Annex I to the 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: **Not applicable**

Contact details for dossier submitter:

Danish Environmental Protection Agency

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

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1 PHYSICAL HAZARDS

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This endpoint is not addressed in the CLH report.

1.2 Flammable gases (including chemically unstable gases)

This endpoint is not addressed in the CLH report.

1.3 Oxidising gases

This endpoint is not addressed in the CLH report.

1.4 Gases under pressure

This endpoint is not addressed in the CLH report.

1.5 Flammable liquid

This endpoint is not addressed in the CLH report.

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This endpoint is not addressed in the CLH report.

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This endpoint is not addressed in the CLH report.

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This endpoint is not addressed in the CLH report.

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This endpoint is not addressed in the CLH report.

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This endpoint is not addressed in the CLH report.

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This endpoint is not addressed in the CLH report.

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This endpoint is not addressed in the CLH report.

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This endpoint is not addressed in the CLH report.

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This endpoint is not addressed in the CLH report.

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This endpoint is not addressed in the CLH report.

2 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

This endpoint is not addressed in the CLH report.

3 HEALTH HAZARDS

Acute toxicity

This endpoint is not addressed in the CLH report.

3.1 Skin corrosion/irritation

This endpoint is not addressed in the CLH report.

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This endpoint is not addressed in the CLH report.

3.3 Respiratory sensitisation

This endpoint is not addressed in the CLH report.

3.4 Skin sensitisation

This endpoint is not addressed in the CLH report.

3.5 Germ cell mutagenicity

Specific mutagenicity studies not described in the CLH report. Assessment relies on previous expert assessments (see CLH report).

3.6 Carcinogenicity

3.6.1 Animal data

3.6.1.1 Study 1: Carcinogenicity study in mice, oral route

Study reference:

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 mice (feed studies). February 2006. National Toxicity Program. Toxicity Report 5333. NIH publication No.06-4469

Detailed study summary and results:

Test type

A carcinogenesis bioassay of Benzophenone in mice was conducted by the National Toxicology Program (NTP 2006) following a guideline similar to OECD TG 451 and in accordance with the GLP principles.

Test substance

- Benzophenone; CAS No. 119-61-9 (identical to substance identified in CLH dossier)
- *Degree of purity:* >99%
- *Impurities:* not further specified
- *Batch number:* lot 10803KG

Test animals

- *Species/strain/sex:* Male and female B6C3F1 mice
- *No. of animals per sex per dose:* 50 males and 50 females in each group
- *Age at the study initiation:* 8 weeks

Administration/exposure

- *Route of administration:* Oral (via diet)
- *duration of test/exposure period:* 105 weeks. The animals were observed twice daily. Animals were weighed initially, on day 8, at 4-week intervals thereafter, and at the end of the studies. Clinical findings were recorded on day 36 and at 4-week intervals (mice had one interval each at 2, 3, 5 or 6 weeks) throughout the study. Feed consumption was recorded for 1 week out of every 4 weeks beginning the first week of the study.

- *doses/concentration levels, rationale for dose level selection:* B6C3F1 mice were exposed via the diet containing 0, 312, 625, or 1250 ppm Benzophenone for 105 weeks. These dietary concentrations corresponded to doses of 40, 80, and 160 mg Benzophenone/kg bw/day for males and 35, 70, and 150 mg Benzophenone/kg bw/day for females. The high dose was set based on the minimal toxicity observed at this level in the 14-week study (NTP 2000) with regard to liver weight.
- *frequency of treatment:* daily via diet
- *control group and treatment:* yes, control group receiving no benzophenone in the diet.
- *historical control data:* yes (see below)
- *post exposure observation period:* none
- *vehicle:* diet containing 0, 312, 625, or 1250 ppm Benzophenone
- *test substance formulation/diet preparation, achieved concentration, stability and homogeneity of the preparation:* The dose formulations were prepared at least once a month by mixing benzophenone with feed. Formulations were stored in plastic buckets at 5° C for up to 35 days. Homogeneity studies of the 312 and 1,250 ppm dose formulations and stability studies of the 312 ppm dose formulation were performed by the analytical chemistry laboratory using high performance liquid chromatography (HPLC). Periodic analyses of the dose formulations of benzophenone were conducted by the study laboratory using HPLC. During the 2-year studies, the dose formulations were analyzed at least every 11 weeks.
- *actual doses (mg/kg bw/day):* The dietary concentrations corresponded to doses of 40, 80, and 160 mg Benzophenone/kg bw/day for males and 35, 70, and 150 mg Benzophenone/kg bw/day for females.

Vehicle: diet containing 0, 312, 625, or 1250 ppm Benzophenone.

- *satellite groups and reasons they were added:* no satellite groups included

Results and discussion

Describe the relevant findings. If no effects occurred, explicitly note "No effects".

- *mortality and time to death (indicate number died per sex per dose and time to death):* Survival of treated mice was similar to that of the controls (> 80%), except for the high-dose females for which a not statistically significantly decreased survival towards the end of the study was recorded (survival rate of 62%).
- *clinical signs:* No clinical findings other than those associated with morbidity (e.g. nasal/eye discharge, thinness, ruffled fur) were attributed to benzophenone exposure.
- *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 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).
- *food/water consumption:* No effects. Feed intake of the treated mice of both sexes was similar to that of the controls throughout the study.

