# Committee for Risk Assessment

# RAC

## 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

11 June 2020

CLH-O-0000006808-62-01/F

# OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

**Chemical name:** **Benzophenone**

**EC Number:** **204-337-6**

**CAS Number:** **119-61-9**

The proposal was submitted by **Denmark** and received by RAC on **23 May 2019.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

# PROCESS FOR ADOPTION OF THE OPINION

**Denmark** has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **12 August 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **11 October 2019**.

### ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Stine Husa**

Co-Rapporteur, appointed by RAC: **Christine Bjørge**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **11 June 2020** by **consensus**.

**Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)**

| | Index No | Chemical name | EC No | CAS No | Classification | | Labelling | | | Specific Conc. Limits, M-factors and ATE | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hazard Class and Category Code(s) | Hazard statement Code(s) | Pictogram, Signal Word Code(s) | Hazard statement Code(s) | Suppl. Hazard statement Code(s) | | |
| Current Annex VI entry | No current Annex VI entry | | | | | | | | | | |
| Dossier submitters proposal | TBD | Benzophenone | 204-337-6 | 119-61-9 | Carc. 2 | H351 | GHS08 Wng | H351 | | | |
| RAC opinion | TBD | Benzophenone | 204-337-6 | 119-61-9 | Carc. 1B | H350 | GHS08 Dgr | H350 | | | |
| Resulting Annex VI entry if agreed by COM | TBD | Benzophenone | 204-337-6 | 119-61-9 | Carc. 1B | H350 | GHS08 Dgr | H350 | | | |

# GROUNDS FOR ADOPTION OF THE OPINION

# HUMAN HEALTH HAZARD EVALUATION

## RAC evaluation of germ cell mutagenicity

### Summary of the Dossier Submitter's proposal

Germ cell mutagenicity was not assessed by the DS. However, a summary of the conclusion document of the member state CA conducting the substance evaluation (Danish EPA (2018), together with the conclusion of an EFSA report (2017) on the safety of benzophenone used as a flavouring agent, was provided. Overall these two evaluations indicate that benzophenone is not genotoxic. On this basis the DS considered that a genotoxic mode of action in relation to the carcinogenic potential of benzophenone is unlikely.

### Comments received during public consultation

This hazard was not open to commenting during the consultation of the CLH report.

### Assessment and comparison with the classification criteria

Germ cell mutagenicity has not therefore been evaluated by RAC.

## RAC evaluation of carcinogenicity

### Summary of the Dossier Submitter's proposal

The DS included two high-quality oral carcinogenicity studies in mice and rats, respectively, performed and reported by NTP (2006). Furthermore, two relatively old dermal carcinogenicity studies of lower quality by Stenbäck & Shubik (1974) using mice and by Stenbäck (1977) using rabbits were summarised in the CLH report.

Based on the available data the DS concluded that a classification of benzophenone in Category 2, H351 is warranted based on increased incidences of the rare tumour histiocytic sarcoma in female mice and female rats (single sex, two species) and the likewise rare hepatoblastoma in male mice at above historical background levels.

In addition, an increased incidence of hepatocellular adenoma in male and female mice above high spontaneous incidences as well as increased incidences of mononuclear cell leukaemia and of renal tubular tumours in male rats were used as supporting evidence.

The DS considered the evidence on the mode of action for the above-mentioned tumours insufficient to dismiss their relevance to humans.

## Comments received during public consultation

Comments were provided by 3 MSCA. Two MSCA supported the proposed classification as Carc. 2, however one MSCA indicated that Carc. 1B should be considered based on induction of rare malignant tumours relevant for humans in two species, namely the histiocytic sarcoma in female mice and rats and hepatoblastoma in male mice.

## Assessment and comparison with the classification criteria

The DS included four studies for the evaluation of carcinogenicity. This included two oral carcinogenicity studies in mice and rats and two dermal carcinogenicity studies in mice and rabbits. The studies are summarised in the table below.

