Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

2,2-dibromo-2-cyanoacetamide; [DBNPA]

EC Number: 233-539-7
CAS Number: 10222-01-2

CLH-O-0000001412-86-289/F

Adopted

13 June 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2,2-DIBROMO-2-CYANOACETAMIDE; [DBNPA]

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: 2,2-dibromo-2-cyanoacetamide; [DBNPA]
EC number: 233-539-7
CAS number: 10222-01-2
Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	France		MemberState	1
Comment received				
Page 1: The minimum purity validated in Biocide dossier is 98% and not 98.66%, therefore the CLP report should be amended with this minimum purity.				
Dossier Submitter's Response				
Sorry, this is a mistake. The minimum purity should be reflected as 98.00-100%.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	Germany		MemberState	2
Comment received				
The values for water solubility in Section 7 of the CLH-Report do not contain a unit. Please clarify. In the descriptions of the studies on skin irritation the dosages of DBNPA are given in g or mg. It would be desirable if the dosages could also be given in ppm and %. In the skin sensitization studies, skin irritations were also observed in both animals and humans as a result of exposure to DBNPA. Here the dosages are given in ppm or % DBNPA. By uniformly indicating the dosages in these two chapters, the data for both endpoints could be considered in one context which would be more transparent.				
Dossier Submitter's Response				
Regarding the missing values for water solubility: Sorry, this is a mistake and should be amended accordingly. Regarding the descriptions of the studies: Thank you for this proposal. We agree to this and could add values as appropriate.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2,2-DIBROMO-2-CYANOACETAMIDE; [DBNPA]

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	3

Comment received

As manufacturers we welcome the opportunity to comment on the Dossier Submitters proposed harmonized classification and labelling of DBNPA. In general we are in agreement with the proposals for the following hazard classes: Acute Inhalation Cat 2, Skin Irritation Cat 2, Eye Damage 1, Skin Sensitisation 1, Aquatic Acute 1 and Aquatic Chronic 2 however, we would like to provide additional comments for consideration as relevant to the discussions.
Please note, The purity of the substance DBNPA provided in Tables 1 and 2, i.e. 98.66 - 100% w/w, is not in line with the purity agreed during the BPR Analytical WG in January 2017, i.e. min 98%.
Furthermore, in addition to the data provided and summarized in the report and accompanying annexes, a 2 week inhalation toxicity study is also available for DBNPA and provided as confidential attachment. This study demonstrates evidence of local effects of respiratory irritation in response to exposure to DBNPA. This response is expected based on the irritating nature of DBNPA. While classification for acute inhalation toxicity and skin and eye irritation indicate that this substance is likely also to be irritating to the respiratory tract, we propose appropriate classification in order to be health protective by providing a specific warning of the potential for irritation to the respiratory tract.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats .docx

Dossier Submitter's Response

Regarding presentation of purity of active substance in tables 1 and 2, the value of 98.66 is a mistake and should be amended to reflect 98.00 %

Regarding the 2 week inhalation toxicity study "DBNPA Inhalation Tox Study in Rats", the dossier submitter has not had this study available for the CLH proposal and thus has not evauated the classification potential of this.

Comparison with the CLP criteria: The dossier submitter proposes STOT RE 1 due to significant histopathologic effects seen in larynx at 0,5 mg/m3/6h as the lowest effect dose (0.0005 mg/L/6 hours) DBNPA corresponding to STOT RE 1 in the CLP guidance. In addition significant local effects were seen in the nasal tissues and the lower respiratory tract/lungs at 5.37 mg/m3 and 31.1. mg/m3 and thus several organs are targeted. Seen as DBNPA is also classified for Acute Inhalation toxicity 2, the dosages used were compared between the two of the studies in order to evaluate whether or not the effects seen in the respiratory tract were because of a true repeated exposure effect and not in relation to the acute effects. As no rats in 0.10 mg/L dose group in the Acute Inhalation Study A6.1.3/01 died, a comparison of the histopathological effects were made between the two dosages of 0.10 mg/L and 0.51 mg/m3. No respiratory histopathologic effects were seen in the 0.10 mg/L dose group at termination. Comparing this with the effect level for the 2 week repeated dose study submitted, respiratory effects were seen in the 0.51 mg/m3 (corresponding to 0.00051 mg/L) and thus the effects are concluded to be of true repeated dose local toxicity for the upper and lower respiratory tract.

Pleasse see comment 19 for our proposal of amendment of the CLH report in relation to the STOT RE classification.

The relevant effects from the study are summarized here:
Treatment-related histopathologic observations were present in the nasal tissues, larynx and lungs. The larynx was the most sensitive target organ, with treatment-related effects occurring in male and female rats at all exposure levels (0.51 mg/m3, 5.37 mg/m3 and 31.1 mg/m3).

