CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

Benzophenone

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

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

Index Number: **-**

Contact details for dossier submitter:

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Version number: 2 **Date: 23 May 2019**

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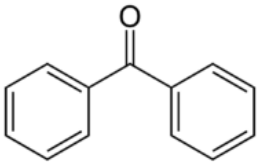
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Benzophenone, di(phenyl)methanone, diphenyl ketone, diphenyl methanone, diphenylmethanone, methanone, diphenyl-
Other names (usual name, trade name, abbreviation)	Diphenyl ketone Diphenylmethanone
EC number (if available and appropriate)	204-337-6
EC name (if available and appropriate)	Benzophenone
CAS number (if available)	119-61-9
Molecular formula	$C_{13}H_{10}O$
Structural formula	
SMILES notation (if available)	C1=CC=C(C=C1)C(=O)C2=CC=CC=C2
Molecular weight or molecular weight range	182
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not UVCB substance
Degree of purity (%) (if relevant for the entry in Annex VI)	Not relevant for classification purpose

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
Benzophenone	Monoconstituent substance No information on purity given in the publicly available version of the REACH registration	none	REACH registration: STOT Rep. Exp. 2 (oral) H373: May cause damage to organs (liver, kidnyes) through prolonged or repeated exposure.

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
			Aquatic Chronic 3, H412: Harmful to aquatic life with long lasting effects One out of 50 CLP notifications uses a Carc 2 classification.

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Benzophenone	No information on impurities given in the publicly available version of the REACH registration			

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
Benzophenone	No information on additives given in the publicly available version of the REACH registration				

Table 5: Test substances (non-confidential information) (this table is optional)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
Benzophenone	>99%			NTP (2006) studies

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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	none	benzophenone	204-337-6	119-61-9	none	none	none	none			
Dossier submitters proposal	TBD	benzophenone	204-337-6	119-61-9	Carc. 2	H351	GHS08	H351			
Resulting Annex VI entry if agreed by RAC and COM	TBD	benzophenone	204-337-6	119-61-9	Carc. 2	H351	GHS08	H351			

Table 7: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	hazard class not assessed in this dossier	No
Oxidising gases	hazard class not assessed in this dossier	No
Gases under pressure	hazard class not assessed in this dossier	No
Flammable liquids	hazard class not assessed in this dossier	No
Flammable solids	hazard class not assessed in this dossier	No
Self-reactive substances	hazard class not assessed in this dossier	No
Pyrophoric liquids	hazard class not assessed in this dossier	No
Pyrophoric solids	hazard class not assessed in this dossier	No
Self-heating substances	hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	hazard class not assessed in this dossier	No
Oxidising liquids	hazard class not assessed in this dossier	No
Oxidising solids	hazard class not assessed in this dossier	No
Organic peroxides	hazard class not assessed in this dossier	No
Corrosive to metals	hazard class not assessed in this dossier	No
Acute toxicity via oral route	hazard class not assessed in this dossier	No
Acute toxicity via dermal route	hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	hazard class not assessed in this dossier	No
Skin corrosion/irritation	hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	hazard class not assessed in this dossier	No
Respiratory sensitisation	hazard class not assessed in this dossier	No
Skin sensitisation	hazard class not assessed in this dossier	No
Germ cell mutagenicity	hazard class not assessed in this dossier	No
Carcinogenicity	*harmonised classification proposed*	*Yes*
Reproductive toxicity	hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	hazard class not assessed in this dossier	No
Aspiration hazard	hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	hazard class not assessed in this dossier	No
Hazardous to the ozone layer	hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Not included in Annex VI to CLP.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

The present proposal for harmonised classification concerns carcinogenicity, thus covered by CLP article 36 1 (b) with no justification needed. Benzophenone has been suject to substance evaluation under REACH and the evaluating member state identified toxicological data considered relevant for harmonised classification for carcinogenicity (Danish EPA 2018).

5 IDENTIFIED USES

According to ECHA´s web-site substance information on benzophenone:
https://echa.europa.eu/substance-information/-/substanceinfo/100.003.943 (retrieved November 2018)
benzophenone is used in the following products:
air care products, polishes and waxes, washing & cleaning products, anti-freeze products, biocides (e.g. as a odoriferous agent in disinfectants, pest control products), inks and toners, perfumes and fragrances, pharmaceuticals and cosmetics and personal care products.

6 DATA SOURCES

The primary documentation used in this dossier ise:

- Registration dossier information on benzophenone publicly available from ECHA dissemination page (consulted 2018).
- Danish EPA (2018). SUBSTANCE EVALUATION CONCLUSION as required by REACH Article 48 and EVALUATION REPORT for Benzophenone. 5 April 2018.
- EFSA (2017). Safety of Benzophenone to be used as flavouring. The EFSA Journal 15(11):5013 http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.5013/epdf
- IARC (2013). Benzophenone in: Some Chemicals Present in Industrial and Consumer Products, Food and Drinking-water. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans vol 101. http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-007.pdf
- NTP (2006). National Toxicology Program (2006) Technical Report on the toxicology and carcinogenesis studies of benzophenone (CAS No. 119-61-9) in F344/N rats and B6C3F1 and B6C3F1 mice (feed studies). February 2006. National Toxicity Program. Toxicity Report 5333. NIH publication No.06-4469.

7 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties **(from Danish EPA 2018)**

Property	**Value**
Physical state at 20°C and 101,3 kPa	Organic solid. White crystals or flakes with a geranium or sweet, rose-like odour.
Melting/freezing point	48.5 °C (HSDB)
Boiling point	299.49 °C (calculated) (Registrant(s) dossier publicly available at ECHA´s homepage) 305.4 °C (HSDB)
Vapour pressure	0.00257 hPa at 25 °C

Property	Value
Water solubility	137 mg/L (at 25 °C) (HSDB)
Partition coefficient n-octanol/water	3.18 at 25°C (measured) (HSDB)
Flammability	Not susceptible to ignition on contact with air; however, the flammability range of gaseous Benzophenone is reported to be 0.7 - 5.4 vol%
Explosive properties	Dust can form an explosive mixture with air
Oxidising properties	No oxidising properties
Granulometry	Median diameter D (v, 0.1)=23.18 µm, D (v, 0.5)=228.04µm, D (v, 0.9)=695.93 µm, D (4, 3)=302.12 µm, and D (3, 2)=60.16 µm The particle size distribution of Benzophenone crystals was analysed by laser diffraction technology.
Stability in organic solvents and identity of relevant degradation products	Stable in organic solvents based on structural aspects
Dissociation constant	No content of functional groups that are susceptible to dissociation.