- *ophthalmoscopic examination:* not examined
- *clinical chemistry:* not examined
- *haematology:* not examined
- *urinalysis:* not examined
- *organ weights:*not examined
- *statistical methods and results (unless already described with specific test results above):* The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Non-neoplastic histopathological findings in mice:

Males				
Dose levels, ppm (mg/kg bw/day)	**0 (0)**	**312 (40)**	**625 (80)**	**1250 (160)**
Liver				
Hypertrophy hepatocytes	0/50	44/50**	50/50**	48/50**
Micronucleated hepatocytes	0/50	41/50**	47/50**	48/50**
Active chronic inflammation	33/50	47/50**	44/50**	42/50*
Hepatocyte degeneratiom	0/50	0/50	5/50*	30/50**
Kidney				
Nephropathy	49/50	48/50	50/50	50/50
Severity grade average	1.2	1.4	1.7	3.0
Spleen				
Hyperplasia of lymphoid follicles	17/50	31/50**	34/50*	32/50**
	0/50	1/50	4/50	12/50**

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

Females				
Dose levels, ppm (mg/kg bw/day)	**0 (0)**	**312 (35)**	**625 (70)**	**1250 (150)**
Liver				
Hypertrophy of hepatocytes	0/50	29/50**	44/50**	37/50**
Kidney				
Nephropathy	21/50	33/50**	31/50*	30/50*
Mineralisation	15/50	31/50**	36/50**	49/50**
Severity grade average	1.2	1.1	1.5	1.7
Spleen				
Hyperplasia of lymphoid follicles	24/50	36/50**	37/50**	22/50
Hematopoietic cell proliferation	16/50	35/50**	32/50**	27/50*

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

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

Neoplastic findings in mice:

Males				
Dose levels, ppm (mg/kg bw/day)	**0 (0)**	**312 (40)**	**625 (80)**	**1250 (160)**
hepatocellular adenoma[a]	11/50 22%	15/50 30%	23/50 46%*	23/50 46%*
Hepatocellular carcinoma[b]	8/50 16%	5/50 10%	6/50 12%	6/50 12%
Hepatoblastoma[c]	0/50 0%	1/50 2%	1/50 2%	3/50 6%
Hepatocellular adenoma, carcinoma or hepatoblastoma[d]	18/50 36%	20/50 40%	25/50 50%	29/50 58%*
Histiocytic sarcoma in the haematopoietic system	1/50	0/50	0/50	0/50

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

[a] historical incidences: 12-63% (mean 33.2%) in 1257 controls, all routes.
[b] historical incidences: 8-46% (mean 22.9%) in 1257 controls, all routes
[c] historical incidences 0-13% (mean 1.9%) in 1257 controls, all routes
[d] historical incidences 20-85% (mean 50.4%) in 1257 controls, all routes

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

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

[a] historical control values of 6-12% (mean 9.6%) in 460 controls from feeding studies.
[b] historical control values of 8-16% (mean 11.8%) in 460 controls from feeding studies
[c] historical incidences: 0-8% (mean 1.5%) in 1258 controls, all routes

Discussion as cited from NTP (2006):
"Female mice in all exposed groups had increased incidences of spleen hematopoietic cell proliferation. The proportions of these cells varied from animal to animal. Hematopoietic cell proliferation, also termed extramedullary hematopoiesis, is a common and normal phenomenon in the spleen of mice, to a greater degree in females than males. The incidence in the control female group in this study is consistent with previous NTP studies (Ward et al., 1999). Increased hematopoietic cell proliferation has been associated with anemia and chronic inflammatory lesions. Evidence of an anemia with minimal severity was observed in rats and mice during the 14-week studies at higher doses than were used in the 2-year study (NTP, 2000).

Increases in the incidences of hepatocellular adenoma were observed in male and female mice. Hepatoblastomas were also observed in exposed males; however, the increased incidence was not statistically significant. Female mice showed more hepatocellular adenomas than expected in the 625 and 1,250 ppm groups when corrected for decreased body weight (0 ppm: 6.8 expected, 5 observed; 312 ppm: 7.0 expected, 4 observed; 625 ppm: 6.2 expected, 10 observed; 1,250 ppm: 4.3 expected, 8 observed) (Haseman et al., 1997). Hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas represent a biological and morphological continuum in progression of proliferative lesions. Because the malignant potential of hepatoblastomas and hepatocellular carcinomas appears similar and hepatoblastomas are often observed within hepatocellular neoplasms (mostly carcinomas), it is appropriate to combine the incidences of hepatoblastoma with those of adenoma and carcinoma when interpreting the carcinogenic potential of a chemical. The combined incidence of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma was significantly increased in 1,250 ppm males, and the incidences showed a positive trend. This was considered some evidence of carcinogenicity. The response in females was considered equivocal."
Further, the findings regarding the occurrence of histiocytic sarcoma in female mice was discussed with the similar findings in the NTP (2006) study in rats:

"Benzophenone exposure resulted in a positive trend in the incidence of histiocytic sarcoma in female mice, and one 625 ppm and two 1,250 ppm female rats had histiocytic sarcomas. This neoplasm is rare; none have been observed in historical feed study control rats, and only two have been observed in feed study control mice given the NTP-2000 diet. In historical controls from all routes of exposure, histiocytic sarcoma was observed in one of 1,209 (0.08%) historical control rats and 18 of 1,258 historical control mice (1.4%). Histiocytic sarcomas are classified as hematopoietic tumors of the mononuclear phagocyte system based upon the morphology of the neoplastic cells and the presence of lysozyme, Mac-2, and mononuclear phagocyte antigens. The specific origin of the neoplastic histiocytic cells is undetermined. One or more cell populations may be involved. Bone marrow cells, tissue histiocytes, Kupffer's cells in the liver, and circulating macrophages have been suggested. Histiocytic sarcomas are slightly more common in female than male mice and in mice than rats (Frith et al., 1993). Although the spontaneous incidence of this tumor is low in both mice and rats, the frequency varies widely among different strains of mice and rats. Histiocytic sarcomas are more common in Sprague-Dawley rats, with an overall incidence of 4.7%, than in the Fischer 344, used by the NTP, and Osborne-Mendel strains. In mice exposed to benzophenone, the liver and lung were involved in all affected animals. In the 1,250 ppm female mice, the histiocytic sarcomas were highly invasive. Multiple organs throughout the body had neoplastic histiocytic lesions. All affected rats exposed to benzophenone had lung lesions. Only one rat in the 625 ppm group had organs affected throughout the body. Chemical-associated increases in the incidences of histiocytic sarcomas have not been seen in rats in NTP studies and are uncommon in mice. Increased incidences in mice occurred in studies of 1,3-butadiene (NTP, 1993), tetrafluoroethylene (NTP, 1996a), and phenolphthalein (NTP, 1996b). The increased incidences in the 625 and 1,250 ppm female groups and the increased invasiveness in the 1,250 ppm mice were considered related to benzophenone exposure and some evidence of carcinogenicity. The low incidence of this rare neoplasm in female rats was considered equivocal evidence of carcinogenic activity".

NTP (2006) concluded:
"There was some evidence of carcinogenic activity of benzophenone in male B6C3F1 mice based on increased incidences of hepatocellular neoplasms, primarily adenoma. There was some evidence of carcinogenic activity of benzophenone in female B6C3F1 mice based on increased incidences of histiocytic sarcoma; the incidences of hepatocellular adenoma in female B6C3F1 mice may have been related to benzophenone exposure."

Historical Incidence of Histiocytic Sarcoma in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence in Feed Controls Given NTP-2000 Diet	
Benzophenone	0/50
Citral	0/99
p,p'-Dichlorodiphenyl sulfone	0/50
trans-Cinnamaldehyde	2/100
2-Methylimidazole	0/50
o-Nitrotoluene	0/60
p-Nitrotoluene	0/50
Overall Historical Incidence: Feed Studies	
Total (%)	2/459 (0.4%)
Mean ± standard deviation	0.3% ± 0.8%
Range	0%-2%
Overall Historical Incidence: All Routes	
Total (%)	18/1,258 (1.4%)
Mean ± standard deviation	1.5% ± 2.2%
Range	0%-8%

[a] Data as of April 19, 2004

Historical Incidence of Liver Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Historical Incidence in Feed Controls Given NTP-2000 Diet				
Benzophenone	11/50	8/50	0/50	18/50
Citral	20/100	13/100	0/100	28/100
p p′-Dichlorodiphenyl sulfone	6/50	9/50	0/50	15/50
trans-Cinnamaldehyde	14/100	13/100	0/100	26/100
2-Methylimidazole	7/50	4/50	0/50	10/50
o-Nitrotoluene	18/60	12/60	1/60	28/60
p-Nitrotoluene	14/50	8/50	0/50	20/50
Overall Historical Incidence: Feed Studies				
Total (%)	90/460 (19.6%)	67/460 (14.6%)	1/460 (0.2%)	145/460 (31.5%)
Mean ± standard deviation	20% ± 7.1%	14.9% ± 3.9%	0.2% ± 0.6%	32.4% ± 9.1%
Range	12%-30%	8%-20%	0%-2%	20%-47%
Overall Historical Incidence: All Routes				
Total (%)	398/1,257 (31.7%)	275/1,257 (21.9%)	22/1,257 (1.8%)	607/1,257 (48.3%)
Mean ± standard deviation	33.2% ± 12.1%	22.9% ± 9.4%	1.9% ± 3.4%	50.4% ± 16.1%
Range	12%-63%	8%-46%	0%-13%	20%-85%

[a] Data as of April 19, 2004

3.6.1.2 Study 2: Carcinogenicity study in rats, oral route

Study reference:

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 mice (feed studies). February 2006. National Toxicity Program. Toxicity Report 5333. NIH publication No.06-4469

Detailed study summary and results:

Test type

A carcinogenesis bioassay of Benzophenone in rats was conducted by the National Toxicology Program (NTP 2006) following a guideline similar to OECD TG 451 and in accordance with the GLP principles.

