

Benzophenone Substance Summary

Summary

Benzophenone has no ACGIH TLV, NIOSH REL, or OSHA PEL. Only one authoritative body has recommended an exposure limit. Benzophenone is a solid at room temperature and presents vapor and particulate exposures. Benzophenone is well absorbed through the skin. There is limited toxicological data on benzophenone and no chronic inhalation study in animals with which to assess its health hazard. A metabolite of benzophenone has estrogenic activity and has been weakly linked to such effects in humans.

A PEL of 0.25 mg/m³ based on kidney effects is recommended for discussion. The key target endpoint for the human hazard assessment of benzophenone are kidney and liver effects. Non-neoplastic and neoplastic effects were observed in both these organs in chronic feeding studies in two species. Alpha-2-globulin has not been implicated in the kidney lesions observed in male rats so it is appropriate to use the male rat kidney data for hazard assessment. Liver hypertrophy has been attributed to p450 induction (see EFSA). Benzophenone has been shown to be non-genotoxic and not or weakly endocrine-active in numerous assays. A skin notation is recommended.

Physical Properties

Substance name: Benzophenone

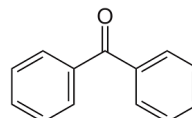
CAS: 119-61-9

MW: 182.22

Synonyms: Diphenylmethanone, Phenyl ketone, Benzoylbenzene, Diphenyl ketone, α -Oxidiphenyl methane

Molecular formula: C₁₃H₁₀O

Structural formula:



Conversion factors at 25 °C and 760 mm Hg: 1 ppm = 7.45 mg/m³

Physical appearance at room temp: white, flaked/crystalline solid

Boiling Point: 305 °C

Melting Point: 48.5 °C

Vapor Pressure: 0.006 mmHg at 48 °C

Solubility: insoluble in water, soluble in organics such as alcohol, ether, chloroform

Special physical characteristics if any: rose or geranium-like odor

Flammability and other hazards: Flash point 144°C (closed cup)

Uses & Applications

Benzophenone is a naturally occurring compound used in flavoring and perfumes. It is used as fixative for heavy perfumes in soaps, detergents, and room deodorizers. It is used as a flavoring agent, ultraviolet absorber in inks and coatings, and as a polymerization inhibitor for styrene. It is used in the manufacture of antihistamines, hypnotics, and insecticides.

Occupational Exposure Limits (OELs) and Other Recommendations

Table 1: Occupational Exposure Limits

Benzophenone has no ACGIH TLV, NIOSH REL, or OSHA PEL.

| Source | Findings/Recommendations | Basis/Source/Ref(s) | Discussion and Assessment |
|---------------------|--|--|--|
| AIHA/OARS-WEEL 2003 | 0.5 mg/m ³ as an 8 hour TWA, no skin notation | benzophenone caused liver injury in two subchronic studies and was likely not genotoxic. | An uncertainty factor of 40 was based on interspecies differences, differences in route of exposure, extrapolation from subchronic data and variability in worker susceptibility |

Table 2: Other Recommendations of Other Authoritative Bodies

| Source | Findings/Recommendations | Basis/Source/Ref(s) | Discussion and Assessment |
|----------------|--|--|---------------------------|
| Prop 65 (2012) | Listed | | |
| NTP (2006) | Some evidence of carcinogenic activity in male F344/N rats and male & female B6C3F mice; equivocal evidence of carcinogenic activity in female F344/N rats | NTP TR 533 NIH Publication No. 06-4469 | |
| IARC (2013) | Possibly carcinogenic to humans (Group 2B) | IARC Monographs 101-007 | |

Health Effects

There are subchronic and chronic feeding studies and a 2-generation reproductive gavage study of benzophenone in rodents. No inhalation study of benzophenone has been conducted. There are extensive mutagenicity and endocrine activity data for benzophenone. There are no data on health effects in humans.