8 EVALUATION OF PHYSICAL HAZARDS

Physical hazards not evaluated.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not further evaluated.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

Hazard class not evaluated.

10.1 Acute toxicity - oral route

Hazard class not evaluated.

10.2 Acute toxicity - dermal route

Hazard class not evaluated.

10.3 Acute toxicity - inhalation route

Hazard class not evaluated.

10.4 Skin corrosion/irritation

Hazard class not evaluated.

10.5 Serious eye damage/eye irritation

Hazard class not evaluated.

10.6 Respiratory sensitisation

Hazard class not evaluated.

10.7 Skin sensitisation

Hazard class not evaluated.

10.8 Germ cell mutagenicity

This hazard end-point is not subjected to further detailed analysis and discussion as the conclusion on this end-point is based on previous evaluations:

Danish EPA (2018). Member state substance evaluation conclusion document.

EFSA (2017). Safety of Benzophenone to be used as flavouring.

In the substance evaluation conclusion document Danish EPA, 2018 it was concluded:

"The results of genotoxicity assays with Benzophenone showed no evidence of genotoxicity both in in vitro and in vivo tests. In one assay, the use of human recombinant P450 enzyme preparations, including P450 family 1 enzymes, in a Salmonella typhimurium umu gene expression assay with Benzophenone and two metabolites, benzhydrol and p-benzoylphenol, produced dose-related increases in gene expression (Takemoto et al., 2002). However, this assay is not an OECD guideline assay and moreover Benzophenone was negative in the bacterial in vitro OECD guideline test, Salmonella typhimurium gene mutation assay. Benzophenone was also negative in another bacterial assay, the unscheduled DNA synthesis test, as well as in the OECD guideline test using mammalian cells, the mouse lymphoma assay. Two reported in vivo micronucleus tests of Benzophenone in mice gave negative results.

Based on this the evaluating MS has taken the overall conclusion that Benzophenone is not genotoxic."

The report from EFSA on benzophenone as a flavouring agent (2017) concluded:

"Overall, the Panel considered that based on the available data, which covers all relevant genetic endpoints (i.e. gene mutations, structural and numerical chromosomal aberrations) there is no concern with respect to genotoxicity of benzophenone".

Overall, the evaluations from Danish EPA (2018) and EFSA (2017) indicate that benzophenone is not genotoxic. In the Danish EPA conclusion document (2018), it is further stated that no further assessment of the genotoxic potential for benzophenone is needed. Thus, a genotoxic mode of action in relation to a carcinogenic potential of benzophenone is considered unlikely by the dossier submitter as well.

10.9 Carcinogenicity

Data on benzophenone (BP) regarding carcinogencity pertains to two high-quality oral carcinogenicity studies in mice and rats, respectively, performed and reported by NTP (2006). Further, two relatively old dermal carcinogenicity studies of lower quality are available and reported by Stenbäck & Shubik (1974) using mice and by Stenbäck (1977) using rabbits.

Table **9:** Summary table of animal studies on carcinogenicity, oral exposure

<table>
<tr><th>Method, guideline, deviations if any, Klimish score, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr><td>Carcinogenicity study, corresponding to OECD TG 451 and in accordance with GLP principles. Klimish score 1.

<u>B6C3F1 mice</u>

50 males and 50 females in each group</td><td>Benzophenone (BP) (purity > 99%)

Oral via diet

0, 312, 625, or 1250 ppm BP 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%)

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.

Clinical signs: No clinical signs in either sex per dose group except in moribund animals).

<u>Neoplastic findings</u>:
<table>
<tr><th colspan="5">Males</th></tr>
<tr><th>Dose levels, ppm
(mg/kg bw/day)</th><th>0
(0)</th><th>312
(40)</th><th>625
(80)</th><th>1250
(160)</th></tr>
<tr><td>hepatocellular adenoma[a]</td><td>11/50
22%</td><td>15/50
30%</td><td>23/50
46%*</td><td>23/50
46%*</td></tr>
<tr><td>Hepatocellular carcinoma[b]</td><td>8/50
16%</td><td>5/50
10%</td><td>6/50
12%</td><td>6/50
12%</td></tr>
<tr><td>Hepatoblastoma[c]</td><td>0/50
0%</td><td>1/50
2%</td><td>1/50
2%</td><td>3/50
6%</td></tr>
<tr><td>Hepatocellular adenoma, carcinoma</td><td>18/50
36%</td><td>20/50
40%</td><td>25/50
50%</td><td>29/50
58%*</td></tr>
</table></td><td>NTP (2006)</td></tr>
</table>

Method, guideline, deviations if any, Klimish score, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference

or hepatoblastoma[d]				
Histiocytic sarcoma[e]	1/50	0/50	0/50	0/50

*Significantly different (P≤0.05) from the control group
[a] historical incidences[1],feed: 9/460, range 12-30%, (mean 20%).
[b] historical incidences, all routes: 8-46% (mean 22.9%) in 1257 controls.
[c] historical incidences,feed: 1/460, range 0-2%, (mean 0.2%)
[d]historical incidences,feed:145/460 range 20-47%, mean of 32%.
[e]no information on HCD for histiocytic sarcoma in males available.

Females				
Dose levels, ppm (mg/kg bw/day)	**0 (0)**	**312 (35)**	**625 (70)**	**1250 (150)**
hepatocellular adenoma [a]	5/50 10%	4/50 8%	10/50 20%	8/50 16%
hepatocellular carcinoma	0/50 0%	1/50 2%	0/50 0%	1/50 2%
hepatocellular adenoma or carcinoma [b]	5/50 10%	5/50 10%	10/50 20%	9/50 18%
*Hepatoblastoma***	0/50	0/50	0/50	0/50
Histiocytic sarcoma[c],	0/50 0%	0/50 0%	5/50 10%*	3/50 6%

* Significantly different (P≤0.05) from the control group
** findings not reported.
[a] historical incidences,feed:[1] :40/457, range 6-12% (mean 9.6%)
[b] historical incidences,feed 53/457,range 8-16% (mean 11.8%)
[c] historical incidences,feed : 2/459 0-2% (mean o.3%).