In male and female rats exposed to the low exposure concentration of 0.51 mg/m3, all of the rats had hyperplasia (very slight) and squamous metaplasia (very slight or slight) of the respiratory epithelium which overlies the seromucinous glands at the anterior aspect of the larynx. All of the low exposure level male and female rats also had very slight or slight subacute to chronic inflammation in the lamina propria adjacent to the seromucinous glands and/or the ventral pouch of the larynx. One female rat from the low concentration group had very slight multifocal fibrosis in the lamina propria of the larynx. Most of the male and female rats exposed to 5.37 or 31.1 mg/m3 had slight diffuse hyperplasia of the respiratory epithelium, involving the anterior, middle and posterior aspects of the larynx. The hyperplasia was accompanied by very slight or slight multifocal squamous metaplasia of the respiratory epithelium in all male and female rats exposed to 5.37 or
31.1 mg/m3. Three male and three female rats exposed to 5.37 mg/m3, and two male and two female rats exposed to 31.1 mg/m3 had very slight or slight, multifocal squamous metaplasia of the seromucious glands. All of the male and female rats exposed to 5.37 or
31.1 mg/m3 had multifocal subacute to chronic inflammation (very slight, slight or moderate) of the lamina propria of the respiratory epithelium. *All male and female* rats exposed to 5.37 or 31.1 mg/m^3 had slight multifocal hypertrophy of the submucosal glands, characterized by increased cytoplasmic volume of the epithelial cells of the seromucinous glands in the anterior larynx, and of the mucinous glands in the posterior larynx. With the exception of one high-exposure concentration group male, all male and female rats exposed to 5.37 or 31.1 mg/m^3 had multifocal fibrosis (very slight, slight or moderate) of the lamina propria underlying the respiratory epithelium of the larynx. One male rat exposed to 5.37 mg/m^3 and most of the male and female rats exposed to 31.1 mg/m^3 had very slight mucous cell metaplasia of the respiratory epithelium in the posterior aspect of the larynx. *Most of the male and female rats* exposed to 5.37 or 31.1 mg/m3 had very slight multifocal necrosis of individual respiratory epithelial cells on the luminal surface of the posterior aspect of the larynx. Slight multifocal hyperplasia of the cartilage at the base of the epiglottis was present in one male and one female rat exposed to 5.37 mg/m3, and in three male and three female rats exposed to 31.1 mg/m3. Slight focal or multifocal necrosis of the cartilage at the base of the epiglottis, or of the arytenoid cartilage, was present in one male rat exposed to 5.37 mg/m3 and in two males and one female exposed to 31.1 mg/m3. Very slight, slight or moderate necrosis of the lamina propria adjacent to the seromucinous glands, or adjacent to the arytenoid cartilage, was present in three males and one female exposed to 5.37 mg/m3, and in two male rats exposed to 31.1 mg/m3.

All of the male and female rats exposed to 5.37 or 31.1 mg/m^3 had the following treatment-related **lung effects:** very slight alveolar histiocytosis; very slight or slight multifocal hyperplasia of bronchiolar epithelium; very slight or slight multifocal hypertrophy of bronchial and bronchiolar epithelium; very slight or slight multifocal peribronchial and perivascular subacute inflammation; very slight or slight multifocal mucous cell metaplasia of the bronchial and bronchiolar epithelium; and very slight

multifocal necrosis of bronchiolar epithelial cells. In addition, two males exposed to 5.37 mg/m^3 and three males and one female exposed to 31.1 mg/m^3 had treatment-related very slight or slight multifocal hyperplasia of the peribronchial lymphoid tissue. There were no treatment-related lung effects in male or female rats exposed to 0.51 mg/m^3.

Male and female rats exposed to 5.37 or 31.1 mg/m^3 had the following treatment-related **nasal tissue effects**: very slight or slight hyperplasia of the squamous epithelium that lines the ventral meatus; very slight or slight hyperplasia and hypertrophy of goblet cells in the respiratory epithelium; and very slight, slight or moderate chronic-active inflammation of the respiratory, transitional and olfactory epithelium. Nasal effects that were restricted to the high-exposure of 31.1 mg/m^3 consisted of the following: very slight or slight, focal or multifocal degeneration of the olfactory epithelium in five male and two female rats; very slight or slight multifocal degeneration of the olfactory nerves in two male and one female rat; slight multifocal hyperplasia of the respiratory and transition epithelium in all male and female rats; slight focal or multifocal respiratory epithelial metaplasia of the olfactory epithelium in one male and one female rat; very slight, slight or moderate squamous metaplasia of the nasal epithelium in five male and four female rats; and slight multifocal ulceration of the transitional epithelium of the nasoturbinate that was accompanied by slight multifocal osseous necrosis of the bones of the nasoturbinate in one male rat. In general, all of the nasal tissue effects were most prominent in the anterior aspect of the nasal passages. There were no treatment-related effects in the nasal tissues of male or female rats exposed to 0.51 mg/m3.