***Table**: Summary of animal carcinogenicity studies, oral exposure to Benzophenone (BP)*

<table>
<tr><th>Method, guideline, test substance, deviations, Klimisch score, species, strain, sex, no/group, dose levels duration of exposure</th><th>Results</th><th>Ref.</th></tr>
<tr><td>Carcinogenicity study, corresponding to OECD TG 451<br><br>BP (purity > 99%)<br><br>Oral via diet<br><br>GLP<br><br>Klimisch score 1<br><br>B6C3F1 mice<br><br>50 m/f per group<br><br>0, 312, 625, or 1250 ppm for 105 weeks. Corresponding to 40, 80, and 160 mg BP/kg bw/day for males and 35, 70, and 150 mg BP/kg bw/day for females</td><td>Mortality: Non-significant decreased survival in high dose females (62 % vs 80% in controls). Other groups similar survival to controls (>80%)<br><br>Body weights: No effect on mean body weights of exposed males. In females, body weights were decreased from week 37 in the high dose group (14% decrease at study termination) from week 52 in the mid-dose group (8% decrease at study termination) and from week 92 in the low-dose group (7% decrease at study termination). No effect on feed intake.<br><br>Clinical signs: No clinical signs in either sex per dose group except in moribund animals).<br><br><u>Neoplastic findings</u>:
<table>
<tr><th colspan="6">Males /females (50/50)</th></tr>
<tr><td>Dose levels, ppm (mg/kg bw/d</td><td>0 (0/0)</td><td>312 (40/35)</td><td>625 (80/70)</td><td>1250 (160/150)</td><td>HCD</td></tr>
<tr><td>Hepato-cellular adenoma</td><td>11/5<br>22%/10%</td><td>15/4<br>30%/8%</td><td>23*/10*<br>46%/20%</td><td>23*/8*<br>46%/16%</td><td>Males (feed): 9/460, range 12-30%, mean 20%, Females: 40/457, range 6-12%, mean 9.6%</td></tr>
<tr><td>Hepato-cellular carcinoma</td><td>8/0<br>16%/0%</td><td>5/1<br>10%/2%</td><td>6/0<br>12%/0%</td><td>6/1<br>12%/2%</td><td>Males (all routes): 8-46%, mean 22.9%, 1257 controls.</td></tr>
<tr><td>Hepato-blastoma</td><td>0/-<br>0%/-</td><td>1/-<br>2%/-</td><td>1/-<br>2%/-</td><td>3/-<br>6%/-</td><td>Males (feed): 1/460, range 0-2%, mean 0.2%. Females: not reported.</td></tr>
<tr><td>Hepato-cellular adenoma, carcinoma or hepato-blastoma (males)</td><td>18/-<br><br>36%/-</td><td>20/-<br>40%/-</td><td>25/-<br>50%/-</td><td>29*/-<br>58%/-</td><td>Males (feed): 145/460, range 20-47%, mean 32%.</td></tr>
</table></td><td>NTP (2006)</td></tr>
</table>

| | | | | | | |
|---|---|---|---|---|---|---|
| | Hepato-cellular adenoma or carcinoma( females) | -/5 -/10% | -/5 -/10% | -/10 -/20% | -/9* -/18% | Females: 53/457, range 8-16%, mean 11.8% |
| | Histiocytic sarcoma | 1/0 0%/0% | 0/0 0%/0% | 0/5* 0%/10% | 0/3 0%/6% | Males; not available. Females:2/459, range 0-2%, mean 0.3% |