Non-neoplastic findings:

Males				
Dose levels, ppm (mg/kg bw/day)	**0 (0)**	**312 (40)**	**625 (80)**	**1250 (160)**

[1] Historical control data (HCD): The HCD are reported in the NTP-carcinogenicity study with BP (published in 2006). The data are from 7 NTP-2000 feed studies performed in the period from 1995-2004. For some tumour types, reference to 23 studies from all routes is used. The feed "NTP-2000" was introduced in 1995. The study period of the BP study was from sept 1999 through sept 2001 for mice. and from aug 1999 through aug 2001 for rats. The strains of choice of NTP were the F334/N rats until 2006 and the B6C3F1 mice, and the latter is still the preferred mice strain by NTP. It is therefore presumed that the HCD in the database are for the same strains as used in the carcinogenicity study with BP.

<table>
<tr><th>Method, guideline, deviations if any, Klimish score, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Liver</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hypertrophy hepatocytes</td><td>0/50</td><td>44/50**</td><td>50/50**</td><td>48/50**</td></tr>
<tr><td>Micronucleated hepatocytes</td><td>0/50</td><td>41/50**</td><td>47/50**</td><td>48/50**</td></tr>
<tr><td>Active chronic inflammation</td><td>33/50</td><td>47/50**</td><td>44/50**</td><td>42/50*</td></tr>
<tr><td>Hepatocyte degeneration</td><td>0/50</td><td>0/50</td><td>5/50*</td><td>30/50**</td></tr>
<tr><td>Kidney</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Nephropathy</td><td>49/50</td><td>48/50</td><td>50/50</td><td>50/50</td></tr>
<tr><td>Severity grade average</td><td>1.2</td><td>1.4</td><td>1.7</td><td>3.0</td></tr>
<tr><td>Spleen</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hyperplasia of lymphoid follicles</td><td>17/50</td><td>31/50**</td><td>34/50*</td><td>32/50**</td></tr>
<tr><td>Testes</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mineralisation in testes</td><td>0/50</td><td>1/50</td><td>4/50</td><td>12/50**</td></tr>
</table>
* Significantly different (P≤0.05) from the control group
** P≤0.01
<table>
<tr><td colspan="5">Females</td></tr>
<tr><td>Dose levels, ppm (mg/kg bw/day)</td><td>0 (0)</td><td>312 (35)</td><td>625 (70)</td><td>1250 (150)</td></tr>
<tr><td>Liver</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hypertrophy hepatocytes</td><td>0/50</td><td>29/50**</td><td>44/50**</td><td>37/50**</td></tr>
<tr><td>Kidney</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Nephropathy</td><td>21/50</td><td>33/50**</td><td>31/50*</td><td>30/50*</td></tr>
<tr><td>Mineralisation</td><td>15/50</td><td>31/50**</td><td>36/50**</td><td>49/50**</td></tr>
<tr><td>Severity grade average</td><td>1.2</td><td>1.1</td><td>1.5</td><td>1.7</td></tr>
<tr><td>Spleen</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hyperplasia of lymphoid follicles</td><td>24/50</td><td>36/50**</td><td>37/50**</td><td>22/50</td></tr>
<tr><td>Hematopoietic cell proliferation</td><td>16/50</td><td>35/50**</td><td>32/50**</td><td>27/50*</td></tr>
</table>
* Significantly different (P≤0.05) from the control group
** P≤0.01

Further, metaplasia of the olfactory epithelium was significantly increased in the high-dose group of males and females.
</td><td></td></tr>
<tr><td>Carcinogenicity study, corresponding to OECD TG</td><td>Benzophenone (BP) (purity > 99%)</td><td>Mortality: 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%).

Body weights: In males, body weights were decreased from week 62</td><td>NTP (2006)</td></tr>
</table>

<table>
<tr><th>Method, guideline, deviations if any, Klimish score, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr><td>451 and in accordance with GLP principles. Klimish score 1.

<u>F344/N rats</u>

50 males and 50 females in each group</td><td>Oral via diet

0, 312, 625, or 1250 ppm BP for 105 weeks. Corresponding to 15, 30, and 60 mg BP/kg bw/day for males and 15, 30, and 65 mg BP/kg bw/day for females</td><td>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.

Clinical signs: No clinical signs were reported in either sex per dose group except in relation to morbidity.

<u>Neoplastic findings</u>:

<table>
<tr><td><u>Males</u></td><td></td><td></td><td></td><td></td></tr>
<tr><td><u>Dose levels, ppm</u>
<u>(mg/kg bw/day)</u></td><td><u>0</u>
<u>(0)</u></td><td><u>312</u>
<u>(15)</u></td><td><u>625</u>
<u>(30)</u></td><td><u>1250</u>
<u>(60)</u></td></tr>
<tr><td><u>Mononuclear cell leukemia</u> [a]</td><td><u>27/50</u>
<u>54%</u></td><td><u>41/50*</u>
<u>82%</u></td><td><u>39/50*</u>
<u>78%</u></td><td><u>24/50</u>
<u>48%</u></td></tr>
<tr><td><u>Histiocytic sarcoma</u></td><td><u>0/50</u></td><td><u>0/50</u></td><td><u>0/50</u></td><td><u>0/50</u></td></tr>
<tr><td><u>Renal tubule adenoma</u>[b]</td><td><u>2/50</u>
<u>4%</u>[b]</td><td><u>2/50</u>
<u>4%</u></td><td><u>7/50</u>
<u>14%</u></td><td><u>8/50</u>
<u>16%</u></td></tr>
</table>
<u>* Significantly different (P≤0.05) from the control</u>
<u>** no findings reported, and no HCD available for histiocytic sarcomas in males.</u>
<u>[a] historical incidences,feed[2]:: 231/460, 30 mean 49.1%)</u>
<u>[b] historical incidences,feed:: 0- 2% in 1152 control animals, all routes.</u>