The dossier supplier wishes to amend the conclusion of the classification for STOT to reflect the results obtained from the newly submitted study:

Amendment of section 10.12.3 to the following:
Classification for specific target organ toxicity is required under the terms of Regulation (EC) No 1272/2008 and subsequent amendments to that legislation as STOT RE 1 due to the local effects seen in the upper and lower respiratory tract.

RAC's response

Thank you for submitting this well-conducted study. We agree with the DS that the effects on the respiratory tract observed in this study are best addressed by a classification as STOT RE 1 (respiratory tract). Your support for Acute Tox. 2 (H330), Skin Irrit. 2, Eye Dam. 1, Skin Sens. 1 and aquatic hazards is noted.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	Germany		MemberState	4

Comment received

Thyroid follicular hyperplasia in rats was considered treatment-related. Therefore, it is important to receive information on incidences and severity for an independent assessment. Please provide a table with the incidences and severity of thyroid follicular hyperplasia in male and female rats of the toxicity/oncogenicity study after interim sacrifice after 12 months and after final sacrifice after 24 months.

Dossier Submitter's Response

The tables are included in the CLH report at page 84 and listed as table 81 and 82 respectively.

Following the discussion at the Endocrine Disruptor Expert Group meeting in October 2018 (the meeting was held after the public consultation of the CLH process) the discussion/conclusion on carcinogenicity should also be amended to the effects being relevant for humans. But seen as no neoplastic changes was observed and no other studies show signs of oncogenic effects, the treatment-related hyperplasia is concluded not relevant for oncogenic classification, but only relevant for thyroid dysfunction. Hyperplasia could potentially be a prestage for neoplasia, but seen as no neoplastic changes was observed at the 24 months sacrifice in the 2 year rat study and rats are sensitive to developing thyroid tumors indications of neoplastic changes other than hyperplasia would be expected also and thus there is not enough evidence to support classifying for carcinogenicity.

The text should therefore be amended as follow in the CLH report at page 83(added text in red):
The primary treatment-related histopathologic effect in animals from the 24-month sacrifice consisted of statistically-identified increases in the incidence of very slight or slight diffuse follicular cell hyperplasia in the thyroid glands of males and females given 150 mg/kg/day, and in males given 20 mg/kg/day. Treatment-related thyroid follicular hyperplasia was also present at the 12-month sacrifice in males and females given 150 mg/kg/day. The hyperplasia did not appreciably worsen during the final 12 months of the study. This effect was interpreted to be caused by the bromine component of DBNPA as thyroid follicular cell hyperplasia is a commonly recognized effect of exposure to exogenous compounds containing bromine. The increase seen in incidence of follicular cell hyperplasia of the follicular epithelium in rats after a chronic exposure during 2 years was very slight. During the two years the change was not associated with increased cancer risk and the genotoxicity studies were negative. According to a Commission group of specialized experts the rat is a more sensitive species with regards to changes of the thyroid and development of epithelial thyroid tumors after long term exposure to non-genotoxic agents and the changes should not be considered representative for humans with regard to oncogenicity. Seen as no neoplastic cells were observed and no other studies show signs of neoplastic effects, the treatment-related hyperplasia is not relevant for oncogenic classification, but only relevant for thyroid dysfunction, as there is observed no progression towards carcinogenicity. Hyperplasia could potentially be a prestage for neoplasia, but seen as no neoplastic changes was observed at the 24 months sacrifice in the 2 year rat study and rats are sensitive to developing thyroid tumors it would be expected that there were indications of neoplastic changes other than hyperplasia also at this point.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	5

Comment received

No comment

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats.docx

Dossier Submitter's Response

Thank you for providing the study. It has been considered under the relevant hazard class.

RAC's response
Thank you for providing the study. It has been considered under the relevant hazard class.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	6
Comment received				
No comment ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats.docx				
Dossier Submitter's Response				
Thank you for providing the study. It has been considered under the relevant hazard class.				
RAC's response				
Thank you for providing the study. It has been considered under the relevant hazard class.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	7
Comment received				
Developmental Toxicity The dossier submitter maintains that a developmental toxicity study in the second species has not been conducted for DBNPA (Table 65; Section 10.10.5, second to last paragraph) however this is incorrect. As part of the BPR evaluation of the active substance DBNPA, an OECD 414 compliant study conducted in accordance with GLP was submitted for review. The rat developmental toxicity study is not summarized in the CLH report, although it is summarized in the Human Health Annex provided during the public consultation. According to the study summary, no developmental effects were observed, a conclusion agreed by the Danish RMS and reviewed by the BPR TOX Working Group in January 2018 as part of the active substance approval. As such DBNPA is considered not to be a developmental toxicant. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats .docx				
Dossier Submitter's Response				
This is a mistake. The data should be provided in the table and the conclusion should remain the same. In addition we will amend the sentence in the mentioned paragraph to also include the study.				
RAC's response				
Thank you for spotting this mistake. RAC agrees that this well-conducted rat PNDT study is negative and that DBNPA does not meet the criteria for classification for developmental toxicity.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	8

