Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Benzophenone

EC Number: 204-337-6

CAS Number: 119-61-9

CLH-O-0000006808-62-01/F

Adopted

11 June 2020

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

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: benzophenone
EC number: 204-337-6
CAS number: 119-61-9
Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
24.09.2019	Germany		MemberState	1
Comment received				
In table 2 the numerical identifier is missing. In table 3 and 4 only the impurities or additives should be stated and not the substance itself.				
Dossier Submitter's Response				
The DS (Dossier Submitter) agrees that the table of constituents (table 2) should have included the cas (119-61-9) and EC number (204-337-6) of the substance. Also the information on the impurities and additives tables (tables 3 and 4) should have been presented without including the name of the substance.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
24.09.2019	Germany		MemberState	2
Comment received				
There are no relevant human data on the carcinogenicity of benzophenone available. Benzophenone induced an increased incidence of tumours in several tissues of mice and rats, investigated in two oral carcinogenicity studies, performed according to OECD TG 451. Two non-guideline dermal carcinogenicity studies did not show any increase in incidence of several tumours in benzophenone-treated mice or rabbits compared to controls. However, performances of these studies, using open dermal application as well as a low number of test animals weaken their relevance. Guideline-compliant studies revealed that benzophenone resulted in an increase of occurrence of tumours with high spontaneous incidence, namely benign hepatocellular adenomas in both sexes of B6C3F1 and mononuclear cell leukaemia in male and female F334/N rats, compared to controls and historical control incidence. A dose-dependent effect on the incidence of renal tubule adenoma in male rats was reported;				

correspondingly the incidences of renal tubule hyperplasia increased dose-dependently and significantly in all dose groups of males and female rats in comparison to the low incidence in the control groups. Whether chronic progressive nephropathy (CPN), a common spontaneous kidney disease in laboratory rats, may be discussed as a supporting factor in the development of renal tubule tumours is debatable. In this study, CPN occurred in almost all animals of all groups, at minimal severity grade in the control animals and at dose-related increased higher severity grades in dose groups of both sexes. Its role in adenoma development remains uncertain. Renal tubular lesions (regeneration, dilatation, protein casts) and necrosis of the renal papillae were already seen in treated rats of the 14-week study (see NTP Report). Thus, it could not be excluded that the findings reported as high severity grades of CPN in the mid and high dose mask substance-related degenerative/regenerative effects. Overall, the view of a remaining concern given by the kidney tumours is supported. As the assessment of organ/tissue toxicity in subacute/subchronic/chronic studies is needed to interpret data from cancer studies, a supplementary documentation of repeated dose studies would be appreciated. Nevertheless, significant increases of hepatocellular adenoma in female and male mice and of mononuclear cell leukaemia (MNCL) in both sexes of rats give supportive evidence for classification of benzophenone as carcinogen. Evidence for a carcinogenic potential of benzophenone comes from the increased incidences of rare tumour forms, such as histiocytic sarcoma in female mice and female rats, and hepatoblastoma in male mice. As benzophenone is not a genotoxic substance and tumours appear to be induced in one sex a gender specific mechanism could be speculated. However, the mode of action has not been clarified. Taking into account observed increases of several tumour types, the remaining uncertainties, and that the criteria for category 1B are not fulfilled, it is agreed with the dossier submitter that classification of benzophenone as carcinogen, category 2 is warranted.

