MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

July 10, 2015

TO: File for Benzophenone (CAS No. 119-61-9)

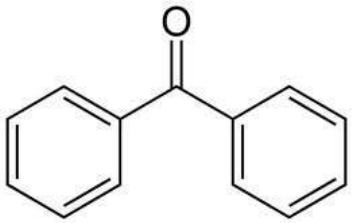
FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Screening Level

The initial threshold screening level (ITSL) for benzophenone is 100 µg/m³ with an annual averaging time. The initial risk screening level (IRSL) and secondary risk screening level are 0.2 µg/m³ and 2 µg/m³, respectively, with annual averaging times.

The following information sources were searched in order to update the screening levels for benzophenone: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS, 2012), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) Online (1993- October 2012), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration (RfC) for benzophenone. California Office of Environmental Health Hazard Assessment (Cal-OEHHA) has not established reference exposure levels for benzophenone. The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) has not established a chronic minimal risk level for benzophenone. Neither the ACGIH nor NIOSH have established occupational exposure levels. The molecular formula for benzophenone is $C_{13}H_{10}O$ and the molecular structure is shown in figure 1. The molecular weight of benzophenone is 182.2 g.

Figure 1. Molecular Structure of Benzophenone



It was noted that the American Industrial Hygiene Association (AIHA, 2011) established a Workplace Environmental Exposure Level (WEEL) for benzophenone at 0.5 µg/m³ with an 8-hr average. If Rule 225(1)(c) were used to derive a screening level, the ITSL would be 5 µg/m³ with an 8-hr averaging time. However, since AIHA (2011) does not provide documentation for the derivation of this occupational exposure limit (OEL), one cannot

evaluate the underlying toxicological data to determine if the OEL would be appropriate for ITSL derivation. Therefore, the WEEL was not used to derive an ITSL.

Summary of Toxicological Database (HSDB, 2012)

Developmental or Reproductive Toxicity: The reproductive toxicity of benzophenone (BZP) was evaluated in a two generation test in which male and female Sprague-Dawley (SD) rats, parental (F0) and first generation (F1), were exposed to BZP by feeding diet containing BZP at concentrations of 0 (control), 100, 450 or 2000 ppm. With regard to the effects of BZP on the F0 and F1 parental animals, inhibition of body weight gain and food consumption, significantly elevated renal weights, dilatation of the renal proximal tubules, and regeneration of the proximal tubular epithelium were recognized at doses of 450 ppm and 2000 ppm, along with an increase in hepatic weight and centrilobular hepatocytic hypertrophy, considered as vital adaptive changes, at the doses of 100 ppm or more. Obvious effects on the endocrine system and reproductive toxicological effects were not found even at the dose of 2000 ppm in the F0 or F1 parent. There were no test substance related changes in the estrous cycle, reproductive capability, delivery and lactation, sperm parameters, serum hormone levels, or necropsy findings. As for effects on the offspring, inhibition of body weight gain was observed in both the F1 and F2 males and females of the 2000 ppm group. No effects of BZP treatment were recognized in the number of male and female F1 or F2 pups delivered, viability, anogenital distance (AGD), physical development, the results of reflex and response tests, or on the observation results of external abnormalities. From the present study of BZP administered to rats over two successive generations, the no observed effect level (NOEL) on the parental animals is concluded to be less than 100 ppm. Concerning the effects on the endocrine system and the reproductive toxicity in the parental animals, the NOEL is 2000 ppm. In terms of the effects on the offspring, the NOEL is considered to be 450 ppm. [Hoshino N et al; J Toxicol Sci 30 Spec No: 5-20 (2005)]