Comment received

Acute Oral Toxicity
We disagree with the conclusion of the dossier submitter that classification as Category 3 for acute oral toxicity is appropriate. This conclusion is drawn by simply selecting the lowest calculated LD50 estimate in a single sex despite no obvious sex linked difference in toxicity.
As noted in the dossier a number of acute oral toxicity studies are available for DBNPA. The most relevant study for selection as key study is referenced as A6.1.1/01. The dossier submitter notes that this study used constant volume application as required per OECD guidance and also had a greater number of dose levels which allow for a more reliable estimation of the true LD50 value. Using the combined LD50 value of 308mg/kg/day the correct classification for DBNPA would be Acute toxicity Category 4 via the oral route.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats .docx

Dossier Submitter's Response

The conclusion was not drawn by simply selecting the lowest calculated LD50. The conclusion was drawn by a Weight of Evidence approach and in relation to the proposed strategy by the CLP classification guideline. As there are two key studies following the OECD 401 guideline, and 3 out of the 4 LD50 values attained from these studies would classify as Acute Tox 3 we believe this classification to be appropriate.

RAC's response

There are six studies for this endpoint and none has been found totally unreliable. Thus, there are about 10 acute toxicity estimates in total, and all but one are consistent with Category 3. Therefore, RAC agrees with the DS that classification with Acute Tox. 3 is appropriate. In addition, RAC proposes an ATE of 118 mg/kg bw (LD50 from the most sensitive species, rabbit and guinea pig; A6.1.1/04).

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	Finland		MemberState	9

Comment received

Acute oral toxicity has been investigated in two OECD 401 guideline studies. The lowest LD50, value reported is 167 mg/kg in female Fisher 344 rats. The proposal of ATE of 167 mg/kg and subsequent classification Acute Tox. 3; H301 is justified according to the criteria in CLP.

The administration of DBNPA by inhalation according to OECD 403 guideline with respirable particles resulted in an LC50 of 0.31 and 0.24 mg/L for males and female, respectively. The pro-posal of classification Acute Tox; 2; H330 is justified according to the criteria in CLP.

Dossier Submitter's Response

Thank you for your support.

RAC's response
Thank you for your comment. RAC agrees that Acute Tox. 3 is justified for the oral route and Acute Tox. 2 for inhalation. As to the harmonized oral ATE, in line with the CLP guidance RAC proposes to choose the lowest LD50 from the most sensitive species, i.e. 118 mg/kg bw (rabbit and guinea pig, A6.1.1/04).

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	Finland		MemberState	10
Comment received				
In an OECD 404 guideline study all animals showed erythema with an average score 3.3. No necrosis or corrosive responses was observed. Classification as Skin Irrit. 2; H315 is supported.				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Thank you. RAC agrees that classification with Skin Irrit. 2 is warranted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	Germany		MemberState	11
Comment received				
Based on the key study A6.1.4/02 (OECD 404, Reliability 1, 500 mg DBNPA administered/patch, purity 98.2%, exposure 4 hrs, observation period 15 days) and another Guideline study (OECD 404, Reliability 2, 500 mg DBNPA, purity not reported, exposure 4 hrs, observation period not reported) the German CA can agree to the DK proposal for classification of DBNPA as skin irritant. Blisters, scaling, scabs, erythema (mean score 3.3), oedema (mean score 2.1) and exfoliation are reported after single application of the test substance. In two Human Patch Tests (A6.12.6/01 and A6.12.6/02, see endpoint skin sensitization) even after repeated exposure to DBNPA, only mild irritation and "Exciting Skin Syndrom" are reported. Therefore, according to Regulation (EC) No 1272/2008 DBNPA should be classified as Skin Irrit. 2; H315. However, some arguments could be found to classify DBNPA as Skin Corr. 1, H314, in light of three further experimental studies (A6.1.4/04b, /05b and /06b) and a Health and Safety report (A6.12.2). It is acknowledged that these studies show deficiencies (e.g. non-guideline, non GLP, dose and purity and/or the exposure time not reported, no controls etc.). Nevertheless, skin necrosis (slight to moderate), scabs (slight to moderate), exfoliation, scars and scarring were observed after repeated or single application of DBNPA on intact or abraded skin after different exposure periods. According to the Health and Safety report (A6.12.2), severe skin lesions appeared as sub-epidermal blisters associated with necrotic or apoptotic keratinocytes and dense lymphocytic infiltration in the epidermis of two accidentally exposed industrial workers.				
Dossier Submitter's Response				
Thank you for challenging the classification of Skin Irrit. 2; H315. When evaluating the data provided a Weight of Evidence approach was followed. Following this approach most weight was given to the observed effects seen in the OECD 404 study (A6.1.4/02)and in the two Human Patch Tests (A6.12.6/01 and A6.12.6/02) as the OECD 404 is the most reliable study. Less weight was given to the non-GLP studies (A6.1.4/04b, A6.1.4/05b and A6.1.4/06b) due to the mentioned deficiencies which interferes with finding of				