Dossier Submitter's Response

Thank you for your comments and your support for our evaluation of the carcinogenicity of benzophenone as category 2, H351.
The DS agrees that the modes of action of benzophenone are not clarified. The DS also agrees that information from repeated dose studies may bring information that may qualify evaluation of the carcinogenic potential of a substance. In the case of benzophenone, the NPT studies themselves are combined studies, at thus contain information on chronic non-neoplastic effects as well as on carcinogenic effects. The DS evaluated that this information on non-neoplastic findings in rats and mice over 104 weeks was sufficient for the evaluation of the classification of carcinogencity benzophenone. Therefore, the DS did not include two available publicly available shorter term repeated dose toxicity studies: a 28-day study in rats (Burdock G.A., Pence D.H., Ford R.A. 1991. Safety evaluation of benzophenone. Food Chem. Toxicol. 29(11): 741-750) and a 14-week studies in rats and mice conducted by NTP (NTP Technical Report on the Toxicity Studies of Benzophenone (CAS No. 119-61-9) Administered in Feed to F344/N Rats and B6C3F1 Mice. NIH Publication No.00-3943. https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox061.pdf?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=tox061) in the classification report for benzophenone.
The 14-week NTP study is mentioned in the classification report, as it was used by NTP for dose setting in the 104 week studies. However, the DS has become aware that the 14 week study in rat and mice was erroneously referred in the CLH-report as a 14-day study (p. 22, point 9.10.1.4).
The DS has evaluated the 28-days and the 14 week studies with benzophenone, when rapporteur for the substance under substance evaluation, to confirm the liver and kidney as the target organs of the toxicity of benzophenone. The DS considers that the

information from these shorter term repeated dose studies does not add substantial information on the development of the carcinogenicity of benzophenone.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2019	France		MemberState	3
Comment received				
The analysis presented in the dossier is fully supported in relation to increased incidence of hepatocellular adenomas in male and female mice, mononuclear cell leukaemia in male and female rats and renal adenomas in male tubule rats. The view is shared that they only provide supportive evidence for classification because these tumours are benign and in some cases, their relevance for humans under debate. However, the induction of malignant tumours relevant for human in two species (histiocytic sarcomas in female mice and rats and hepatoblastomas in male mice) strictly fulfil the criteria for classification 1B as sufficient evidence of carcinogenicity. This was indeed the IARC conclusion that there is sufficient evidence in experimental animals for the carcinogenicity of benzophenone. The incidence of histiocytic sarcomas in female mice is non-marginally above historical control data in both the mid- and high-dose groups. It is statistically significant in the mid-dose group and the absence of dose response and absence of statistical response at the high dose may be linked to the difference in survival between groups as survival in high dose females was lower (62% instead of 80% in control females), although not significantly. The relationship of this tumour with treatment to BP is therefore well established. As mentioned in the dossier, this tumour is considered relevant for human. Therefore, it provides clear evidence of carcinogenicity in female mice. For hepatoblastomas in male mice and histiocytic sarcomas in female rats, the incidences of these rare tumours are not significant and are only slightly above historical control data. However, in both case, the incidence at lower dose(s) is also at the upper limit of the HCD, which increase the likelihood of a relation to treatment. The fact that an uncommon tumour type, histiocytic sarcomas, is found in both mice and rats females also add some weight in the assessment of the level of evidence for histiocytic sarcomas in female rats. This should be carefully considered to conclude on the most appropriate classification Carc 1B or 2 and altogether points toward a classification 1B.				
Dossier Submitter's Response				
Thank you for your comments, and your support for our evaluation of the hepatocellular adenomas and MCL. The DS agrees that the interpretation on especially the rare tumour form histiocytic sarcoma needs careful examination. The DS has noted the higher mortality in the high dose group of female mice, where the tumour incidence is lower than in the mid-dose group. However, most mortalities occur late in the study (later week 90), and the DS has thus not found reason to suspect a supressed development of late occurring tumours as a major explanation for the lack of dose-response. The DS has evaluated that the lack of statistical significance to concurrent controls in female rats seen for histiocytic sarcomas, although exceeding HCD, reduced the concern for this species. A similar argumentation was considered in the weight of evidence evaluation for the hepatoblastomas in male mice and led the DS to its overall conclusion that a category 2 classification for carcinogenicity was the most appropriate.				
RAC's response				
Noted. RAC concluded that classification in category 1B was warranted.				

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Date	Country	Organisation	Type of Organisation	Comment number
11.10.2019	Sweden		MemberState	4
Comment received				
The Swedish CA supports the proposal of harmonised classification of benzophenone as Carc. 2, H351 based on limited evidence in mice and rats.				
Dossier Submitter's Response				
Thank you for your support to the proposal for classification of benzophenone as Carc.2, H351.				
RAC's response				
Noted.				