<table>
<tr><td>Females</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Dose levels, ppm
(mg/kg bw/day)</td><td>0
(0)</td><td>312
(15)</td><td>625
(30)</td><td>1250
(65)</td></tr>
<tr><td>Mononuclear cell leukemia [a]</td><td>19/50
38%</td><td>25/50
50%</td><td>30/50*
60%</td><td>29/50
58%</td></tr>
<tr><td>Histiocytic sarcoma [b]</td><td>0/50</td><td>0/50</td><td>1/50</td><td>2/50</td></tr>
</table>
</td><td></td></tr>
</table>

[2] Historical control data (HCD): The HCD are reported in the NTP-carcinogenicity study with BP (published in 2006). The data are from 7 NTP-2000 feed studies performed in the period from 1995-2004. For some tumour types, reference to 23 studies from all routes is used. The feed "NTP-2000" was introduced in 1995. The study period of the BP study was from sept 1999 through sept 2001 for mice. and from aug 1999 through aug 2001 for rats. The strains of choice of NTP were the F334/N rats until 2006 and the B6C3F1 mice, and the latter is still the preferred mice strain by NTP. It is therefore presumed that the HCD in the database are for the same strains as used in the carcinogenicity study with BP.

Method, guideline, deviations if any, Klimish score, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference

	0%	0%	2%	4%

* Significantly different (P≤0.05) from the control group
[a] historical incidences,feed[3]: 112/460, range 12-38% (mean 24.6%)
[b]historical incidences,feed: 0/460. HCD all routes 0-2 % (mean 0.1%) 1/1209

Non-neoplastic findings:

Males				
Dose levels, ppm (mg/kg bw/day)	**0 (0)**	**312 (15)**	**625 (30)**	**1250 (60)**
Liver				
Hepatocytes, centrilobular Hypertrophy	0/50	17/50**	31/50**	19/50**
Degeneratiom, cystic	8/50	11/50	20/50*	15/50*
Inflammation chronic active	22/5	21/50	35/50*	33/50*
Kidney				
Renal tubule hyperplasia	3/50	11/50*	30/50*	40/50*
Severity grade of nephropathy	1.3	2.4	3.3	3.8

* Significantly different (P≤0.05) from the control group
** P≤0.01

Females				
Dose levels, ppm (mg/kg bw/day)	**0 (0)**	**312 (15)**	**625 (30)**	**1250 (65)**
Liver				
Hepatocytes, centrilobularhypertrophy	0/50	27/50*	30/50*	33/50*
Bile duct hyperplasia	10/50	35/50*	39/50*	40/50*
Inflammation chronic active	46/50	38/50*	29/50*	30/50*

[3] Historical control data (HCD): The HCD are reported in the NTP-carcinogenicity study with BP (published in 2006). The data are from 7 NTP-2000 feed studies performed in the period from 1995-2004. For some tumour types, reference to 23 studies from all routes is used. The feed "NTP-2000" was introduced in 1995. The study period of the BP study was from sept 1999 through sept 2001 for mice. and from aug 1999 through aug 2001 for rats. The strains of choice of NTP were the F334/N rats until 2006 and the B6C3F1 mice, and the latter is still the preferred mice strain by NTP. It is therefore presumed that the HCD in the database are for the same strains as used in the carcinogenicity study with BP.

Method, guideline, deviations if any, Klimish score, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		Kidney renal tubule hyperplasia: 1/50	8/50*	10/50*	7/50* severty neprhopathy: 1.1	1.4	1.7	2.0 * Significantly different (P≤0.05) from the control	

Table **10:** Summary table of animals studies of carcinogenicity, dermal exposure

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Non-guideline Dermal carcinogenicity lifetime study in Swiss mice: Klimish score 2(-3). 50 female mice/group	Benzophenone (BP) 0.2 ml of 5, 25 and 50% BP in acetone. Twice weekly in 110 weeks	No significant effects on survival or body weight gain were noted.	Stenbäck & Shubik 1974

Group / Number	Control (untreated/ acetone)	5% BP	25% BP	50% BP	Positive control DMBA
Tumour bearing mice	64/22	26	16	14	39
Lymphomas	26/12	15	11	6	6
Lung adenomas	17/9	3	3	6	4
Liver heman-giomas	4/2	1	1	2	1
Thymomas	6/0	1	1	0	0
Skin tumours	3/2	2	1	0	75
Other tumours	16/6	16	5	4	0

Non-guideline dermal lifetime study in New Zealand rabbits. Klimish score	BP 0.2 ml of 5, 25 and 50% BP (Acetone or methanol) Twice weekly up	No effects on clinical signs, survival and body weight gain were noted. 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	Stenbäck 1977

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
2/(3). 5 females and 5 males /group	to 160 weeks	histologically. 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.	

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

The carcinogenic potential of benzophenone (BP) has been investigated in different species. Two-year oral carcinogenicity studies were performed in rats and mice, in accordance with OECD guidelines and GLP (see table above). Further, two carcinogenicity studies with dermal application were performed in mice and rabbits, respectively. These studies were non-guideline studies, and limited information on the studies are available from the publications.

The major findings relevant for the end-point of carcinogenicity in the four studies are described below.

10.9.1.1 Carcinogenicity studies, oral exposure

Mice

B6C3F1 mice orally were exposed via the diet to 0, 312, 625, or 1250 ppm BP, corresponding to 0, 35, 70, and 150 mg BP/kg bw/day for females and 0, 40, 80, and 160 mg BP/kg bw/day for males. Mortality was increased in the high dose females but not in males. Body weights were affected in females from all dose groups with 14% and 7% and 8% reduction at study termination in high, mid and low dose, respectively, compared to controls, whilst male 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.