reliable results. As for the effects reported in the Health and Safety Report (A6.12.2) there are no data on the mixture and thus coformulants cannot be identified. The eCA finds that identification of coformulants is of essential value for classification of skin hazard.
RAC's response
RAC agrees with the DS's proposal of Skin Irrit. 2 based primarily on the OECD-guideline and GLP-compliant study A6.1.4/02. The studies A6.1.4/04b, /05b and /06b used non-guideline designs (e.g., low number of animals, non-guideline application durations) and the reporting is limited. The severe symptoms in the human case report (A6.12.2) were related to sensitisation, not corrosion.

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	12
Comment received				
No comment ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats .docx				
Dossier Submitter's Response				
Thank you for providing the study. It has been considered under the relevant hazard class.				
RAC's response				
Thank you for providing the study. It has been considered under the relevant hazard class.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	13
Comment received				
No comment ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats .docx				
Dossier Submitter's Response				
Thank you for providing the study. It has been considered under the relevant hazard class.				
RAC's response				
Thank you for providing the study. It has been considered under the relevant hazard class.				

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	Finland		MemberState	14
Comment received				
In an OECD 405 guideline study instillation of 100 mg DNBPA resulted in opacity, discharge and chemosis of the highest grade of severity and conjunctival ulceration. The mean corneal score was 4 for all animals. Classification as Eye Dam. 1; H318 is supported.				

Dossier Submitter's Response
Thank you for your support.
RAC's response
Thank you. RAC agrees that classification with Eye Dam. 1 is warranted.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	Finland		MemberState	15
Comment received				
The three available animal studies are of variable degree of reliability and show conflicting re-sults. Overall, skin sensitisation potency of the substance appears to be weak since the key study was negative. In humans positive HRIPT tests have been conducted with DBNPA of un-known purity. Moreover, quantitative information cannot be derived from these studies. One clinical occasion, where two exposed (unknown purity of the substance, unknown duration of exposure) industrial workers developed erythema multiforme like lesions has been reported. Classification of DBNPA as Skin Sens. 1; H317 is supported, although the available evidence is not strong.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. RAC agrees that classification with Skin Sens. 1 is warranted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	Germany		MemberState	16
Comment received				
Concerning the animal experiment A6.1.5/02 on guinea pigs (chapter 10.7). Only an indication of the DBNPA dosage of 5 % is given here. Did that apply to both induction and the challenge? Also the results in the control animals are not mentioned in the results section. Does this mean that they did not react to DBNPA? Please clarify.				
Dossier Submitter's Response				
Yes, the 5% applies for both induction and challenge. Results from the positive control group should be mentioned and are 8/10 responding to 15% (w/v) epoxy resin in 9:1 mixture of Dowanol DPM: Tween 80.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	17
Comment received				
The classification and labeling section (Table 2) indicates Skin Sens 1B is being proposed while the text in sections 10.7.2 and 10.7.3 provide justification for Skin Sens 1 without sub-categorization. Based on Annex I, Section 3.4.2.2.1.1 of the Guidance on the Application of the CLP Criteria (ECHA, 2017), a dermal sensitizer should be classified in Category 1 where data are not sufficient for sub-categorization. Using weight of evidence our conclusions are that subcategorization is not possible for DBNPA since: a) There are conflicting results from animal studies where studies conducted on formulations containing DBNPA are positive but similar studies conducted using technical				

grade material are negative. b) There are positive results obtained in human volunteer studies in which DBNPA formulations were applied repeatedly to the skin. c) There are very few, if any, case reports in the open literature indicating DBNPA as a cause of allergic contact dermatitis. d) There are deficiencies in reporting in the human volunteer studies meaning the dose/surface area applied cannot be determined. Overall the human information suggests that DBNPA is able to induce an allergic response in individuals e.g. as demonstrated by the volunteer studies but that the frequency of response is very low when examining the lack of case reports in the open literature. As such the potency from human data would indicate that it is of low potency. In agreement with this potency assessment are animal data where testing of formulations indicate a potential subcategorization as 1B. However in vivo testing of the technical grade material was negative indicating that the positive response obtained was due to formulation effects or an impurity present in the material tested. Overall, given the information available, we conclude that DBNPA has the potential to cause dermal sensitisation but that subcategorization is not appropriate. As a result we propose DBNPA is classified as Category 1 with a corresponding generic concentration limit of 1%. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats .docx
Dossier Submitter's Response
Thank you for this comment. Skin Sens. 1 was infact also the eCAs conclusion based on the same argumentation. It was a mistake in table 2, p. 2 and should be amended for the CLH proposal.
RAC's response
Thank you. RAC agrees that classification with Skin Sens. 1 is warranted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	18
Comment received				
No comment ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats .docx				
Dossier Submitter's Response				
Thank you for providing the study. It has been considered under the relevant hazard class.				
RAC's response				
Thank you for providing the study. It has been considered under the relevant hazard class.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	Germany		MemberState	19