Animal Studies

Toxicology and Carcinogenicity

NTP Technical Report on the Toxicology and Carcinogenicity Studies of Benzophenone (CAS No. 119-61-9) in F3444/N Rats and B6C3F1 Mice (Feed Studies) 2006.

https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr533.pdf

Below are the NTP abstracts and toxicology/carcinogenicity conclusions of the two rodent studies with benzophenone. Study details and significant findings are outlined in Tables 3 and 4.

Two-year study in Rats: Groups of 50 male and 50 female rats were fed diets containing 0, 312, 625, or 1,250 ppm benzophenone (equivalent to average daily doses of approximately 15, 30, and 60 mg benzophenone/kg body weight to males and 15, 30, and 65 mg/kg to females) for 105 weeks. There was a positive trend in the incidences of renal tubule adenoma in males, and the incidences in 625 and 1,250 ppm males exceeded the historical control range for all routes; these neoplasms were accompanied by significantly increased incidences of renal tubule hyperplasia. The incidences of pelvic transitional epithelium hyperplasia and the severity of nephropathy were significantly increased in all exposed groups of male rats. Increased incidences of mononuclear cell leukemia in all exposed groups of females exceeded the historical control range from feed studies, and the incidence in 625 ppm females was significantly greater than that in the controls. Male rats exposed to 312 or 625 ppm had significantly increased incidences of mononuclear cell leukemia. One 625 ppm female and two 1,250 ppm females had histiocytic sarcomas, and the incidence in the 1,250 ppm group exceeded the range in the historical controls. Incidences of mammary gland fibroadenoma in females exposed to 625 or 1,250 ppm were lower than expected after adjusting for body weight.

Two-year study in Mice: Groups of 50 male and 50 female mice were fed diets containing 0, 312, 625, or 1,250 ppm benzophenone (equivalent to average daily doses of approximately 40, 80, and 160 mg/kg body weight to males and 35, 70, and 150 mg/kg to females) for 105 weeks. In male mice, there were significantly increased incidences of hepatocellular adenoma in the 625 and 1,250 ppm groups, and these incidences exceeded the historical control range. All hepatocellular neoplasms combined occurred with a positive trend. In female mice, the incidences of hepatocellular adenoma in the 625 and 1,250 ppm groups were higher than expected after adjusting for the lower body weights in these groups. Incidences of centrilobular hepatocyte hypertrophy were significantly increased in all exposed groups of males and females. The incidence of histiocytic sarcoma in 625 ppm females was significantly increased and exceeded the historical control range. The incidences of kidney nephropathy and mineralization in exposed groups of females and the severity of nephropathy in exposed groups of males were significantly increased. Study details and significant findings are outlined in Tables 3 and 4.

Toxicology/Carcinogenicity: In male rats, renal tubule hyperplasia increased significantly and was accompanied by a dose-dependent enhancement of the severity of nephropathy in all treatment groups. In female rats, a significantly enhanced severity of nephropathy was found at 30 and 65 mg/kg body weight per day. In mice, mild to moderate hyperplasia in centrilobular hepatocytes was observed in all treatment groups. Additionally, increased incidences of a number of liver lesions were found in treated male mice (clear cell foci, multinucleated hepatocytes, necrosis, chronic active inflammation and cystic degeneration). The incidences of nephropathy in exposed females as well as the severity of nephropathy in exposed males were significantly increased. Effects observed in the spleen were increased haematopoietic cell proliferation in females and hyperplastic changes in all treated mice. In male mice an increased mineralization in the testes was reported. Rare histiocytic sarcomas were observed in female rats and mice in the mid and high dose groups (70 and 150 mg/kg body weight per day).

No NOAELs could be derived from these studies. The LOAEL for the rat study was 15 mg/kg body weight per day based on increased incidences of mononuclear cell leukemia and bile duct hyperplasia in all treated females and nephropathy and renal tubule hyperplasia in all treated males. The LOAEL for mice was 312 ppm (35 mg/kg body weight per day) based on multiple hepatocellular adenoma in treated males and nephropathy accompanied by mineralization in treated females and increased severity of nephropathy in treated males.