Test substance

- Benzophenone; CAS No. 119-61-9 (identical to substance identified in CLH dossier)
- *Degree of purity:* >99%
- *Impurities:* not further specified
- *Batch number:* lot 10803KG

Test animals

- *Species/strain/sex:* Male and female F344/N rats
- *No. of animals per sex per dose:* 50 males and 50 females in each group
- *Age at the study initiation: 6* weeks

Administration/exposure

- *Route of administration:* Oral (via diet)
- *duration of test/exposure period:* 105 weeks. The animals were observed twice daily. Animals were weighed initially, on day 8, at 4-week intervals thereafter, and at the end of the studies. Clinical findings were recorded on day 36 and at 4-week intervals (rats had one interval at 3 and 5 weeks throughout the study. Feed consumption was recorded for 1 week out of every 4 weeks beginning the first week of the study.
- *doses/concentration levels, rationale for dose level selection:* F344 rats were exposed via the diet containing 0, 312, 625, or 1250 ppm Benzophenone for 105 weeks. These dietary concentrations corresponded to doses of 15, 30, and 60 mg Benzophenone/kg bw/day for males and 15, 30, and 65 mg Benzophenone/kg bw/day for females. The high dose was set based on the minimal toxicity observed at this level in the 14-week study (NTP, 2000) with regard to reduction in body weight gain and increases in liver weights in females and males.

- *frequency of treatment:* daily via diet
- *control group and treatment:* yes, control group receiving no benzophenone in the diet.
- *historical control data:* yes (see below)
- *post exposure observation period:* none
- *vehicle:* diet containing 0, 312, 625, or 1250 ppm Benzophenone
- *test substance formulation/diet preparation, achieved concentration, stability and homogeneity of the preparation:* The dose formulations were prepared at least once a month by mixing benzophenone with feed. Formulations were stored in plastic buckets at 5° C for up to 35 days. Homogeneity studies of the 312 and 1,250 ppm dose formulations and stability studies of the 312 ppm dose formulation were performed by the analytical chemistry laboratory using high performance liquid chromatography (HPLC). Periodic analyses of the dose formulations of benzophenone were conducted by the study laboratory using HPLC. During the 2-year studies, the dose formulations were analyzed at least every 11 weeks.
- *actual doses (mg/kg bw/day):* The dietary concentrations corresponded to doses of 15, 30, and 60 mg Benzophenone/kg bw/day for males and 15, 30, and 65 mg Benzophenone/kg bw/day for females. Vehicle: diet containing 0, 312, 625, or 1250 ppm Benzophenone
- *satellite groups and reasons they were added:* no satellite groups included

Results and discussion

Describe the relevant findings:

- *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%).
- *clinical signs:* No clinical findings other than those associated with morbidity (e.g., nasal/eye discharge, thinness, ruffled fur) were attributed to benzophenone exposure.
- *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).
- *food/water consumption:* Feed consumption by 1250 ppm males was less than that by the controls after week 70 of the study; feed consumption by 1250 ppm females was generally less than that by the controls throughout the study.
- *ophthalmoscopic examination:* not examined
- *clinical chemistry:* not examined
- *haematology:* not examined

- *urinalysis:* not examined
- *organ weights:* not examined

Non-neoplastic histopathological findings in rats:

Males				
Dose levels, ppm (mg/kg bw/day)	**0 (0)**	**312 (15)**	**625 (30)**	**1250 (60)**
Liver				
Centrilobular hepatocytes hypertrophy	0/50	17/50**	31/50**	19/50**
Cystic Degeneration	8/50	11/50	20/50*	15/50*
Chronic active Inflammation	22/50	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

Females				
Dose levels, ppm (mg/kg bw/day)	**0 (0)**	**312 (15)**	**625 (30)**	**1250 (65)**
Liver				
Centrilobular hepatocyte hypertrophy	0/50	27/50*	30/50*	33/50*
Bile duct hyperplasia	10/50	35/50*	39/50*	40/50*
Chronic active Inflammation	46/50	38/50*	29/50*	30/50*
Kidney				
Renal tubule hyperplasia	1/50	8/50*	10/50*	7/50*
severity grade of nephropathy	1.1	1.4	1.7	2.0

Neoplastic findings in rats:

Males				
Dose levels, ppm (mg/kg bw/day)	**0 (0)**	**312 (15)**	**625 (30)**	**1250 (60)**
Mononuclear cell leukemia	27/50 54%	41/50* 82%[a]	39/50* 78%[a]	24/50 48%
Histiocytic sarcoma	0/50	0/50	0/50	0/50
Renal tubule adenoma	2/50 4%[b]	2/50 4%[b]	7/50 14%[b]	8/50 16%[b]

* Significantly different (P≤0.05) from the control
** no findings reported

[a] Exceeding historical incidences: 22-68% in 1159 control animals, all routes
[b] Exceeding historical incidences: 0- 2% in 1152 control animals, all routes