Comment received

The description of histopathological thyroid gland changes needs to be clarified in the 90-day oral toxicity study in the dog. In Table 71 (90-day oral, dog; p. 69) it is written that a very slight increase in the amount of colloid in the follicles of the thyroid gland was observed upon microscopy. This change could also be described as thyroid follicular hypertrophy. This is in contrast to changes observed in the carcinogenicity study in rats where a follicular hyperplasia of the thyroid gland was described.
Please consider endocrine disrupting properties of the test substance. In the carcinogenicity study in rats it is reported that follicular cell hyperplasia in the thyroid gland occurred at the 24-month sacrifice. The effect was interpreted to be caused by the bromide released in vivo from DBNPA. Thus, the molecular initiating event (MIE) was an imbalance of the iodine transport into the thyroid gland. Unfortunately thyroid hormones were not measured, a decrease of circulation T3 and T4 could be expected (KE1). EATS specific adversity is demonstrated by histopathological changes of the thyroid gland, in the form of cell hyperplasia (KE2). Thyroid tumors as an adverse outcome (AO) were not observed in any sex.

Dossier Submitter's Response

We have indeed considered the endocrine disruption potential of DBNPA and have concluded that these two dossier studies combined with other information proposes DBNPA to have endocrine disruptive properties. The assessment of the two studies should be amended accordingly to reflect this in the relevant hazard categories. Please also refer to comment no 4 above relating to the assessment of carcinogenicity.

Following the dosages for effects, no classification for STOT RE 2 is required by CLP legislation for the 2 year rat study, as the effect dose level was at 150 mg/kg bw/day for the histopathologic changes at the 12 months sacrifice and according to CLP legislation it should be within <25 mg/kg/bw/day following Haber's rule. Following the ED Expert Group discussion in ECHA in October 2018 it was concluded that effects seen in the 90 day dog study indeed were adverse and thus the evaluation for STOT RE for this study should also be amended in the CLH report as the effect dose level was 10.7 mg/kg bw/day for the histopathologic effects seen in the females and thus would require a STOT RE 2. Please see our proposed amendments to the CLH report below:

Amendment of section 10.12.1, p 76 in the CLH report regarding the 90 day dog study:
"Considering the treatment related effects on the thyroid weight in combination with the very slight increase in the amount of colloid in most of the follicles of the thyroid gland, the effects could not be disregarded when establishing the NOAEL for the study at 5.9 mg/kg/day to ensure that the effects are covered by the risk assessment performed for the substance. However, the effect is only seen in the 90 days dog study and in the 2 year rat study, where the effect did not progress over time (see summary below), but not in other species or subchronic studies. The changes to the thyroid weight were within or close to the historical control ranges and no evidence of degradation, inflammation, necrosis or a proliferative response of the thyroid follicular epithelium or parafollicular cells was present at any dose level, However, it could not be disregarded that there is thyroid dysfunction due to the similar effects seen also in the 2 year rat study and

consultation from endocrine experts on thyroid pathology in dogs. It is therefore the conclusion of the RMS that A classification of STOT RE 2 is appropriate based on the effect dose level being 10.7 mg/kg bw/d for the female dogs.

Amendment to section 10.12.2, p. 93 to the following:
Three 90 day dietary studies were conducted, in F344 rats, CD-1 mice, and Beagle dogs. In rats, an increase in extramedullary hematopoiesis and urinary ketones was observed at high doses. It is not until dosages of 133 and 130 mg/kg/day are administered that potentially significant (but not severe) responses are observed. In mice, toxicity was secondary to reductions in body weight. The NOAEL was established at 133 mg/kg bw/d for males and 45 mg/kg bw/d for females on the basis of reduced body weight and body weight gains. Therefore, no target organ was identified. In Beagle dogs, an increase in follicular hypertrophy in the thyroid gland was observed. The changes to the thyroid weight were within or close to the historical control ranges and there was no histopathological evidence of injury (inflammation, necrosis, proliferation) However, it could not be disregarded that there is thyroid dysfunction due to the similar effects seen also in the 2 year rat study and consultation from endocrine experts on thyroid pathology in dogs.