GENOTOXICITY: The genotoxic potential of benzophenone and its metabolically related compounds, benzhydrol and p-benzoylphenol, was investigated using human cytochrome P450 (P450) enzymes. Benzophenone and its two metabolites (0.1-1mM) showed a suppression of bacterial growth without any P450 system, but no induction of umu gene expression was observed in Salmonella typhimurium TA1535/pSK1002. Human liver microsomes induced the bacterial cytotoxicity of these compounds without any umu gene expression. On the other hand, with the addition of Escherichia coli membranes expressing recombinant human P450 2A6 and NADPH-cytochrome P450 reductase (NPR), benzophenone showed umu gene expression (64 umu units/min/nmol) P450 2A6). Moderate activation of benzophenone by P450 1A1/NPR membranes, 1A2/NPR membranes, or 1B1/NPR membranes was also observed. Activation of benzhydrol and p-benzoylphenol by the P450/NPR system was similar to that of benzophenone. These results suggest that benzophenone and its metabolically related benzhydrol and p-benzoylphenol can be bioactivated by P450 2A6 and P450 family 1 enzymes. Until now, benzophenone has been investigated mainly in terms of estrogenic activity and cytotoxicity, however, the genotoxic activation of benzophenone by human cytochrome P450s should be examined in terms of the risks to humans. [Takemoto K et al; Mutat Res 519 (1-2): 199-204 (2002)] PubMed Abstract

Benzophenone was negative for genotoxic effects in a DNA damage and repair assay conducted using Escherichia coli at 500 ug/plate without metabolic activation. [European Chemicals Bureau; IUCLID Dataset, Benzophenone (CAS No. 119-61-9) (2000 CD-ROM edition). Available from, as of November 15, 2006: http://ecb.jrc.ec.europa.eu/esis/]

OTHER TOXICITY INFORMATION: Benzophenone (BP) is a suspected endocrine disrupter that is found in our environment. BP undergoes metabolic and photochemical activation. In this study, photoproducts of BP were identified using high-performance liquid

chromatography and mass spectrometry and their estrogenic activity was determined using both in vitro and in vivo assays. Although BP showed no estrogenic activity, two estrogenic photoproducts were detected after irradiating an aqueous solution of BP with UV or sunlight. These active products were identified as 3-hydroxy BP (BP-3OH) and 4-hydroxyBP (BP-4OH). The formation of hydrogen peroxide (H(2)O(2)) was detected with increasing levels of UV, and the addition of H(2)O(2) to the BP solution increased BP-3OH and BP-4OH production under UV irradiation. BP hydroxylation was also observed in the reaction with the Fenton reagent generating hydroxyl radical without UV irradiation. These results suggest the involvement of photochemically generated H(2)O(2) and hydroxyl radical in the BP hydroxylation. BP-4OH was more potent than BP-3OH for promoting estrogen receptor (ER)-mediated transcription and uterotrophic activity, although both of them showed same affinity in ER binding. In conclusion, BP can be converted into ring-hydroxylated derivatives that have estrogenic activity after exposure to light. [Hayashi T et al; Toxicol Lett 167 (1): 1-7 (2006)]

The authors: gave benzophenone orally ... (100 or 400 mg/kg) ... once per day for 3 days, to ovariectomized Sprague-Dawley (SD) rats, and all rats were killed 24 h after being given the last dose. ... At 24 hr after the last dose, the mean serum concentrations of benzophenone, benzhydrol and p-hydroxybenzophenone in the high-dosed rats were 10.4+/-1.0, 1.5+/-0.3, and 0.7+/-0.2 (mean +/- SE) µmol/L, respectively, whereas in the serum of low-dosed rats these compounds were not detected. When a single oral administration of benzophenone (100 or 400 mg/kg) was given to intact female rats, serum concentrations of benzophenone, benzhydrol and p-hydroxybenzophenone increased in a dose-dependent manner 6 hr later. ... [Nakagawa Y, Tayama K; Arch Toxicol 76 (12): 727-31 (2002)]

Special Note About Male Rat Kidney Lesions

Animal tumor findings are generally judged to be relevant to humans (EPA, 2005; page 1-10). However, some chemicals induce accumulation of alpha 2u-globulin (alpha 2u-g), a low molecular weight protein, in the male rat kidney. For these chemicals, the use of kidney lesions are not appropriate for extrapolation to humans and should not be used in the risk assessment process. EPA (1991) describes this phenomenon:

> The alpha 2u-g accumulation initiates a sequence of events that appears to lead to renal tubule tumor formation. Female rats and other laboratory mammals administered the same chemicals do not accumulate low molecular weight protein in the kidney, and they do not develop renal tubule tumors. Because humans appear to be more like other laboratory animals than like the male rat, in this special situation, the male rat is not a good model for assessing human risk.