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.

Table 3. Summary of NTP 2-year oral studies of benzophenone in rodents

| | Male F344/N Rats | Female F344/N Rats | Male B6C3F1 Mice | Female B6C3F1 Mice |
|-------------------------------|--|--|---|---|
| Concentrations in feed | 0, 312, 625, 1,250 ppm | 0, 312, 625, 1,250 ppm | 0, 312, 625, 1,250 ppm | 0, 312, 625, 1,250 ppm |
| Body weights | 625 and 1,250 ppm groups less than control | 625 and 1,250 ppm groups less than control | Exposed groups similar to the control group | 312, 625, 1,250 ppm groups less than control |
| Non-neoplastic effects | Kidney: renal tubule, hyperplasia, combined evaluations (3/50, 11/50, 30/50, | Kidney: renal tubule, hyperplasia, , combined evaluations (1/50, 8/50, 10/50, 7/50); | Liver: hepatocyte, centrilobular, hypertrophy (0/50, 44/50, 50/50, 48/50); hepatocyte, multinucleated | Liver: hepatocyte, centrilobular, hypertrophy (0/50, 29/50, 44/50, 37/50) |

| | Male F344/N Rats | Female F344/N Rats | Male B6C3F1 Mice | Female B6C3F1 Mice |
|-------------------------------|--|---|---|--|
| Concentrations in feed | 0, 312, 625, 1,250 ppm | 0, 312, 625, 1,250 ppm | 0, 312, 625, 1,250 ppm | 0, 312, 625, 1,250 ppm |
| | 40/50); pelvis, transitional epithelium, hyperplasia (1/50, 11/50, 29/50, 34/50); severity of nephropathy (1.3, 2.4, 3.3, 3.8) Liver: hepatocyte, centrilobular, hypertrophy (0/50, 17/50, 31/50, 19/50); degeneration, cystic (8/50, 11/50, 20/50, 15/50) | severity of nephropathy - (1.1, 1.4, 1.7, 2.0) Liver: hepatocyte, centrilobular, hypertrophy (0/50, 27/50, 30/50, 33/50); bile duct, hyperplasia (10/50, 35/50, 39/50, 40/50) | (0/50, 41/50, 47/50, 48/50); inflammation, chronic active (33/50, 47/50, 44/50, 42/50); hepatocyte, degeneration, cystic (0/50, 0/50, 5/50, 30/50) Kidney: severity of nephropathy (1.2, 1.4, 1.7, 3.0) Nose: olfactory epithelium, metaplasia (0/50, 2/50, 2/50, 24/50) Spleen: lymphoid follicle, hyperplasia, (17/50, 31/50, 34/50, 32/50) | Kidney: nephropathy (21/50, 33/50, 31/50, 30/50); mineralization (15/50, 31/50, 36/50, 49/50); severity of nephropathy - (1.2, 1.1, 1.5, 1.7) Nose: olfactory epithelium, metaplasia (0/50, 0/50, 0/50, 39/50) Spleen: lymphoid follicle, hyperplasia, lymphoid (24/50, 36/50, 37/50, 22/50) |
| Neoplastic effects | Kidney: renal tubule, adenoma (standard evaluation - 1/50, 1/50, 2/50, 4/50; standard and extended evaluations combined - 2/50, 2/50, 7/50, 8/50) | None | Liver: hepatocellular adenoma (11/50, 15/50, 23/50, 23/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (18/50, 20/50, 25/50, 29/50) | Histiocytic sarcoma: (0/50, 0/50, 5/50, 3/50) |
| Equivocal findings | Mononuclear cell leukemia: (27/50, 41/50, 39/50, 24/50) | Mononuclear cell leukemia: (19/50, 25/50, 30/50, 29/50) Histiocytic sarcoma: (0/50, 0/50, 1/50, 2/50) | None | Liver: hepatocellular adenoma (5/50, 4/50, 10/50, 8/50) |