*: Significantly different (P≤0.05) from the control group
-: not reported

*Non-neoplastic findings:*

| **Males/females (50/50):** | | | | |
|---|---|---|---|---|
| Dose levels, ppm (mg/kg bw/d | 0 (0/0) | 312 (40/35) | 625 (80/70) | 1250 (160/150) |
| *Liver* | | | | |
| Hypertrophy hepatocytes | 0/0 | 44**/29** | 50**/44** | 48**/37** |
| Micronucleated hepatocytes | 0/- | 41**/- | 47**/- | 48**/- |
| Active chronic inflammation | 33/- | 47**/- | 44**/- | 42*/- |
| Hepatocyte degeneration | 0/- | 0/- | 5/- | 30**/- |
| *Kidney* | | | | |
| Nephropathy | 49/21 | 48/33** | 50/31* | 50/30* |
| Mineralisation | -/15 | -/31** | -/36** | -/49** |
| Severity grade | 1.2/1.2 | 1.4/1.1 | 1.7/1.5 | 3.0/1.7 |
| *Spleen* | | | | |
| Hyperplasia of lymphoid follicles | 17/24 | 31**/36** | 34*/37** | 32**/22 |
| Hematopoietic cell proliferation | -/16 | -/35** | -/32** | -/27* |
| *Testes* Mineralisation | 0/- | 1/- | 4/- | 12**/- |

Significantly different from the control group: * (P≤0.05), ** P≤0.01
-: not reported

Further, metaplasia of the olfactory epithelium was significantly increased in the high-dose group of males and females.

| | | |
|---|---|---|
| Carcinogenicity study, corresponding to OECD TG 451<br>BP (purity > 99%)<br>Oral via diet<br>GLP<br>Klimisch score 1<br>F344/N rats<br>50 m/f per group<br>0, 312, 625, or 1250 ppm BP for 105 weeks. Corresponding to 15, 30, and 60 mg | Severely decreased survival seen in high dose males (4% vs 44% in controls). Low and mid-dose male groups and all female groups have similar or higher survival compared to controls (≥54%).<br><br>Body weights: In males, body weights were decreased from week 62 in the high dose group (36% decrease at study termination), from week 86 in the mid-dose group (11% decrease at study termination). In females, body weights were decreased from week 10 in the high dose group (14% decrease at study termination), and mid-dose group (9% decrease at study termination). Feed consumption was reduced in high dose males from week 70 and in high dose females throughout the study.<br><br>Clinical signs: No clinical signs were reported in either sex per dose group except in relation to morbidity. | NTP (2006) |

BP/kg bw/day for males and 15, 30, and 65 mg BP/kg bw/day for females

*Neoplastic findings:*

| **Males/females (50/50)** | | | | | |
|---|---|---|---|---|---|
| Dose levels, ppm (mg/kg bw/d) | 0/0 (0/0) | 312/312 (15/15) | 625/625 (30/30) | 1250/1250 (60/65) | HCD |
| Mononuclear cell leukemia | 27/19 54%/38% | 41*/25 82%/50 % | 39*/30* 78%/60 % | 24/29 48%/58% | (feed), Males: 231/460, range 30-68% (mean 49.1%), Females: 112/460, range 12-38%, mean 24.6%) |
| Histiocytic sarcoma | -/0 -/0% | -/0 -/0% | -/1 -/2% | -/2 -/4% | Males: not available. Females (feed): 0/460. All routes range 0-2%, mean 0.1%, 1/1209 |
| Renal tubule adenoma | 2/- 4% | 2/- 4% | 7/- 14% | 8/- 16%* | 0-2% in 1152 controls |

* Significantly different (P≤0.05) from the control
-: not reported

*Non-neoplastic findings:*

| **Males/females (50/50)** | | | | |
|---|---|---|---|---|
| Dose levels, ppm (mg/kg bw/d) | 0/0 (0/0) | 312/312 (15/15) | 625/625 (30/30) | 1250/1250 (60/65) |
| *Liver*<br>Hepatocytes, centrilobular hypertrophy | 0/0 | 17**/27* | 31**/30* | 19**/30* |
| Degeneration, cystic | 8/- | 11/- | 20*/- | 15*/- |
| Inflammation chronic active | 22/46 | 21/38* | 35*/29* | 33*/30* |
| Bile duct hyperplasia | -/10 | -/35* | -/39* | -/40* |
| *Kidney*<br>Renal tubule hyperplasia | 3/1 | 11*/8* | 30*/10* | 40*/7* |
| Severity grade of nephropathy[a] | 1.3/1.1 | 2.4/1.4 | 3.3/1.7 | 3.8/2.0 |