Amendment of section 10.12.1 on the assessment of the 2 yer rat study at page 83 to the following:
The primary treatment-related histopathologic effect in animals from the 24-month sacrifice consisted of statistically-identified increases in the incidence of very slight or slight diffuse follicular cell hyperplasia in the thyroid glands of males and females given 150 mg/kg/day, and in males given 20 mg/kg/day. Treatment-related thyroid follicular hyperplasia was also present at the 12-month sacrifice in males and females given 150 mg/kg/day. The hyperplasia did not appreciably worsen during the final 12 months of the study. This effect was interpreted to be caused by the bromine component of DBNPA as thyroid follicular cell hyperplasia is a commonly recognized effect of exposure to exogenous compounds containing bromine. The increase seen in incidence of follicular cell hyperplasia of the follicular epithelium in rats after a chronic exposure during 2 years was very slight. During the two years the change was not associated with increased cancer risk and the genotoxicity studies were negative. According to a Commission group of specialized experts[1] the rat is a more sensitive species with regards to changes of the thyroid and development of epithelial thyroid tumors after long term exposure to non-genotoxic agents and the changes should not be considered representative for humans. However, this only applies to oncogenetic potential and not thyroid function. The dose does not trigger classification for STOT RE as the lowest effect dose was 150 mg/kg bw/day at the 12 months sacrifice and should be below 25 mg/kg bw/day following Haber's rule to classify for STOT RE 2.

Amendment to section 10.12.2, p. 94 to the following:
The available studies demonstrate that exposure to DBNPA targets the thyroid and upper and lower respiratory tract on repeated exposure that is relevant for the exposure pathway (exposure by inhalation for the upper and lower respiratory tract effects, oral for thyroid effects) and human relevance. .

Thyroid changes were observed in both the 90 day dog study and 2 year cancer study in rats, In rats after a chronic exposure during 2 years the increase in incidence of follicular cell hyperplasia of the follicular epithelium was very slight. The dosage from the 2 year

[1] Summary record – Commission group of specialised experts in the fields of Carcinogenicity, mutagenicity and reprotoxicity, ECBI/49/99, 1999, excerpt of agenda item 3.1

rat study does not trigger classification for STOT RE, however they support thyroid pathology is evidentIt is therefore concluded that the effects seen in the 2 year rat study is not sufficient to trigger classification as STOT RE, but the 90 dog study is sufficient to trigger classification as STOT RE 2 based on dosages being 10.7 mg/kg bw/day for females when seeing effects at both thyroid weight and histopathologic changes, and seen as the 2 year rat study shows evidence of thyroid pathology, it is found to be sufficient to trigger for STOT RE.

Please also see comment no 3 as there is evidence to support STOT RE 1 in other organs and thus the classification of STOT RE 2 is not relevant.

RAC's response

Thank you for your comment. Please note that not only presence/absence of an effect but also its severity is taken into account in STOT RE classification. While the weak thyroid effects in the 90-day dog study are likely to be treatment-related, RAC considers that they are not of sufficient toxicological significance to meet the STOT RE criteria for classification. The effects in the rat occurred above the guidance values.

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	20

Comment received

No comment

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats .docx

Dossier Submitter's Response

Thank you for providing the study. It has been considered under the relevant hazard class.

RAC's response

Thank you for providing the study. It has been considered under the relevant hazard class.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
08.08.2018	United Kingdom		MemberState	21

Comment received

We agree with the Aquatic Acute 1 (M=1) proposal.

Section 11.7.2 states that 'Based on the above data DBNPA is not considered to be ready biodegradable.' However, section 11.8 concludes that DBNPA is 'readily biodegradable' and therefore proposes Aquatic Chronic 2 considering chronic endpoints in the range 0.01 to 0.1 mg/l.

Please can you clarify if DBNPA is rapidly degradable for the purpose of hazard classification? On the basis of presented data it would appear that DBNPA is not rapidly degradable and that Aquatic Chronic 1 (M=1) is appropriate.

Dossier Submitter's Response

Sorry it is a mistake that we in section 11.8 concludes that DBNPA is 'readily biodegradable' and therefore proposes Aquatic Chronic 2 considering chronic endpoints in

the range 0.01 to 0.1 mg/l. DBNPA is not rapidly degradable and Aquatic Chronic should be 1 (M=1).
RAC's response
Thank you for the clarification and the new classification proposal.