Table 4. Summary of non-neoplastic and neoplastic lesions in chronic feeding studies.

| Male Rat – 50 animals | 0 ppm | 312 ppm | 625 ppm | 12450 ppm |
|---|-------------------------------|--------------------------------|-------------------------------|--------------------------------|
| Renal Tubule, Hyperplasia, # of animals (severity of lesions) | 3 (1.0) | 11* (1.3) | 30** (1.8) | 40** (2.1) † |
| Pelvis, transitional epithelium hyperplasia | 1 (1.0) | 11** (1.2) | 29** (1.5) | 34** (1.7) |
| Nephropathy severity (incidence) | 1.3 (50) | 2.4 (45) † | 3.3 (50) † | 3.8 (50) † |
| Renal Tubule, Adenoma | 2/50 p=0.004 | 2/50 p =0.688 | 7/50 p=0.093 | 8/50 p =0.017 |
| Mononuclear Cell Leukemia | 27/50 p=0.508 | 41/50 p=0.003 | 39/50 p=0.005 | 24/50 p =0.454 |
| Rat - female | | | | |
| Renal Tubule, Hyperplasia | 1 (1.0) | 8* (1.5) | 10** (2.2) | 7* (2.0) |
| Nephropathy severity (incidence) | 1.1 (47) | 1.4 (49) | 1.7 (48) † | 2.0 (49) † |
| Mononuclear Cell Leukemia | 19/50 p=0.058 | 25/50 p= 0.25 | 30/50 p=0.048 | 29/50 p=0.068 |
| Mouse - male | | | | |
| Hepatocyte, Centrilobular, Hypertrophy | 0 | 44** (2.0) | 50** (2.0) | 48** (3.0) |
| Hept.Adenoma/Carcinoma/Hepatoblastoma | 18/50 p =0.013 | 20/50 p=0.434 | 25/50 p =0.118 | 29/50 p=0.027 |
| Mouse - female | | | | |
| Hepatocyte, Centrilobular, Hypertrophy | 0 | 29** (2.0) | 44** (2.0) | 37** (2.9) |
| Hepatocellular Adenoma or Carcinoma | 5/50 p=0.081 | 5/50 p =0.624 | 10/50 p =0.131 | 9/50 p=0.165 |
| Histiocytic Sarcoma | 0/50 p=0.074 | 0/50 - | 5/50 p=0.031 | 3/50 p=0.108 |

Corresponding rat doses are 15, 30, and 60 mg benzophenone/kg body weight to males and 15, 30, and 65 mg/kg to females and mice

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test, ** $P \leq 0.01$. Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidences are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.

Reproductive Toxicology

NTP conducted several range-finding developmental toxicity studies with benzophenone in rats and rabbits in which effects on the fetus were only observed in the presence of maternal toxicity. Benzophenone was administered by gavage to rats on gestational days (GD) 6 to 19 at doses of 0, 100, 200, or 300 mg/kg bw/day (NTP 2002). Maternal toxicity was observed at all doses, including clinical signs (lethargy, piloerection, weight loss) and significantly increased maternal liver and kidney weights. Decreased fetal body weight was noted at the highest dose, and what were considered “mild developmental delays with a high probability of recovery during early postnatal development” were observed at all doses. The incidences of unossified sternebrae were increased in all dose groups and the incidence of extra rib was increased in the two highest dose groups. The maternal toxicity

lowest-observed-adverse-effect level (LOAEL) was reported as 100 mg/kg /day (no NOAEL was established).