<table>
<tr><td></td><td>* Significantly different (P≤0.05) from the control group<br>** P≤0.01<br>-: not reported<br>[a]Severity grade: 1=minimal, 2=mild, 3=moderate, 4=marked</td><td></td></tr>
<tr><td>Dermal carcinogenicity lifetime study in Swiss mice<br><br>Non-guideline<br><br>Klimisch score 2(-3).<br><br>50 female mice/group<br><br>0.2 mL of 5, 25 and 50% BP in acetone<br><br>Twice weekly in 110 weeks</td><td>No significant effects on survival or body weight gain were noted.<br><br><table><tr><th></th><th>Control (untreated/ acetone)</th><th>5% BP</th><th>25% BP</th><th>50% BP</th><th>Positive control DMBA</th></tr><tr><td>Tumour bearing mice</td><td>64/22</td><td>26</td><td>16</td><td>14</td><td>39</td></tr><tr><td>Lymphomas</td><td>26/12</td><td>15</td><td>11</td><td>6</td><td>6</td></tr><tr><td>Lung adenomas</td><td>17/9</td><td>3</td><td>2</td><td>6</td><td>4</td></tr><tr><td>Liver heman-giomas</td><td>4/2</td><td>1</td><td>1</td><td>2</td><td>1</td></tr><tr><td>Thymomas</td><td>6/0</td><td>1</td><td>1</td><td>0</td><td>0</td></tr><tr><td>Skin tumours</td><td>3/2</td><td>2</td><td>1</td><td>0</td><td>75</td></tr><tr><td>Other tumours</td><td>16/6</td><td>16</td><td>5</td><td>4</td><td>0</td></tr></table></td><td>Stenbäck & Shubik, 1974</td></tr>
<tr><td>Dermal lifetime study in New Zealand rabbits.<br><br>Non-guideline<br><br>Klimisch score 2/(3)<br><br>5 m/f per group<br><br>0.2 mL of 5, 25 and 50% BP (Acetone or methanol)<br><br>Twice weekly up to 160 weeks</td><td>No effects on clinical signs, survival and body weight gain were noted.<br><br>Autopsy was performed on all animals. Skin samples, grossly observed tumours and other lesions of the lung, liver, kidney etc. from all animals were studied histologically.<br><br>No abnormalities were detected, as well as no skin tumours or other tumours in animals treated with BP. A nephroblastoma was observed in an untreated animal. In the positive control group 12 tumours were recorded including 7 papillomas, 2 keratoacanthomas and 3 squamous cell carcinomas.</td><td>Stenbäck, 1977</td></tr>
</table>

**The historical control data (HCD)** reported in the carcinogenicity study with BP (NTP, 2006) are from 7 NTP feed studies performed from 1995-2004. For some tumour types, reference to 23 studies for all routes is used. The study period for the BP study was from September 1999 through September 2001 for mice and from August 1999 through August 2001 for rats.

### *Oral studies*

Mice

The DS included one carcinogenicity study (corresponding to OECD TG 451, GLP) with B6C3F1 mice (50/sex/dose group) orally exposed to 0, 312, 625, or 1250 ppm Benzophenone (diet), corresponding to 0/0, 40/35, 80/70, and 160/150 mg Benzophenone /kg bw/day for

males/females (NTP, 2006). Increased mortality was observed for females in the high dose group. Body weights were reduced in exposed females by 8%, 7% and 14% for low-, mid-, and high dose group respectively, compared to controls. In males, body weights were only slightly affected. No significant clinical signs were reported except in moribund animals. Tumours were reported in the liver and in the haematopoietic system of females and in the liver of male mice. Non-neoplastic changes in the liver, kidney and spleen were also reported as well as in the testes in the males.