Hepatocellular adenoma, mice
The incidences of hepatocellular adenoma after exposure to BP showed a positive trend in males with 11/50 (22%), 15/50 (30%), 23/50 (46%) and 23/50 (46%) in the groups receiving 0, 312, 625 and 1250 ppm, respectively, with clear dose-response relationship and significant differences from controls in the two highest dose groups. The incidences exceeded historical control range (12-30%, mean 20%) NTP-2000 feed studies in the mid and high dose groups. In females, incidences of hepatocellular adenomas were 5/50 (10%) in controls, 4/50 (8%) in the low, 10/50 (20%) in the middle and 8/50 (16%) in the high-dose groups. The incidences in treated females were not statistically significantly different from the concurrent controls, but exceeded the NTP feed historical controls for the period (1995-2004) (range 6-12%, mean 9.6%). Also, when correction for weight decrease was performed the incidences in the two highest dose groups expected numbers.
According to two articles describe B6C3F1 mice carry hepatocellular tumour susceptibility loci that results in a high susceptibility to chemically induced cellular hepatocarcinogenesis and therefore a risk of overestimation of the carcinogenic potential in the liver exists (Gariboldi *et al*., 1993; Manenti *et al*., 1994).

Based on this, the relevance to human risk assessments 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 dossier submitter evaluates the findings of hepatoadenomas in mice to be supportive evidence for the carcinogenicity of BP, taking into account the benignity of the tumour form and the increased susceptibility of the mouse strain used. The dossier submitter also notes that the increases in hepatocellular adenoma at the two highest doses occur at higher incidences than spontaneous incidence levels in both male and female mice and thus may be attributed to the BP treatment.

Hepatoblastomas and hepatocellular carcinomas, mice
Malignant hepatic tumours recorded in the mice in the present study include hepatoblastomas and hepatocellular carcinomas in male mice, and hepatocellular carcinomas in female mice.

With regard to the incidence of *hepatoblastomas* that only occurred in male mice, a positive trend in the incidence of this tumour implies a relation to the treatment (0/50, 1/50, 1/50 and 3/50 in control and low, medium and high dose, respectively). The incidences of this rare tumour were not statistically significant different from that in the controls, but they exceed the NTP-2000-feed historical control incidence range of 0-2% (mean 0.2%). Hepatoblastoma is an uncommon tumour in B6C3F1 micewith shifting incidences in the control B6C3F1 mice in NTP studies (i.e. 0.3 % between 1986 and 1992, and 1.6 % between 1993 and 1999) (Turusov *et al*., 2002).

The *hepatocellular carcinomas* in the treated males occurred at non-significant levels incidences of 5/50 (10%), 6/50 (12%) and 6/50 (12%) in the low, mid and high dose, respectively, whilst control males incidences were 8/50 (17%) and with no dose-response was demonstrated. For hepatocellular carcinomas, historical controls data in the male B6C3F1 mice were available for an earlier time span (a range of 6-29 %, Maronpot, 1999) No information from the NTP-2000 feed database were reported for hepatocarcinomas alone, only for combined adenoma, carcinoma and hepatoblastoma in male B6C3F1 mice (NTP, 2006) In females, the single incidence of hepatocellular carcinoma in the low and high dose group could be an incidental, non treatment related finding considering that the incidence of spontaneous hepatocarcinoma in female B6C3F1 mice is highly variable as indicated by the range 0-20 % (Maronpot, 1999). The NTP report on BP only included historical control data from the NTP-2000 feed studies for combined adenoma and carcinomas in female mice, and not for hepatocarcinomas alone (NTP, 2006).

Thus, the low non-significant incidences of hepatoblastomas and hepatocellular carcinomas in mice lead to uncertainty as to concluding on their relation to BP. However, some concern remains to the occurrence of hepatoblastomas as this is a rare and severe tumour form and even a small increase in such type of tumours should be considered in the context of classification.

Concerning liver tumours in mice as a whole, the NTP concluded that there was *"some evidence of carcinogenic activity"* of BP in males, based on the increased incidences of hepatocellular neoplasms, primarily adenomas and that the incidences of hepatoadenoma in females may have been related to BP exposure,.

Histiocytic sarcomas, mice
In relation to carcinogenicity in the haematopoietic system , the occurrence of histiocytic sarcomas is noted in female B6C3F1 mice treated with BP. The incidence reported in the study is statistically significant in the mid-dose, but not at the high dose, (0/50, 0/50, 5/50 (10%), 3/50 (6%) in the control, low-, middle- and high-dose groups, respectively). Histiocytic sarcoma is a rare tumor form. The incidences in the mid- and high dose groups treated with BP exceed the historical incidence reported by the authors of the study: Mean of 0.3%; range 0-2 % from NTP-2000 feed studies, and mean 1.5%; range 0-8 % based on all routes from historical controls from NTP-studies (1995-2004),)and in earlier historical feed studies from the literature (mean 1.4 %, range 0-4 % from Maronpot, 1999;). Also, a positive trend in the incidences of this tumour in female mice was reported, and indicates a relation to treatment even if a clear dose response is not apparent. The concern for a carcinogenic effect to the hematopoietic system is supported by the statistically significant

increase in incidence of the hematopoietic cell proliferation in the spleen in all dosed female groups (16/50, 35/50, 32/50, 27/50).

Based on the finding of increased occurrence of the rare tumour histiocytic sarcoma, the NTP concludes that BP shows "*some evidence of carcinogenic activity"* in female mice. The dossier submitter considers this effect to the hematopoietic system of relevance to the classification for carcinogenicity of BP.

Rats

F334/Nrats were exposed orally via the diet to 0, 312, 625, or 1250 ppm BP which led to mean intakes of 0, 15, 30, and 65 mg BP/kg bw/day for females and 0, 15, 30, and 60 mg BP/kg bw/day for males. The doses were selected based on results from a 14 day-study in which body weights were significantly decreased in all female groups from 1250 ppm to 20,000 ppm and in males from 2500 ppm. Significant non-neoplastic effects were reported from the 14 day study in the liver and kidney from 1250 ppm and in the females from 2500 and 5000 ppm, respectively.

In the carcinogenicity study, mortality was significantly increased in the high dose group males, but not in females at any dose. Body weights in males were decreased in the high dose group (36% decrease at study termination), and in the mid-dose group (11% decrease at study termination). In females, body weights were decreased 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 animals of both sexes. No clinical signs in either sex per dose group except in relation to morbidity.