Females				
Dose levels, ppm (mg/kg bw/day)	**0 (0)**	**312 (15)**	**625 (30)**	**1250 (65)**
Mononuclear cell leukemia	19/50 38%	25/50 50%	30/50* 60%[a]	29/50 58%[a]
Histiocytic sarcoma	0/50 0%	0/50 0%	1/50 2%	2/50 4%[b]

* Significantly different (P≤0.05) from the control group
[a] Exceeding historical incidences: 12-52% (mean 28%) in 1209 control animals, all routes
[b]Exceeding historical incidences: 0-2 % (mean 0.1%) in 1209 control animals, all routes

Discussion as cited from NTP (2006):

"In the 2-year rat study, exposed animals exhibited a positive trend in the incidences of renal tubule adenoma. The NTP has found that examination of the entire kidney, by step sectioning of residual tissues, enables a more precise evaluation of the potential chemical-related induction of renal proliferative lesions than observations made from single sections, particularly when the proliferative lesions are small and identified only by microscopic examination (Eustis et al., 1994). For benzophenone, this extended evaluation of the male rat kidney showed significant increases in the incidences of renal tubule adenoma in 625 and 1,250 ppm males and increased incidences of hyperplasia in all exposed groups of males. Incidences of renal tubule hyperplasia in all exposed female groups were significantly greater than that of the control group when the single and step section evaluations were combined.

Within the NTP 2-year carcinogenicity studies, the kidney is the second most commonly affected site in male rats for chemically associated site-specific neoplasms (NTP, 2004b). In the majority of the studies, the increases are primarily of adenomas, and in many instances there is a concurrent dose-related increase in the severity of chronic progressive nephropathy. Chronic nephropathy may influence the induction, development, or progression of renal neoplasms in several ways, including a reduction in target cell population and/or increased number of cells in the replicative cycle due to chronic inflammation and continued degeneration and necrosis, alterations in vascularity as a result of fibrosis, or other alterations in microenvironment. The pathogenesis of chemically induced renal tubule neoplasms has not been determined; however it appears to be complex with genotoxic and nongenotoxic modes (Barrett and Huff, 1991; Short, 1993; Hard, 1998). Data from retrospective reviews of NTP 2-year carcinogenesis studies suggest that an increased severity of nephropathy may contribute to overall tumor response (Seely et al., 2002). However, any contribution appears to be marginal, and additional factors are likely involved.

In female rats, the incidence of mononuclear cell leukemia was marginally increased in the 625 ppm group. Male rats exposed to 312 or 625 ppm benzophenone exhibited significantly increased incidences of mononuclear cell leukemia. Significantly increased incidences were not observed in females exposed to 1,250 ppm, and the incidence in males exposed to 1,250 ppm was similar to the incidence in control males. Mononuclear cell leukemia is generally a late developing neoplasm with most observed in animals after 18 months on study. The incidence of mononuclear cell leukemia in males exposed to 1,250 ppm may have been somewhat higher had survival not been reduced in the last quarter of the study. The incidences of mononuclear cell leukemia in 312 and 625 ppm males and all exposed groups of females were outside the historical control ranges of 30% to 68% in male controls from 2-year NTP feed studies and 12% to 38% in control females; however, the incidence in the female control group was also outside the historical range. The data from this study of benzophenone were included in the historical control dataset, and the 38% incidence was the highest in the dataset. There is no obvious explanation for the higher incidence in the control group.

Mononuclear cell leukemia, a common neoplasm in F344/N rats, is generally thought to arise within the spleen. The spleen is the first and most commonly affected organ, followed by involvement of the liver. With progression, mononuclear cell leukemia becomes widespread and involves multiple organs. Earlier onset and wider distribution of mononuclear cell leukemia in exposed groups would indicate that the increased incidences of mononuclear cell leukemia were treatment related; however, there was no evidence that mononuclear cell leukemia occurred earlier in exposed groups than in control groups in this study. Assessment of the distribution of mononuclear cell leukemia in exposed and control males and females (Table 11) demonstrated lesser involvement of the spleen and liver in the 625 and 1,250 ppm male groups and greater involvement of the spleen and liver in the 625 and 1,250 ppm female groups when compared to the control groups. Although a hint of increased grade 3 mononuclear cell leukemia was observed in exposed females, there was no significant increase in the average severity grade in exposed versus control groups. The average severity grade was significantly decreased in males. Even though the incidences in exposed groups often exceeded the historical control ranges, because the incidences in the 1,250 ppm groups were not significantly increased and there was no evidence of early occurrence or wider distribution in exposed groups, the increased incidences were only considered equivocal evidence of carcinogenicity."