In a similar study, developmental toxicity of benzophenone was investigated in rabbits, administered benzophenone by gavage in doses of 0, 5, 25 and 45 mg/kg /day on gestational days 6–29 (NTP 2004). Maternal body weights and feed consumption decreased in a dose-related manner, but no effects on liver and kidney weights were observed. There were no effects on prenatal viability. However, the number of successful deliveries was decreased with increasing dose of benzophenone. Fetal body weight was significantly decreased in the highest dose group. In rabbits, dose-related increases in the incidences of abortion or early delivery were reported in the mid- and high-dose groups, along with dose-related reductions in maternal body weight (not reversed) and fetal body weight. The LOAEL was considered to be 25 mg/kg bw/day for maternal toxicity and early termination of pregnancy and NOAEL was determined to be 5 mg/kg bw/day. The conclusion by the authors was that developmental toxicity was only noted in the presence of maternal toxicity.

No reproductive toxicity or effects on endocrine systems were apparent in a two-generation study in which SD rats were exposed to benzophenone in the diet at 0, 6, 29 and 130 mg/kg bw/day (males) and 0, 9, 40, and 170 mg/kg bw/day (females) (Hoshino, 2005). However, in both sexes of F0 and F1 parents, inhibition of body weight gain and food consumption, significantly elevated renal weights and changes in renal tubules, and significantly increased hepatic weight and centrilobular hepatocytic hypertrophy were observed in mid- and high-dose groups. In both generations, no effects were observed on male and female reproduction (sperm analysis, oestrous cycle, serum levels of testosterone, estradiol, follicle-stimulating hormone (FSH) and luteinising hormone (LH), mating and fertility index, gestational length, number of implantation sites, number of offspring at birth and sex ratio). No effect of treatment was found on viability, physical development, including vaginal opening and preputial separation of the penis, results of reflex and response tests or on external abnormalities. Anogenital distance (AGD) was statistically significantly decreased in the low- and mid-dose group in females of the F1 generation, but not in the high dose or in the F2 generation or in males. The decrease in F1 female AGD was up to 11%, statistically significant and based on reasonable numbers (n = 22–24) that accounted for the litter effect. A decreased female AGD may be adverse and could be an indication of developmental and/or endocrine consequences. However, the effect on AGD was not dose-dependent and no effects on fertility were observed.

The estrogenic activity of benzophenone and its metabolites, benzhydrol and 4-hydroxybenzophenone, were investigated in vivo by uterotrophic assay in juvenile female Sprague-Dawley (SD) rats (Nakagawa Y and Tayama K, 2001). Juvenile female rats (21-days-old) were given s.c. injections of benzophenone, its metabolites, and 17 beta-estradiol for 3 days. Administration of p-hydroxybenzophenone (100-400 mg/kg) elicited an increase in absolute and relative uterine weights in a dose-dependent manner and 17 beta-estradiol (10 micrograms/kg) increased uterine weight approximately fourfold relative to control. The uterine response caused by both compounds was accompanied by an increase in luminal epithelial height and stromal cells in the uterus and an increase in thickness of vaginal epithelial cell layers with cornification. In contrast, benzophenone and benzhydrol at a dose of 400 mg/kg affected neither uterine weight nor histological changes of the

uterus and vagina. These results indicate that p-hydroxybenzophenone, a metabolite of benzophenone, exhibits intrinsic xeno-estrogenic activity in the female reproductive tract.

The study was repeated by delivering benzophenone and its metabolites by gavage (100 or 400 mg/kg) once per day for 3 days to ovariectomized Sprague-Dawley (SD) rats (Nakagawa Y and Tayama K, 2002). The high dose of benzophenone elicited an approximately 1.9-fold increase in absolute and relative uterine weight while 17beta-estradiol (positive control) increased uterine weight approximately fivefold relative to the control. The uterine response caused by both compounds was accompanied by an increase in luminal epithelium height and stromal cell numbers in the uterus and an increase in the thickness of vaginal epithelium cell layers with cornification. At 24 h 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) micro mol/l, respectively, whereas in the serum of low-dosed rats these compounds were not detected. Based on these findings, the authors concluded that the pro-estrogenic compound benzophenone requires biotransformation to p-hydroxybenzophenone, a metabolite with intrinsic hormonal activity.