EPA stresses the need for full scrutiny of a substantial set of data to determine when it is reasonable to presume that renal tumors in male rats are linked to a process involving alpha 2u-g accumulation (EPA, 1991). In the case of benzophenone, alpha 2u-g accumulation is not present in the male rat kidney. This is based on the absence of hyaline droplet accumulation in the kidney, a key indicator of alpha 2u-g accumulation (see NTP, 2006, Table A5, page 105). Therefore, the extrapolation of kidney dose-response data of kidney lesions (both cancer and non-cancer endpoints) in the male rat are appropriate to use to estimate human health risks from exposure to benzophenone.

Derivation of the ITSL

A Tolerable Daily Intake (TDI) for benzophenone was calculated by the European Food Safety Authority (EFSA, 2009) at 0.03 mg/kg/day. The EFSA (2009) used a 2-year feed

study published by the National Toxicology Program (NTP, 2006) in which male and female mice and rats were fed varying diets of benzophenone. Carcinogenic and non-carcinogenic liver and kidney lesions were observed to increase in a dose dependent manner. EFSA used the animal doses and the incidences of male rate kidney lesions (pelvis, transitional epithelium, hyperplasia) identified in the NTP study as input data for a software program called Benchmark Dose Software (BMDS)(EPA, 2012a, 2012b). The lower 95% confidence limit of the bench mark dose for a 10% effect (BMDL10) was calculated as described by EFSA to be 3.1 mg/kg/day (i.e., $BMDL10_{ANIMAL}$ is 3.1 mg/kg). EFSA used a total uncertainty factor of 100 (10 for interspecies and 10 for intraspecies variability). The derivation of the BMDL10 by the EFSA was evaluated with respect to U.S. EPA methodology and was judged to be appropriate to use to calculate an ITSL. However, using EPA methodology, it was decided to use a dosimetric adjustment factor (DAF) to convert the animal dose to human dose using the EPA (2011) guidance, as shown here:

$$BMDL10_{HUMAN} = BMDL10_{ANIMAL} \times DAF$$

Where,

$BMDL10_{ANIMAL}$ is 3.1 mg/kg

DAF is $(W_a/W_h)^{0.25}$ and DAF is the dosimetric adjustment factor for converting the animal dose to the human dose

W_a is weight of animal (in this case the male rat, 0.47 kg)

W_h is weight of human (70 kg)

$$BMDL10_{HUMAN} = 3.1 \text{ mg/kg} \times (0.47\text{kg}/70\text{kg})^{0.25}$$

$$BMDL10_{HUMAN} = 3.1 \text{ mg/kg} \times 0.286$$

$$BMDL10_{HUMAN} = 0.887 \text{ mg/kg}$$

The RfD was calculated as:

$$RfD = (BMDL10_{HUMAN})/(UF_a \times UF_s)$$

Where,

UF_a is an uncertainty factor of 3 to account for the differences between animals and human (decreased from 10 to 3 because usage of the interspecies DAF decreases the uncertainty)

UF_s is an uncertainty factor of 10 to account for the sensitive individuals in the human population

$$RfD = (0.887)/(3 \times 10)$$

$$RfD = 0.029 \text{ mg/kg},$$

or rounded to 1 significant figure = 0.03 mg/kg

The ITSL was calculated as follows:

$$ITSL = RfD \times 70 \text{ kg}/20\text{m}^3 \times 1000\mu\text{g}/1\text{mg}$$

ITSL = 102 µg/m³ (rounded to 1 significant figure: **100 µg/m³ (annual avg. time)**

Coincidently, the RfD of 0.03 mg/kg/day equals the TDI of 0.03 mg/kg/day.

Rule 232(2)(b) states that the default averaging time for an RfD based ITSL is 24-hours; however, in this case the critical effect and study duration support an annual averaging time as allowed under Rule 229(2)(b).

Derivation of the IRSL

The National Toxicology Program (NTP, 2006) performed a 2-year bioassay in rats and mice and found “some evidence” of carcinogenicity in male rats (kidney) and male (liver) and female (histiocytic sarcoma) mice. The NTP (2006) conclusions are presented here:

> Under the conditions of these 2-year studies, 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. 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.
>
> Administration of benzophenone in feed resulted in increased incidences and/or severities of nonneoplastic lesions in the kidney and liver of male and female rats and in the liver, kidney, nose, and spleen of male and female mice. Decreased incidences of mammary gland fibroadenoma in female rats were related to benzophenone exposure.