Further, the findings regarding the occurrence of histiocytic sarcoma in female rats was discussed in combination with the similar findings in the NTP (2006) study in mice:
"Benzophenone exposure resulted in a positive trend in the incidence of histiocytic sarcoma in female mice, and one 625 ppm and two 1,250 ppm female rats had histiocytic sarcomas. This neoplasm is rare; none have been observed in historical feed study control rats, and only two have been observed in feed study control mice given the NTP-2000 diet. In historical controls from all routes of exposure, histiocytic sarcoma was observed in one of 1,209 (0.08%) historical control rats and 18 of 1,258 historical control mice (1.4%). Histiocytic sarcomas are classified as hematopoietic tumors of the mononuclear phagocyte system based upon the morphology of the neoplastic cells and the presence of lysozyme, Mac-2, and mononuclear phagocyte antigens. The specific origin of the neoplastic histiocytic cells is undetermined. One or more cell populations may be involved. Bone marrow cells, tissue histiocytes, Kupffer's cells in the liver, and circulating macrophages have been suggested. Histiocytic sarcomas are slightly more common in female than male mice and in mice than rats (Frith et al., 1993). Although the spontaneous incidence of this tumor is low in both mice and rats, the frequency varies widely among different strains of mice and rats. Histiocytic sarcomas are more common in Sprague-Dawley rats, with an overall incidence of 4.7%, than in the Fischer 344, used by the NTP, and Osborne-Mendel strains. In mice exposed to benzophenone, the liver and lung were involved in all affected animals. In the 1,250 ppm female mice, the histiocytic sarcomas were highly invasive. Multiple organs throughout the body had neoplastic histiocytic lesions. All affected rats exposed to benzophenone had lung lesions. Only one rat in the 625 ppm group had organs affected throughout the body. Chemical-associated increases in the incidences of histiocytic sarcomas have not been seen in rats in NTP studies and are uncommon in mice. Increased incidences in mice occurred in studies of 1,3-butadiene (NTP, 1993), tetrafluoroethylene (NTP, 1996a), and phenolphthalein (NTP, 1996b). The increased incidences in the 625 and 1,250 ppm female groups and the increased invasiveness in the 1,250 ppm mice were considered related to benzophenone exposure and some evidence of carcinogenicity. The low incidence of this rare neoplasm in female rats was considered equivocal evidence of carcinogenic activity".

And it was concluded:

"There was some evidence of carcinogenic activity of benzophenone in male F344/N rats based on increased incidences of renal tubule adenoma; mononuclear cell leukemia in male F344/N rats may have been related to benzophenone exposure. There was equivocal evidence of carcinogenic activity of benzophenone in female F344/N rats based on the marginally increased incidences of mononuclear cell leukemia and histiocytic sarcoma."

Historical control data (NTP 2006):

Historical Incidence of Renal Tubule Adenoma in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence in Feed Controls Given NTP-2000 Diet	
Benzophenone	0/50
Citral	1/100
p,p′-Dichlorodiphenyl sulfone	0/50
trans-Cinnamaldehyde	0/100
2-Methylimidazole	0/50
o-Nitrotoluene	0/60
p-Nitrotoluene	0/50
Overall Historical Incidence: Feed Studies	
Total (%)	1/460 (0.2%)
Mean ± standard deviation	0.1% ± 0.4%
Range	0%-1%
Overall Historical Incidence: All Routes	
Total (%)	1/1,205 (0.1%)
Mean ± standard deviation	0.1% ± 0.2%
Range	0%-1%

[a] Data as of April 19, 2004

Historical Incidence of Mononuclear Cell Leukemia and Histiocytic Sarcoma in Untreated Female F344/N Rats[a]

Study	Incidence in Controls	
	Mononuclear Cell Leukemia	Histiocytic Sarcoma
Historical Incidence in Feed Controls Given NTP-2000 Diet		
Benzophenone	19/50	0/50
Citral	24/100	0/100
p,p′-Dichlorodiphenyl sulfone	8/50	0/50
trans-Cinnamaldehyde	21/100	0/100
2-Methylimidazole	6/50	0/50
o-Nitrotoluene	21/60	0/60
p-Nitrotoluene	13/50	0/50
Overall Historical Incidence: Feed Studies		
Total	112/460 (24.4%)	0/460
Mean ± standard deviation	24.6% ± 9.5%	
Range	12%-38%	
Overall Historical Incidence: All Routes		
Total (%)	330/1,209 (27.3%)	1/1,209 (0.1%)
Mean ± standard deviation	28.0% ± 11.2%	0.1% ± 0.4%
Range	12%-52%	0%-2%

[a] Data as of April 19, 2004

Historical Incidence of Renal Tubule Adenoma in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence in Feed Controls Given NTP-2000 Diet	
Benzophenone	1/50
Citral	0/100
p,p'-Dichlorodiphenyl sulfone	0/50
trans-Cinnamaldehyde	0/100
2-Methylimidazole	0/49
o-Nitrotoluene	0/60
p-Nitrotoluene	0/50
Step sections	
Stoddard solvent IIC	
Single	0/50
Step section	3/50
Total	3/50
Propylene glycol mono-*t*-butyl ether	
Single	1/50
Step section	0/50
Total	1/50
Overall Total	4/100
Overall Historical Incidence: Feed Studies	
Total (%)	1/459 (0.2%)
Mean ± standard deviation	0.3% ± 0.8%
Range	0%-2%
Overall Historical Incidence: All Routes	
Total (%)	5/1,152 (0.4%)
Mean ± standard deviation	0.5% ± 0.9%
Range	0%-2%