*Liver*

The incidences of hepatocellular adenoma after exposure to Benzophenone showed a positive trend in males with 11 (22%), 15 (30%), 23 (46%) and 23 (46%) in the control, low, mid and high dose groups, respectively. The incidences in the mid and high dose groups were significantly different from the control group and in addition exceeded the HCD (range 12-30%, mean 20%). In females, the incidences of hepatocellular adenomas were 5 (10%), 4 (8%), 10 (20%) and 8 (16%) in the control, low, mid and high dose groups, respectively, however without statistical significance. The HCD (range 6-12%, mean 9.6%) was exceeded for the mid and high dose groups.

The hepatocellular carcinomas in the treated males occurred at non-significant incidences of 8 (17%), 5 (10%), 6 (12%) and 6 (12%) in control, low, mid and high dose groups, respectively. The reported HCD (all routes) for males were 8-46% (mean 22.9%). In females, only single incidences of hepatocellular carcinoma were reported in the low and high dose group which could be considered incidental. No HCD was reported for hepatocellular carcinomas.

Hepatoblastomas were only observed in male mice, with an incidence of 0, 1 (2%), 1 (2%) and 3 (6%) in control and low, medium and high dose, respectively. The findings were not statistically significant, however they exceeded the HCD incidence (range 0-2%, mean 0.2%).

The combined incidence of hepatoadenomas, hepatocarcinomas and hepatoblastomas in male mice reached statistical significance in the high dose group, with an incidence of 18 (36%), 20 (40%), 25 (50%) and 29 (58%) in control, low, mid and high dose groups, respectively. The HCD from seven NTP studies (1995-2004) showed a combined incidence of hepatoadenomas, hepatocarcinomas and hepatoblastomas in male mice of 20 (47%; mean 32%). For female mice the combined incidence of hepatoadenomas and hepatocarcinomas were 5 (10%), 5 (10%), 10 (20%) and 9 (18%) in control, low, mid and high dose groups, respectively. The HCD from these seven NTP studies showed a combined incidence of hepatoadenomas and hepatocarcinomas in female mice of 8-16% (mean 11.8%). Hepatoblastomas were not observed in female mice.

A statistically significant increase in incidences of hypertrophy of hepatocytes was seen in all treated groups and both sexes (0/0, 44/29, 50/44, 48/37 for control, low, mid and high dose for males/females, respectively). Further, active chronic inflammation was reported in males (incidences 33, 47, 44, 42 for control, low, mid and high dose for males, respectively) but not in females.

*Haematopoietic system*

Histiocytic sarcomas were observed in females with an incidence of 0, 0, 5 (10%) and 3 (6%) in the control, low-, middle- and high-dose groups, respectively. The findings were statistically significant at the mid-dose only. The HCD (mean of 0.3%; range 0-2 %) was exceeded in the mid- and high dose groups. The concern for carcinogenicity in the hematopoietic system is supported by a statistically significant increase in hematopoietic cell proliferation in the spleen in female mice (incidences 16, 35, 32 and 27 for control, low, mid and high dose groups, respectively). In the high dose group of female mice, the histiocytic sarcomas were highly invasive. Multiple organs throughout the body had neoplastic histiocytic lesions.

Rats

The DS included one carcinogenicity study in rats (F334/N) exposed orally (diet) to 0, 312, 625, or 1250 ppm Benzophenone corresponding to 0/0, 15/15, 30/30, and 60/65 mg Benzophenone /kg bw/day for males/females (NTP, 2006). Mortality was significantly increased for males in the high dose group (% survival at end of study: 44%, 54%, 62% and 4% in the control, low, mid and high dose males, respectively). Body weights in males/females were decreased by 11%/9% in the mid-dose group and 36%/14% in the high dose group. Feed consumption was reduced in high dose animals of both sexes. No clinical signs were reported. Tumours were reported in the kidney and haematopoietic system of male rats and in the haematopoietic system of females. Non-neoplastic changes in the liver and kidney in both sexes were also reported.

*Kidneys*

The incidences of renal tubule adenoma in male rats increased with increasing doses and reached statistical significance at the high dose level (2 (4%), 2 (4%), 7 (14%) and 8 (16%) for control, low, mid and high dose, respectively). No renal tubule adenomas were observed in female rats. The HCD (range 0-2 %) was exceeded in the in all treated groups, however it was noted that also the incidence in the concurrent control exceeded the HCD range presented.