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	Finland		MemberState	22
Comment received				
FI CA supports the conclusion that DBNPA is not potentially bioaccumulative. The lowest relia-ble acute toxicity was 48 h EC50 value of 0.72 mg/L for aquatic invertebrate. The lowest chronic toxicity was NOEC value of 0.06 mg/L for aquatic invertebrate. Based on classification criteria FI CA supports the proposed environmental classification Aquat-ic Acute 1, H400 with M-factor of 1. In ready biodegradability test (A7.1.1.2.1/01) 58 % mineralisation was achieved within the 10-day window, which is close to the pass level for ready biodegradability as stated in the CLH proposal. In section 11.7 (comparison with the CLP criteria) DBNPA is not considered to be readily biodegradable by dossier submitter. However, chronic classification is based on conclu-sion that DBNPA is rapidly degradable, which is not in the line with previous conclusion about ready biodegradability of DBNPA. We agree with the dossier submitter (page 110) that stud-ies, which only demonstrate primary degradation (e.g. hydrolysis and simulation studies) can-not in this case justify the conclusion that DBNPA is rapidly degradable. In section 11.8 (conclusion on classification and labelling for environmental hazards) it is stated that DBNPA is readily biodegradable, which contradicts previous conclusions in CLH dossier. Thus, FI CA ask clarification about the dossier submitter´s interpretation of rapid degradation of DBNPA. FI CA´s opinion is that if DBNPA is not considered readily biodegradable, it cannot be consid-ered rapidly degradable based on ready biodegradability test (A7.1.1.2.1/01). DBNPA should therefore be classified as Aquatic Chronic 1, H410 with M-factor of 1 (non-rapidly degradable substance). Section 4.1.2.9.5 of CLP indicates that the 10-day window may only be waived for UVCBs or complex multi-constituent substances with structurally similar constituents and this is not the case with DBNPA.				
Dossier Submitter's Response				
Sorry it is a mistake that we in section 11.8 concludes that DBNPA is 'readily biodegradable' and therefore proposes Aquatic Chronic 2 considering chronic endpoints in the range 0.01 to 0.1 mg/l. DBNPA is not rapidly degradable and Aquatic Chronic should be 1 (M=1), H410				
RAC's response				
RAC agrees with the Member State views and welcomes the clarification from the DS.				

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	France		MemberState	23
Comment received				
In section 11.7.2 regarding comparison criteria for long term toxicity, the CLH report mentions that "Based on the above data, DBNPA is not considered to be ready				

biodegradable". However, at the end of this same section, it is mentioned that "As the NOEC value of Daphnia magna is 0.06 mg/L, and DBNPA is rapidly degradable, classification as Chronic Category 2; H411 is required." So, the conclusion on the ready biodegradation is not consistent in this section. According to the available data, DBNPA should be considered as not ready biodegradable. Based on the lowest NOEC = 0.06 mg/L, DBNPA should be classify as chronic category 1 and H410 is required. A chronic M-factor = 1 should be indicated. Therefore, we do not agree with the proposed chronic classification H411.
Dossier Submitter's Response
Sorry it is a mistake that we in section 11.8 concludes that DBNPA is 'readily biodegradable' and therefore proposes Aquatic Chronic 2 considering chronic endpoints in the range 0.01 to 0.1 mg/l. DBNPA is not rapidly degradable and Aquatic Chronic should be 1 (M=1), H410
RAC's response
RAC agrees with the Member State views and welcomes the clarification from the DS.

Date	Country	Organisation	Type of Organisation	Comment number
18.09.2018	Germany		MemberState	24
Comment received				
It is stated that DBNPA is not considered to be ready biodegradable, which is in line with the conclusion of the WGI-2018. The German CA also agrees with the eCA, that the available data on primary degradation of DBNPA do not justify the conclusion that DBNPA is rapidly degradable according to CLP, since degradation products of DBNPA are estimated to have either the same or lower toxicity compared to DBNPA. In conclusion, DBNPA has to be considered not rapidly degradable. Along with the NOEC value of Daphnia magna of 0.06 mg/L, DBNPA thus has to be classified as Chronic Category 1; H410 with an M-factor of 1 instead of Chronic Category 2; H411. In general, details regarding rapid degradability are reported in a very confusing way. The report contains a lot of literal errors. A final conclusion on rapid degradability based on comparison of the available data with the CLP criteria is missing and should be provided.				
Dossier Submitter's Response				
Sorry it is a mistake that we in section 11.8 concludes that DBNPA is 'readily biodegradable' and therefore proposes Aquatic Chronic 2 considering chronic endpoints in the range 0.01 to 0.1 mg/l. DBNPA is not rapidly degradable and Aquatic Chronic should be 1 (M=1), H410				
RAC's response				
RAC agrees with the Member State views and welcomes the clarification from the DS.				

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	25
Comment received				
No comment ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats .docx				
Dossier Submitter's Response				
Thank you for providing the study. It has been considered under the relevant hazard class.				

RAC's response
Thank you for providing the study. It has been considered under the relevant hazard class.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	26
Comment received				
No comment ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats .docx				
Dossier Submitter's Response				
Thank you for providing the study. It has been considered under the relevant hazard class.				
RAC's response				
Thank you for providing the study. It has been considered under the relevant hazard class.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	27
Comment received				
No comment ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DBNPA Inhalation Tox Study in Rats .docx				
Dossier Submitter's Response				
Thank you for providing the study. It has been considered under the relevant hazard class.				
RAC's response				
Thank you for providing the study. It has been considered under the relevant hazard class.				

CONFIDENTIAL ATTACHMENTS
1. DBNPA Inhalation Tox Study in Rats .docx [Please refer to comment No. 3, 5, 6, 7, 8, 12, 13, 17, 18, 20, 25, 26, 27]