The International Agency for Research on Cancer (IARC, 2012) published a thorough review in which they conclude that benzophenone is "possibly carcinogenic to humans" (Group 2B). Furthermore, IARC concluded that there is "sufficient evidence of carcinogenicity in experimental animals."

Using data from the NTP (2006) study, an IRSL was calculated using EPA Benchmark Dose Software (2012a) and the latest guidance provided by EPA (2012b). Table 2. shows the animal slope factors of several cancer endpoints obtained from the incidence rates presented in NTP (2006). The appendix shows the incidence data used in the BMDS to derive the inhalation unit risks. The human equivalent dose was calculated from animal similar to Rule 231(1)(c), except the exponent was changed from ⅓ to ¼ based on EPA (2011) guidance.

The NTP called the evidence for carcinogenicity based on Female Rat Leukemia “equivocal”. However, the dose-incidence data provided a good fit using BMDS methodology. It was decided not to use the Female Rat Leukemia as an endpoint for quantitating human carcinogenic risk based on the equivocal designation by NTP (2006). The geometric mean of the remaining candidate inhalation unit risks (IURs) is 6.57E-06 per µg/m³. This results in an IRSL of 0.152 µg/m³, which when rounded to 1 significant figure is 0.2 µg/m³. Annual Averaging time is applied to the IRSL and SRSL.

Table 2. Initial Risk Screening Level Calculation

Tumor Type From NTP (2006)	Animal Slope Factor per mg/kg	Body Weight (BW) of Animal kg	Human Equivalent Dose (HED) conversion factor ("T")*	IUR-HED per mg/kg	Convert** to Inhalation Unit Risk (IUR)	Candidate IUR per µg/m³	Candidate IRSL µg/m³ (1 sig. fig.)***
Male Rat Kidney Adenoma +Carcinoma	0.0048	4.7E-01	3.49	1.68E-02	2.86E-04	4.79E-06	0.2
Female Rat Leukemia	0.011	3.0E-01	3.91	4.34E-02	2.86E-04	1.24E-05	0.08
Male Mice Hepatocellular Adenoma + Blastoma	0.004	4.3E-02	6.35	2.54E-02	2.86E-04	7.26E-06	0.1
Male Mice Ademoma+Carcinoma + Blastoma	0.0045	4.3E-02	6.35	2.86E-02	2.86E-04	8.16E-06	0.1

* T = (body weight of human)/(body weight of animal)^{¼} or $(BW_h/BW_a)^{0.25}$, where the default BW_h = 70 kg (EPA, 2011)
** daily inhalation volume in humans ÷ default body weight of humans: 20m³/70kg x unit conversion (1µg/1000mg)
*** rounded to 1 significant figure

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APPENDIX

Male Rat Renal Tubular Adenoma + Carcinoma (NTP, page 35) "Some evidence"

Dose ppm	Dose mg/kg	Number of Male Rat (surviving to first sign of cancer)	Renal Tubular Adenoma + Carcinoma
0	0	47	2
312	15	44	3
625	30	47	7
1250	60	44	8

Female Rat Leukemia (NTP, page 39): "Equivocal evidence"

Dose ppm	Dose mg/kg	Number of Female Rats (surviving to first sign of cancer)	Leukemia Incidence
0	0	47	19
312	15	50	25
625	30	50	30
1250	65	50	29

Male Mice Hepatocellular Adenoma (NTP, page 48) "Some evidence"

Dose ppm	Dose mg/kg	Number of Male Mice (surviving to first sign of cancer)	Hepatocellular Adenoma Incidence
0	0	47	4
312	40	48	15
625	80	50	23
1250	160	50	23

Male Mice Hepatocellular Adenoma+Carcinoma+Hepatoblastoma (NTP, page 48) "Some evidence"

Dose ppm	Dose mg/kg	Number of Male Mice (surviving to first sign of cancer)	Hepatocellular Adenoma+ Carcinoma+ Hepatocellular Blastoma
0	0	50	18
312	40	50	20
625	80	50	25
1250	160	50	29