A statistically significant increase in incidences of renal tubule hyperplasia was seen in all treated groups and both sexes (3/1, 11/8, 30/10, 40/7 for control, low, mid and high dose for males/females, respectively). It should be noted that the severity grade increased with increasing dose, especially in male rats.

*Haematopoietic system*

The incidences of mononuclear cell leukaemia (MNCL) were 27/19, 41/25, 39/30, 24/29 for males/females in the control, low, mid and high dose groups, respectively. The finding was statistically significantly increased and outside the reported HCD in the low and mid dose groups of males, and in the mid dose group of females. It should be noted that there was a decreased survival in the high dose males (4 % vs 44% in controls).

Histiocytic sarcomas were observed in one female rat in the mid dose group (1%) and 2 female rats in the high dose group (4%). Histiocytic sarcoma was not observed in the HCD for feed studies (1995-2004), however the HCD for all routes of exposure in the 2-year rat studies ranged from 0-2 % (NTP, 2006).

***Dermal studies***

The DS included one non-guideline dermal carcinogenicity lifetime study with Swiss mice (50 females/group) exposed to Benzophenone by open dermal application of 0.2 mL of 5, 25 and 50% Benzophenone in acetone applied on the dorsal skin of the animals twice weekly for 110 weeks (Stenbäck and Shubik, 1974). A vehicle control group and a positive control group (treated with dimethylbenzanthracene (DMBA)) were included and in addition an untreated control group (150 animals). No increased mortality or body weight changes were observed in the dosed groups and there was no dose response relationship in the total number of tumours observed.

Furthermore, a dermal carcinogenicity lifetime study (non-guideline) in New Zealand White rabbits with 5 rabbits/group (both sexes) was assessed by the DS (Stenbäck, 1977). In this study, the rabbits were exposed by open dermal application of 0.2 mL of 5, 25 and 50% Benzophenone in solvent to the interior left ear twice weekly up to 160 weeks (until animals died spontaneously). No treatment related effect on mortality was observed and the survival at week 160 was 1, 3 and 2 rabbits in the low, mid, and high dose groups, respectively. Two untreated control groups with 5 and 4 animals respectively was included. Survival in these were 3/5 and 0/4 respectively. In addition, a positive control group (15 animals) treated with DMBA was included. The positive

control group was terminated at week 50. No tumours were recorded in the treated groups. One nephroblastoma was observed in the untreated control groups, while twelve tumours were recorded in the positive control group, including seven papillomas, two keratoacanthomas and three squamous cell carcinomas.

***Human data***

No human data are available.

***Weight of evidence assessment***

Tumour type and background incidence

*Histiocytic sarcoma:* An increased incidence in this rare tumour type was observed in female rats and female mice reaching statistical significance in the mid dose female mice and were shown to be more invasive in the high dose female mice compared to the mid-dose group. It is also noted that the findings exceeded the HCD from feeding studies reported in the mid and high dose females (rats and mice). The concern for a carcinogenic effect on the haematopoetic system is further supported by the increased incidence of hematopoietic cell proliferation in the spleen of all dosed groups of female mice.

*Hepatocellular adenoma, carcinoma and hepatoblastoma:* The incidences of hepatocellular adenoma in male mice showed a clear dose-response relationship, with statistically significant differences from controls in the two highest dose groups which exceeded the HCD. In female mice, the incidences observed were not statistically significantly different from the concurrent controls but exceeded the HCD. The malignant hepatic tumours recorded in the mice included hepatoblastomas and hepatocellular carcinomas in male mice, and hepatocellular carcinomas in female mice. The hepatoblastomas in male mice, showed a positive trend in relation to the treatment. This finding was not statistically significantly different from the concurrent control but exceeded the HCD. The hepatocellular carcinomas in the treated males occurred at non-statistically significant levels and showed no dose-response relationship. In females, the single incidence of hepatocellular carcinoma in the low and high dose groups could be an incidental, non-treatment related finding considering that the incidence of spontaneous hepatocarcinoma in female B6C3F1 mice is highly variable. It should be noted that a statistically significant increase in incidences of hypertrophy of hepatocytes was seen in all treated groups for male as well as female mice and that active chronic inflammation was reported in male mice.