An additional two-generation reproductive toxicity studies were performed in rats which utilizing extra parameters to detect endocrine-disrupting activity, AGD included. Rats were given benzophenone via the diet at concentrations of 0, 100, 450 and 2,000 ppm feed (equal to 9, 40.5, and 180 mg/kg per day, using default conversion factors by EFSA Scientific Committee, 2012). According to the authors, no obvious effects on endocrine system and reproductive toxicological effects were detected in the F0 and F1 parents of F1 and F2 offspring (Yamasaki, 2005).

Mutagenicity

Benzophenone was not mutagenic in the standard Ames test using various strains of *Salmonella typhimurium* (Mortelmans et al., 1986) or in the *Escherichia coli* Pol A assay (Fluck et al., 1976). In addition, negative results were reported with benzophenone in the mouse lymphoma L5178Y/tk+/- cell test for induction of trifluorothymidine resistance (CCRIS, 1991). All three of these in vitro assays were performed with and without rodent liver S9 metabolic activation enzymes. Results of a recent investigation of the genotoxic potential of benzophenone showed no induction of DNA damage as measured by umu gene expression in *S. typhimurium* strain TA1535/pSK1002 in the absence or the presence of microsomes from rat, mouse, or human, however significant dose-related increases in umu gene expression were elicited in the presence of recombinant human cytochrome P450s in the same studies (Takemoto et al., 2002). In vivo, benzophenone did not increase the frequency of micronuclei in erythrocytes from bone marrow or from peripheral blood in mice after intraperitoneal injections at 200 to 500 mg/kg bw/day for 3 days or after dietary exposure at 200 to 4200 mg/kg bw/day for 14 weeks (NTP 2006). Benzophenone has been classified as non-genotoxic by several authoritative bodies (IARC; 2013; ECHA, 2016; Health Canada, 2018). Results of mutagenicity testing are provided in Table 5 (Appendix).

NTP (2006) has evaluated the umu gene expression findings:

“The positive results reported for benzophenone in the umu gene expression assay do not directly conflict with the negative results obtained in Salmonella gene mutation assays because the endpoints measured by the two assays differ, as do important aspects of the test protocols. Briefly, the umu assay indirectly detects DNA damage induced anywhere in the Salmonella genome by analyzing fluorescent signals produced by expression of the umu-beta-galactosidase gene complex carried in the pSK1002 plasmid (genes in the umu operon control SOS error-prone DNA repair which is expressed in response to induced damage). The Salmonella assay, in contrast, measures fixed damage induced specifically within defined regions of the histidine operon, resulting in heritable changes in the bacterial DNA directly observable as mutant colonies. Primary DNA damage, such as that detected in the umu assay, may or may not result in mutation. In addition to the endpoint differences, the activation systems contained different liver enzyme mixtures, and the human cytochrome preparations used in the umu assay had specific enzymatic cofactors added to the mixture to ensure the availability of a sufficient number of electrons for metabolic activities to proceed. The pretreatments used to induce rodent S9 liver enzymes in standard bacterial mutation assays may not induce the P450 2A6 and specific other cytochromes that were shown to be effective in transforming benzophenone into a DNA damaging agent in the umu assay.”

In a recent study, benzophenone was found to produce significantly longer tail moments in L5178Y mouse lymphoma cells using the COMET assay after 2 hours of exposure (Jeon, 2017). Significant DNA damage was observed at all benzophenone concentrations (18.0 to 72.1 µg/mL) in the -S9 treatment groups. In the +S9 treatment, BP induced significant DNA damage at concentrations of 25.0 and 50.0 µg/mL ($P < 0.05$).

A recent test using the umu assay found benzophenone had the highest concentration of the substituted benzophenone forms needed to double the response to that of the negative control (Zhao, 2013).