Tumours were reported in the liver, the kidney and haematopoietic system of male rats and in the liver and haematopoietic system of females Non-neoplastic changes in the liver and kidney in both sexes were also reported.

Renal tubule adenoma and hyperplasia, rats
A positive trend in the incidences of renal tubule adenoma was found in the treated males, with a statistically significant increase in the high-dose group.
Spontaneous renal neoplasms in the rat are uncommon (Chandra *et al*., 1993). Background incidences of renal cell adenomas as low as 0.38 % and 0.19 % were reported for male and female F344 rats, respectively (Chandra *et al*., 1993). The association between BP treatment and renal tubule adenoma is supported by the fact that the incidences in the treated male groups exceeded the historical incidence for 2-year control feed studies given NTP-2000 diet (range 0-2 % as reported in NTP, 2006).
Statistically significant increase in incidences of renal tubule hyperplasia was seen in all BP treated groups of males and females. Chronic progressive nephropathy (CPN) is a common, spontaneous disease of the rat kidney (Travlos *et al.* 2011). An association between treatment related chronic progressive nephropathy in 90-day studies and increased incidence of renal tubule tumours at 2 years has been found for 7 chemicals studied by NTP (Travlos *et al*., 2011). It was concluded that CPN leads to renal tubular tumours in male rats and should be considered of no relevance for humans risk assessment as CPN has no counterpart in humans (Travlos *et al*., 2011; Hard *et al*., 2009). However, the possible aetiology and mode of action leading to the development of renal tubular tumours are disputed, based i.a. on an analysis of 60 NTP carcinogenicity studies in rats (Melnick et al, 2012). Based on the morphological hyperplastic changes in the kidney in both the 14-week and the 2-year study of BP, it is clear that BP exacerbates CPN (NTP, 2000; 2006). In the discussion of the results of the NTP carcinogenicity study with BP (NTP 2006) the involvement of chronic nephropathy in development of the renal tubule tumours is assessed to be possible. However, NTP further stresses that the pathogenesis of chemically induced renal tubular tumours has not been determined, but appears to be complex and not solely due to CPN. The NTP concluded that the increased incidence of renal tubule adenomas in male F344/N rats were "*some evidence of carcinogenic activity*" (NTP, 2006).

As the mode of action leading to the increased renal tubule tumour incidence in male rats is not fully elucidated, a residual concern for these tumours remains and the finding should be taken in consideration in the evaluation of Weight of evidence (WoE) to the classification of BP for carcinogenicity.

Mononuclear cell leukemia (MNCL), rats
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. The incidence of MNCL in the male high-dose (48%) group was comparable to that in the control group (54%). Both low (82%) and middle group incidences (78%) were outside the historical range from the NTP control database using NTP-2000 feed between 1995 and 2004 (30-68%) reported by the authors of the study. The lack of dose response for incidences of MNCL in the male rats treated with BP, may be due to reduced survival (deaths) in the high-dose group (the tumour from is generally a late developing neoplasm, and half of the animals died before week 90).
In treated females, the increased incidence of MNCL reached statistical significance only was recorded only in the middle dose (60%) group compared to concurrent controls (38%), which was at the upper end of the historical control data.. All treated females had increased incidences of MNCL compared to historical incidence in controls from 2-year feed studies by NTP (controls given the NTP-2000 diet between 1995 and 2004) was in a range of 12-38 % in females (NTP, 2006).
The human relevance of increased incidences of MNCL in F344 rats is debated. Caldwell (1999) found that MNCL occur in untreated, aged F-344 rats at a high and variable rate, that it is uncommon in most other rat strains, and that its background incidence has increased significantly over time. In relation to MNCL in F-344 rats of both sexes, Caldweel (1999) noted that hemolymphoreticular neoplasm is unique to the rat and is only common in this strain. MNCL has not been found in other mammalian species (e.g. mice and hamsters) and no histologically comparable tumour is found in humans. Thus, Caldwell (1999) concluded MNCL in F344 rats to be of little or no relevance to humans. A similar view is given by Scheepmaker et al. (2005) in a report for RIVM. The authors noted that the mechanism for the induction of MNCL in F344 is unknown, and that several substances increasing MNCL in chronic studies also have a growth stimulating effect on MNCL cells which indicates that increases in MNCL are at least partly caused by stimulation of proliferation of existing MNCL. Overall, Scheepmaker et al. (2005) concluded that substance-induced increases in MNCL in F344 rats should not be considered of human relevance, whereas increases of MNCL in other rat strains and other species should be considered as relevant for humans.
However, Thomas et al. (2007) found that a rare form of human lymphocyte leukemia (natural killer cell large granular lymphocyte leukemia; NK-LGLL) is similar to MNCL observed in F344 rats. They further noted that little is known about the cellular/molecular pathways of leukemogenesis in the F344 rats and found that more mechanistic information is needed for arriving a scientifically sound conclusions as to the relevance in human cancer risk assessment. Pointing towards elements such as levels of significance, nature of dose-response curve, reduction in latency time, genotoxicity, cytotoxicity a.o., the authors called for a more precautious approach and using a weight-of evidence approach when assessing the human relevance of increased MNCL in F344 rats.

Thus, for the increase in MNCL, human relevance cannot completely be ruled out. The NTP concluded that the MNCL in male as well as female F344/N rats contributed to “some evidence of carcinogenic activity”, whilst the marginally increased incidences of MNCL in female rats were indication of *“equivocal evidence of carcinogenic activity”* (NTP, 2006).

Histiocytic sarcomas, rats
Histiocytic sarcomas did not occur in male rats treated with BP but occurred in one female rat in the middle dose group (1%), and 2 female rats in the high dose group (2/50) whilst no histiocytic sarcoma was detected in the controls or in the low-dose group of either sex. Histiocytic sarcoma of haematopoietic system found in the study with BP in female F-344 rats is a rare tumour as indicated by the historical incidence. This malignant neoplasm was not observed in the historical feed control studies between 1995 and 2004of F344 rats given NTP-2000 diet and its incidence for all routes in 2-year rat studies was in a range of 0-2 % (NTP, 2006). The NTP considered the histiocytic sarcoma in females rats to be “*equivocal evidence of carcinogenic activity*” (NTP, 2006)

Although very few incidences are reported, the relation to treatment and histiocytic sarcoma in female rats in the middle- and high-dose groups is supported by the fact that this tumour is very rare, and this finding is therefore evaluated by the dossier submitter to be of relevance to the classification of BP. Furthermore, the findings are supported by the observations of histiocytic sarcomas in female mice (see above).

