 1 for more details.
RAC's response
According to the CLP regulation a classification as STOT RE 1 can be based on reliable and good quality evidence from human cases or epidemiological studies or observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Taking the human epidemiogical studies showing effects, persisting up to 16-18 months after cessation of exposure, on the nervous system into account and supported by the neurological findings in the animal studies, RAC concludes that a classification of NMA as STOT RE 1 (peripheral nervous system) is justified, as was also proposed by the DS.