According to Gariboldi *et al*. (1993) and Manenti *et al*. (1994) B6C3F1, mice are susceptible to chemically induced cellular hepatocarcinogenesis. Further, the human relevance of hepatic tumours in mice, when induced by non-genotoxic compounds, is disputed (Gold & Slone, 1993; Carmichael *et al*., 1997; Boobis *et al*., 2006; Holsaple *et al*., 2006; Billington *et al*., 2010).

Overall, the occurrence of hepatoadenoma in mice can be considered as supportive evidence for the carcinogenicity of Benzophenone, taking into account that the tumours which were formed were benign and the increased susceptibility of the mouse strain used. The low non-significant incidences of hepatoblastomas and hepatocellular carcinomas in mice lead to uncertainty for concluding on their relationship to Benzophenone exposure. However, some concerns are raised from the occurrence of the hepatoblastomas, which are rare tumours and even a small increase in hepatoblastoma could be considered relevant for classification.

*Renal tubular tumours:* A positive trend in the incidences of renal tubule adenoma was found in the treated male rats, with a statistically significant increase in the high-dose group. Further, statistically significant increases in incidences of renal tubule hyperplasia were seen in all Benzophenone treated groups of male and female rats.

Chronic progressive nephropathy (CPN) is considered to be a common spontaneous effect in the rat kidney, and an association between treatment-related CPN from 90-day studies and kidney tumours from 2-year studies has been found (Travlos *et al*., 2011). Therefore, their relevance to humans may be questioned. However, no clear pathogenesis of chemically induced renal tubular tumours has been determined and seems to be complex, with genotoxic and non-genotoxic modes of action (Barret and Huff, 1991; Short, 1993; Hard, 1998). The induction of renal tubule adenomas is considered to indicate limited evidence of carcinogenic activity.

*Mononuclear cell leukaemia (MNCL):* A statistically significant increase in the incidences of MNCL in the low- and middle-dose groups of males, and in the middle-dose group of females was found in rats, however, the human relevance of increased incidences of MNCL in F344 rats has been debated. According to Caldwell (1999) MNCL occur in untreated, aged F344 rats at a high and variable rate. Further, MNCL is uncommon in most other rat strains. The background incidence of MNCL has increased significantly over time. MNCL has not been found in other mammalian species (e.g. mice and hamsters) and no histologically comparable tumour is found in humans. Scheepmaker *et al*. (2005) also noted that the mechanism for the induction of MNCL in F344 is unknown and that several substances have shown increased incidences of MNCL in chronic studies. They concluded that substance-induced increases in MNCL in F344 rats should not be considered to be of human relevance, but they also noted that increases of MNCL in other rat strains and other species should be considered as relevant for humans. However, Thomas *et al*. (2007) indicated that a rare form of human lymphocyte leukaemia (natural killer cell large granular lymphocyte leukaemia; NK-LGLL) is similar to MNCL observed in F344 rats and noted that little is known about the cellular/molecular pathways of leukaemogenesis in the F344 rats. They indicate that more mechanistic information is needed as regards their relevance for humans. Overall, the occurrence of MNCL in rats is considered to be of limited concern for humans.

Multi-site responses

An increased incidence was reported for the rare tumour form histiocytic sarcoma in one sex from two species: female mice and female rats. Likewise, the rare tumour hepatoblastoma were reported in male mice above historical background levels.

In addition, an increased incidence of hepatocellular adenoma in male and female mice above high spontaneous incidences, as well as increased incidence of mononuclear cell leukaemia and renal tubular tumours in male rats was reported. However, the increased incidence of mononuclear cell leukaemia and renal tubular tumours in male rats are considered to be of limited concern for humans. *Progression of lesions to malignancy;*

The histiocytic sarcoma observed in female rats and mice and the hepatoblastoma observed in male mice are considered as malignant tumours.