10.9.1.2 Dermal carcinogenicity studies

A non-guideline dermal carcinogenicity lifetime study was performed in Swiss mice with 50 females per group. BP was by open dermal application exposed to 0.2 ml of 5, 25 and 50% BP in acetone on the dorsal skin of the animals twice weekly in 110 weeks.

In BP treated groups the highest number of animals bearing tumours was in the low-dose group and it was not statistically significantly higher than in the positive control group (26/50 versus 39/50; p>0.05, Fisher's exact test performed by the evaluators). There was no dose response in total number of tumours, lymphomas, thymomas, skin tumours and other tumours. The numbers of liver adenomas and haemangiomas were low and not higher than in the vehicle control group. No increased mortality or body weight changes occurred in the dosed group (other types of effects including organ weight and macroscopic and microscopic changes in organs were reported. Overall, the authors concluded that there was no indication of a carcinogenic potential of BP in mice following a topical administration under conditions of this bioassay. It should be noted that open dermal application was used which may limit the dermal absorption of the substance in this study. Under more optimal conditions for dermal absorption a dermal absorption rate of about 70% was found for BP in rhesus monkeys under occlusive conditons according to Bronaugh et al. (1990), as reported in the REACH registration of the substance.

Further, a non-guideline dermal carcinogenicity lifetime study was also performed in New Zealand rabbits with 5 rabbits (both sexes) per group. BP was exposed by open dermal application to 0.2 ml of 5, 25 and 50% BP in solvent to the interior left ear of the animals twice weekly in up to 116 weeks.

No treatment related effect was found on mortality. The survival at week 160 was 1, 3 and 2 rabbits in the low, middle, and high-dose BP groups, and 3 in the untreated control group, respectively, with an initial number of animals of 5. In another control group (4 rabbits in the start) no survivals were present in week 120.

Complete autopsies were performed on all animals. Skin samples, grossly observed tumours and other lesions of the lungs livers, kidneys etc. from all animals were studies histologically. 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 seven papillomas, two keratoacanthomas and three squamous cell carcinomas.

In summary, no indication of carcinogenic effects of BP was found after dermal application in mice or rabbits. The study in mice was published in 1974, and as such was not performed according to Good Laboratory Practice (GLP) and OECD guidelines. As open dermal application of the test substance was used in both studies the studies are considered most relevant for the assessment of the potential to induce local skin tumours as it is very uncertain to which degree dermal absorption had occurred in the studies. Thus, the studies are considered of limited relevance for assessing the carcinogenic potential of BP in connection with systemic exposure.

10.9.1.3 Mechanistic considerations

As indicated in the evaluation of the oral carcinogenicity studies in mice and rats increases in various tumours have been found and explanations/ mechanisms and relevance for humans have been discussed. Table 11 below provides and overview of the tumour forms and possible mechanistic considerations and indicate a qualitative score for use in a WoE assessment for the tumour form as such (i.e. no dose-response considerations are included):

Table 11. Overview of tumour types and qualitative interpretion with regard to the WoE assessment. The relevance was scored as follows: - Not to be considered; + considered as weak evidence; ++ considered as important evidence.

Species, sex Type of tumours	Explanations/ mechanistic considerations	Relevance to humans	Emphasis for WoE assessment

B6C3F1 mice, female -*Hepatocellular adenoma/carcinoma* -*Histiocytic sarcoma*	B6C3F1 mice carry a hepatocellular tumour susceptibility loci. High spontaneous rate, but below incidences when treated with BP. Rare tumour form. Mechanism not clarified.	Reduced susceptibility in humans Relevant	+ / - ++
B6C3F1 mice, male -*Hepatocellular adenoma/carcinoma* -*Hepatoblastoma*	B6C3F1 mice carry a hepatocellular tumour susceptibility loci. High spontaneous rate, but below incidences when treated with BP. Rare tumour form. Mechanism not clarified.	Reduced susceptibility in humans Relevant	+ / - ++
F344/N rats, female -*Mononuclear cell leukemia* - *Histiocytic sarcoma*	High spontaneous rate. Mechanism not clarified Rare tumour. Mechanism not clarified	Relevance debated but cannot be excluded Relevant	+ ++
F344/N rats, male -*Mononuclear cell leukemia* -*Renal tubule adenoma*	High spontaneous rate. Mechanism not clarified Uncommon tumour form. Mechanism of tumour formation not clarified, albeit in male rats appears related to progression from chemically induced severe nephropathy, which has no counterpart in humans	Relevance debated but cannot be excluded Relevance debated but cannot be excluded	+ -

As indicated in table 11 above very little is know regarding mechanisms of the different types of tumour.

This is in line with evaluation of BP by IARC (2013) who found that mechanistic explanations for the tumours occurring in the NTP (2006) studies currently are not understood in detail. The involvement of generation of reactive oxygen species and/or endocrine disruption through multiple receptors were hypothized. Overall, it was concluded that data for mechanistic explanations were too limited and weak to rule out the human relevance of the tumour response found in the experimental animals (IARC 2013).

In the Substance evaluation conclusion document by the Danish EPA (2018) potential endocrine mechansims for BP were discussed including thyroid peroxidase (TPO) inhibition and estrogenic and anti-androgenic activy. However, no firm conclusion could be drawn from the available data

10.9.1.4 Overall summary

In summary, BP exhibits carcinogenic effects in several organs in two species of rodents as reported in a GLP and OECD guideline study from 2006.

The dose setting for the mouse carcinogenicity was based on the results of a 14-day mouse study conducted by the NTP in 2000 in which doses of 2500 ppm led to dramatic increases in liver weights in males (55%) and females (56%).

The study doses for rats were chosen based on minimal toxicity response at 1250 ppm in a 14-day study conducted by the NTP in 2000, in which 2500 ppm led to body weight gains reductions of 7% and 12% in male and female rats, respectively, liver weight increased of 43 and 28%, respectively, and incidences of kidney lesions were increased.