[a] Data as of April 19, 2004

Historical Incidence of Mononuclear Cell Leukemia in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence in Feed Controls Given NTP-2000 Diet	
Benzophenone	27/50
Citral	68/100
p,p'-Dichlorodiphenyl sulfone	27/50
trans-Cinnamaldehyde	40/100
2-Methylimidazole	15/50
o-Nitrotoluene	30/60
p-Nitrotoluene	24/50
Overall Historical Incidence: Feed Studies	
Total (%)	231/460 (50.2%)
Mean ± standard deviation	49.1% ± 11.9%
Range	30%-68%
Overall Historical Incidence: All Routes	
Total (%)	514/1,159 (44.4%)
Mean ± standard deviation	43.1% ± 12.8%
Range	22%-68%

[a] Data as of April 19, 2004

3.6.1.3 Study 3: Long-term carcinogenicity study in mice, dermal route

Study reference:

Stenbäck F., Shubik P. 1974. Lack of toxicity and carcinogenicity of some commonly used cutaneous agents. Toxicology and Applied Pharmacology 30: 7-13

Detailed study summary and results:

Test type

Dermal lifetime study in mice. The study was published in 1974, and as such was not performed according to Good Laboratory Practice (GLP) and Organisation for Economic Co-operation and Development (OECD) guidelines. However, the design of the study and the reporting of the data are considered appropriate with regard to the endpoint of interest, and the study should be included in the evaluation as a part of supportive evidence.

Test substance

- Benzophenone (identical to substance identified in CLH dossier)
- *Degree of purity:*not indicated
- *Impurities (or a note that the impurities do not affect the classification):* not indicated.
- *Batch number:* not indicated

Test animals

- *Species/strain/sex*: Swiss mice
- *No. of animals per sex per dose:* 50 females mice in each group
- *Age at beginning of study:* 7 weeks

Administration/exposure

- *Route of administration:* Dermal application
- *duration of test/exposure period:* Up to 110 weeks
- *doses/concentration levels, rationale for dose level selection:* concentrations of 5, 25, and 50 % in acetone in a total volume of 0.2 ml was dropped on the dorsal skin between the shoulder blades on an 1-inch square which was shaved regularly.
- *frequency of treatment:* twice a week.
- *control group and treatment:* A vehicle control group received the same treatment with acetone and a positive control was treated in the same manner with dimethylbenzanthracene (DMBA). Further, an additional untreated control group consisted of 150 animals.
- *historical control data:* not described.

- *post exposure observation period:* lifetime exposure
- *vehicle:* acetone
- *test substance formulation/diet preparation, achieved concentration, stability and homogeneity of the preparation:* not indicated
- *actual doses (mg/kg bw/day):* approximately 20, 100, 200 mg/animal per week corresponding to approximately 114, 571, 1143 mg/kg bw/day (assuming 200 mg test solution applied twice a week and a body weight of 25 g)
- *substance concentration (ppm) to the actual dose, if applicable:* 5, 25, 50%
- *satellite groups and reasons they were added:* No satellite groups included

For dermal studies:

- *area covered (e.g. 10% of body surface):* not indicated.
- *occlusion (e.g. semi-occlusive) :* open (not occlusive)
- *total volume applied:* 0.2 ml in acetone
- *removal of test substance (e.g. water or solvent):* No removal of test stubstance after application.

Results and discussion

- *mortality and time to death (indicate number died per sex per dose and time to death):* No effects. All mice in Benzophenone treated groups were dead/killed by week 110, while there were still few survivors in the acetone group (3/50) or in the untreated control group (9/150).
- *clinical signs:* not indicated.
- *body weight gain:* no effects
- *food/water consumption:* not examined
- *ophthalmoscopic examination:* not examined
- *clinical chemistry:* not examined
- *haematology:* not examined
- *urinalysis:* not examined
- *organ weights:* not examined
- *necropsy findings: nature and severity:* not indicated
- *histopathological findings: nature and severity:* not indicated
- *tumour incidence data by sex, dose and tumour type:* See table below

Female mice (50 per group) [dermally exposed to 0.2 ml of Benzophenone solution twice weekly]

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

In benzophenone 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 haemangionas were low and not higher than in the vehicle control group. Overall, the authors concluded that there was no indication of a carcinogenic potential of benzophenone in mice following a topical administration under conditions of this bioassay.

3.6.1.4 Study 4: Long term study in rabbits, dermal

Study reference:

Stenbäck F. 1977. Local and systemic effects of commonly used cutaneous agents: lifetime studies of 16 compounds in mice and rabbits. Acta Pharmacologica et Toxicologica 41: 417-431

Detailed study summary and results:

Test type

Dermal application of benzophenone in rabbits. The study was published in 1977, and as such had not been performed according to GLP and OECD guidelines. The study should be included in the evaluation as a minor supportive evidence.

Test substance

- Benzophenone (identical to substance identified in CLH dossier)
- *Degree of purity:* not indicated

- *Impurities:* not indicated.
- *Batch number:* not indicated.