Regarding the hepatocellular adenomas, limited evidence of progression to malignancy were observed. The hepatocellular carcinomas observed showed no dose-response relationship and were not statistically significantly different from the control groups. As already noted, hepatoblastoma is a rare tumour in mice. According to the NTP (2006) study hepatoblastomas are malignant neoplasms that are presumed to be a primitive form of hepatocellular carcinoma, well demarcated neoplastic masses independent of other hepatocellular tumors. The study by Turusov *et al.* (2002) suggests that the hepatoblastomas observed in mice in NTP-studies arise within hepatocellular adenomas or carcinomas.

Reduced tumour latency

No information is available on tumour latency

Whether responses are in single or both sexes

Histiocytic sarcoma was observed in female mice and female rats. Further, hepatoblastoma were only observed in male mice. Hepatocellular adenoma was observed in male and female mice, while mononuclear cell leukaemia and renal tubular tumours were observed in male rats.

Whether responses are in a single species or several species

Histiocytic sarcoma was observed in rats and mice.

Hepatoblastoma was observed in male mice, in addition mice showed increased incidence of hepatocellular adenoma.

Mononuclear cell leukaemia and renal tubular tumours were only observed in rats.

Structural similarity to a substance(s) for which there is good evidence of carcinogenicity

No information available

Routes of exposure

Routes of exposure of relevance for humans are used in the animal studies (oral exposure)

Comparison of absorption, distribution, metabolism and excretion between test animals and humans

No information available

The possibility of a confounding effect of excessive toxicity at test doses

There was a high level of mortality in the high dose males in the carcinogenicity study with rats (survival 4% at the high dose vs 44% in controls). Low and mid-dose male groups and all female groups showed similar or higher survival compared to controls ($\geqslant$54%). Lower body weights than in controls by 9-36% were reported in mid- and high-dose groups. In the carcinogenicity study with mice, survival was non-significantly affected only in the high dose females, and body weights were lower than in controls by over 10% in that group, whilst males and mid-group females did not exhibit signs of general toxicity.

Mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity

Benzophenone is considered not genotoxic by the Danish EPA (2018) and EFSA (2017). The Danish EPA (2018) further discussed a potential endocrine mechanism including thyroid peroxidase inhibition and estrogenic and anti-androgenic activity. However, no firm conclusion could be drawn from the available data. IARC (2013) hypothesised the involvement of generation of reactive oxygen species and/or endocrine disruption through multiple receptors, however they concluded that ultimately the mechanism is not known.

***In summary***

No human data are available for benzophenone and a classification in category 1A is not justified.

As regards classification in category 1B vs category 2, RAC considers that the available data show evidence of carcinogenicity in two animal species, including increased incidence of the rare tumour histiocytic sarcoma in female mice and female rats. This tumour type is considered to be related to the exposure to benzophenone and to be of biological significance. The low incidences of this tumour is noted. However, due to histiocytic sarcoma being a rare tumour, a low incidence is expected.

Supporting evidence of carcinogenicity included the finding of the rare tumour hepatoblastoma in male mice, and a statistically significantly increased incidence of hepatocellular adenoma in male mice and female mice. In addition renal tubular tumours in male rats and a statistically significantly increased incidence of mononuclear cell leukaemia (MNCL) in male and female rats was observed. However, the high spontaneous incidence of liver tumours in B6C3F1 mice and MNCL in F344 rats as well as the uncertain relevance to humans for MNCL and renal tubular tumour are noted.

Overall, RAC considers that a classification for benzophenone as Carc. 1B is warranted based on sufficient evidence of carcinogenicity in different tissues observed in two species at dose levels which were not excessive.

In conclusion RAC is of the opinion that according to the CLP criteria, **classification as category 1B for carcinogenicity is justified**.

## ANNEXES

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).