In the carcinogenicity study, there was a high level of mortality in the high dose male rats. Body weight decreases of 9-36% were reported in mid- and high-dose groups. In the mice, survival was non-significantly affected only in the high dose females, and body weight decrease over 10% in that group, whilst males and mid-group females did not exibit signs of general toxicity.

It cannot be excluded that higher doses could have been tolerated in the carcinogenicity study by especially male mice and female rats. As some general toxicity is reported at the highest dose group in both the mouse and the rat, the doses administred in the carcinogenicity study by NTP in mice and rats are relevant and the study is considered valid. However, it is possible that higher doses might have enhanced the tumorigenic response and/or led to more clear dose-responses.

The tumour findings for mice following oral exposure to BP show significantly increased dose-related incidences of hepatocellular adenomas in exposed male mice and increased incidence outside the historical control range in female mice. However, no increases in hepatocelluar carcinoma were noted neither in female nor male mice. In male mice a small non-significant number of the rare tumour heptablastoma was noted in the treated groups.

In rats, significantly increased incidences of mononuclear cell leukemia (MNCL) and of renal tubule tumours were observed in males treated with BP for 2 years. The NTP concluded that the MNCL in male as well as female F344/N rats contributed to "some evidence of carcinogenic activity", whilst the marginally increased incidences of MNCL in female rats were indication of *"equivocal evidence of carcinogenic activity"* (NTP, 2006). Thus, the dossier submitter evaluates that the human relevance of the increase in MNCL cannot completely be ruled out.

Further, increases of the rare tumour histiocytic sarcoma were observed i both female mice and female rats. Although not significant the increases exceeded the historical control values in both species.

No increased carcinognenic response was found following dermal exposure of mice and rabbits to BP in pre GLP and pre OECD guideline studies. However, these two studies were not conducted according to today´s standard. As open dermal application of the test substance was used in both studies only lack of carcinogenic potential towards local skin tumours can be concluded from these studies.

10.9.2 Comparison with the CLP criteria

As no relevant human data on the carcinogencity of benzophenone is available, a classificaton in Category 1A is not appropriate.

Classification as carcinogenic in Category 1B: "*presumed to have carcinogenic potential for humans, classification is largely based on animal evidence*" should be considered, if there are animal experiments available *"for which there are sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen)"* (CLP criteria section 3.6.2.1). The criteria for carcinogenicity Category 1B further stipulate that *"a causal relationship should be established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in two or more species of animals"* (CLP criteria section 3.6.2.2.3.).

Arguments for a Categroy 1B classification for benzophenone are:

- Increase of multiple, tumour forms in two species
- Occurrence of increased incidences of the rare tumour forms, histiocytic sarcoma in female mice and female rats, and of hepatoblastomas in male mice
- Supporting evidence from significantly increased findings of hepatocellular adenoma in female mice and male mice, of renal tubular tumours in male rats and of significantly increased findings of mononuclear cell leukemia (MNCL) in female and male rats

However, the dossier submitter does not consider the criteria for classification in Category 1B to be fulfilled for benzophenone for the following reasons:

- For tumours with a high spontaneous incidences as liver tumours in B6C3F1 mice and MNCL in F344 rats the increases in the tumour incidences in exposed animals, seen with BP treatment although beyond background levels, may not provide sufficient certainty of treatment related carcinogenicity.
- The relevance to humans of renal tubular tumours is debated, as these tumours have been suggested to develop from chronic progressive neuropathy, with no counterpart in humans.
- BP is not a genotoxic substance

Classification as carcinogen, category 2 "*Suspected human carcinogen"s* criteria reads: "*The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived either from limited (1) evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.*"

The dossier submitter concludes that a classification of benzophenone in Category 2, H351 is warranted based on the available data.

This classification is based on increased incidences of the rare tumour form *histiocytic sarcoma* in one sex from two species: female mice and female rats and the likewise rare *hepatoblastoma* in male mice above historical background levels.

The increased incidences of *hepatocellular adenoma* in male and female mice above high spontaneous incidences as well as the increased incidences of *mononuclear cell leukaemia* and of *renal tubular tumours* in male rats, with the uncertainty expressed above, further support this classification.

The increased incidences of hepatocellular adenoma in female and male mice and increased incidences of mononuclear cell leukaemia and renal tubular tumours in male rats further support this classification. The relevance to humans of these tumour forms is discussed. However, the evidence on modes of action for the tumours is insufficient to completely dismiss their relevance to humans. Thus, a concern for the multiple organ carcinogencitiy of BP remains.

"No classification" of benzophenone for carcinogenicity is not relevant: The available data from animal studies in both rats and mice at relatively low doses demonstrate increased incidences of various tumour forms and also include rare tumour types in both species. Even though some of the tumours may have low relevance to humans the data show that benzophenone has a carcinogenic potential. Therefore, BP should be classified for carcinogenicity.

10.9.3 Conclusion on classification and labelling for carcinogenicity

Based on the available data and considering the CLP classification criteria and guidance established in connection with these, it is concluded appropriate to classify BP as:

Carcinogenic in Category 2, H351

10.10 Reproductive toxicity

Hazard class not evaluated.

10.11 Specific target organ toxicity-single exposure

Hazard class not evaluated.

10.12 Specific target organ toxicity-repeated exposure

Hazard class not evaluated.

10.13 Aspiration hazard

Hazard class not evaluated.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Hazard class not evaluated

11.2 Environmental transformation of metals or inorganic metals compounds

Hazard class not evaluated

11.3 Environmental fate and other relevant information

Hazard class not evaluated

11.4 Bioaccumulation

Hazard class not evaluated

11.5 Acute aquatic hazard

Hazard class not evaluated

11.6 Long-term aquatic hazard

Hazard class not evaluated

11.7 Comparison with the CLP criteria

Not evaluated.

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Not evaluated

12 EVALUATION OF ADDITIONAL HAZARDS

Hazards not evaluated

13 ADDITIONAL LABELLING

No additional labelling needed.

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15 ANNEXES

Annex 1, dated xxx, to the CLH report for benzophenone.