Test animals

- *Species/strain/sex:* New Zealand rabbits
- *No. of animals per sex per dose:* 5 rabbits/ group, both sexes
- *Age at beginning of study:* 8 weeks

Administration/exposure

- *Route of administration:* Dermal application
- *duration of test/exposure period:* Up to 160 weeks. The treatment continued until the animals died spontaneously
- *doses/concentration levels, rationale for dose level selection:* concentrations of 5, 25, and 50 % in solvent in a total volume of 0.2 ml were applied to interior left ear.
- *frequency of treatment:* twice a week.
- *control group and treatment:* A positive control (15 rabbits/ groups, both sexes, a. number of females and males/group not informed) was treated in the same manner with DMBA (a dosing volume of 0.2 ml) twice a week. Two untreated control groups (4 or 5 rabbits/group, a number of females and males in the group not informed) were also included.
- *historical control data:* Not described
- *post exposure observation period:* None
- *vehicle:* Acetone or methanol (not further specified).
- *test substance formulation/diet preparation, achieved concentration, stability and homogeneity of the preparation:* Not described
- *actual doses (mg/kg bw/day)*: 20 mg, 100 mg and 200 mg per animal per week corresponding to approximately 1, 5, and 10 mg/kg bw/d (assuming 200 mg test sample and a body weight of 3 kg).
- *substance concentration (ppm) to the actual dose, if applicable*: 5, 25, 50%
- *satellite groups and reasons they were added:* No satellite groups included

For dermal studies:

- *area covered (e.g. 10% of body surface):* not indicated
- *occlusion (e.g. semi-occlusive) :* open

- *total volume applied:* 0.2 ml
- *removal of test substance (e.g. water or solvent):* none

Results and discussion

- *mortality and time to death (indicate number died per sex per dose and time to death):* No treatment related effect on mortality. The survival at week 160 was 1, 3 and 2 rabbits in the low, middle, and high-dose Benzophenone groups, and 3 in the untreated control group with an initial number of animals of 5. In another control group (4 rabbits in the start) no survivals were present in week 120. According to the author of the study, the positive control was terminated in week 50 for morphological analyses.
- *clinical signs:* No effects
- *body weight gain:* No effects
- *food/water consumption:* not examined
- *ophthalmoscopic examination:* not examined
- *clinical chemistry:* not examined
- *haematology*: not examined
- *urinalysis:* not examined
- *organ weights:* Not described
- *necropsy findings: nature and severity:* No effects
- *histopathological findings: nature and severity:* No effects
- *tumour incidence data by sex, dose and tumour type:*

  No tumours were recorded in the Benzophenone treated group and in the untreated control groups. In the positive control group 12 tumours were recorded.
- *local or multi-site responses:* not indicated
- *progression of lesions to malignancy:* not indicated
- *gender and/or species-specific responses:* not indicated
- *tumour incidence data by sex, dose and tumour type:* not indicated *mode of action (genotoxic, non-genotoxic):* not indicated
- *toxic response data by sex and dose:* not indicated
- *tumour latency:* not indicated *statistical methods and results (unless already described with specific test results above):* not indicated

Complete autopsies were performed on all animals. Skin samples, grossly observed tomours 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 benzophenone. 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.

3.6.2 Human data

No human data is available

3.6.3 *In vitro* data (e.g. in vitro germ cell and somatic cell mutagenicity studies, cell transformation assays, gap junction intercellular communication tests)

No specific *in vitro* data is available

3.7 Reproductive toxicity

This endpoint is not addressed in the CLH report.

3.8 Specific target organ toxicity – single exposure

This endpoint is not addressed in the CLH report.

3.9 Specific target organ toxicity – repeated exposure

This endpoint is not addressed in the CLH report.

3.10 Aspiration hazard

This endpoint is not addressed in the CLH report.

4 ENVIRONMENTAL HAZARDS

4.1 Degradation

This endpoint is not addressed in the CLH report.

4.2 Bioaccumulation

This endpoint is not addressed in the CLH report.

4.3 Acute toxicity

This endpoint is not addressed in the CLH report.

4.3.1 Short-term toxicity to fish

This endpoint is not addressed in the CLH report.

4.3.2 Short-term toxicity to aquatic invertebrates

This endpoint is not addressed in the CLH report.

4.3.3 Algal growth inhibition tests

This endpoint is not addressed in the CLH report.

4.3.4 *Lemna* sp. growth inhibition test

This endpoint is not addressed in the CLH report.

4.4 Chronic toxicity

4.4.1 Fish early-life stage (FELS) toxicity test

This endpoint is not addressed in the CLH report.

4.4.2 Fish short-term toxicity test on embryo and sac-fry stages

This endpoint is not addressed in the CLH report.

4.4.3 Aquatic Toxicity – Fish, juvenile growth test

This endpoint is not addressed in the CLH report.

4.4.4 Chronic toxicity to aquatic invertebrates

This endpoint is not addressed in the CLH report.

4.4.5 Chronic toxicity to algae or aquatic plants

This endpoint is not addressed in the CLH report.

4.5 Acute and/or chronic toxicity to other aquatic organisms

This endpoint is not addressed in the CLH report.