To address the potential for high concentrations of test compound to inhibit bacterial growth in the Ames assay, Wang (2018) tested 4 strains Ames strains at quantities of (0.05, 0.5, 5, 50, and 500 µg/plate) with and without the S9 fraction. In three strains, no effect of benzophenone was observed at any concentration. In the T102 strain, significant mutagenicity ratios (MR, 2x that of controls) were observed at 0.05 and 0.5 µg/plate without S9 but not at the higher concentrations. No significant MR were observed at any concentration with the S9 fraction. The authors suggested that the S9 fraction could lead to repair of DNA damage from benzophenone.

Interpretation of these recent studies is uncertain given the substantial findings that benzophenone is not genotoxic. Recent computational investigations show that reactions between photo-activated benzophenone and DNA are highly probable but the nature of DNA damage from this interaction unknown (Marazzi, 2016).

Endocrine Activity

Benzophenone had low affinity for the human ER receptor, did not activate ER-mediated gene transcription, did not activate progesterone-mediated gene transcription and had no proliferative effect on MCF—7 cells (human breast cell line). In animal studies, no estrogenic effects of benzophenone have been observed (see Table 6, Appendix). Several rodent studies did not observe endocrine effects from benzophenone, including a 2-generation reproductive study in which treatment had no effect on anogenital distance in F1 and F2 offspring, timing of sexual maturation in F1 offspring, weights and histopathological evaluation of testes, epididymis, prostates, seminal vesicles, ovaries and uterus in F1 parental animals, and levels of testosterone, FSH, LH and estradiol, estrous cyclicity and semen quality in F0 and F1 animals (add REFS). A recent study (Kerdivel, 2013) confirmed that benzophenone was not estrogenic in MCF-7 cells whereas 4-OH-BP was.

The metabolite of benzophenone, 4- OH-BP, has demonstrated estrogenic effects in in vitro assays and animal studies. See Tables 6 (animal assays, Appendix) and 7 (in vitro assay, Appendix) for results with benzophenone and 4-OH-BP.

Epidemiologic Studies

A limited number of epidemiologic studies have been conducted with benzophenone (BP), predominantly by one group (see Table 8, Appendix). These are population studies in which UV filters 1 (BP and 4-OH-BP) and 2 (all others) in the urine from women and urine and seminal fluid were compared with multiple reproduction and developmental endpoints. Only one association between 4-OH-BP, a metabolite of BP, was an endocrine effect (fecundability) marginally significant.

Health Assessments

There are no data available on the human health effects of inhalation exposure to benzophenone and only one authoritative body has formally recommended an occupational exposure limit for benzophenone. The hazards assessments that have been done are based on chronic and subchronic feeding studies. Given the lipophilicity of benzophenone ($K_{ow} = 3.2$), it is likely highly bioavailable in the respiratory tract and lungs.

Several bodies have conducted hazard assessments of benzophenone using the results from the rat feeding studies (Tables 3, 4).

Based on the NTP (2006) study, the European Food Safety Agency (2009, 2017) used the lower 95% confidence limits of the bench mark dose for a 10% effect (BMDL₁₀) value for non-cancer kidney effects, which was 3.1 mg/kg-bw/day. Scaling that dose to a 70 kg human using a $(BW_a/BW_h^{0.25})$ (EPA, 2011) yields a human BMDL₁₀ = 0.887 mg/kg-day. EFSA applied an interspecies uncertainty factor of 3 and intraspecies factor of 10 to give a human RfD of 0.03 mg/kg-day. Assuming 100 % absorption and a 70-kg human breathing 10 m³ in 8 hours converts the oral dose to an 8-hr inhalation concentration of 0.21 mg/m³.

Based on a subchronic study (Burdock, 1991), AIHA developed a WEEL for benzophenone based on a NOAEL taken from a subchronic feeding study in rats (0, 20, 100 or 500 mg/mg-day). As rationale, the authors noted the facts that benzophenone caused liver injury in two subchronic studies, had low

acute toxicology and was likely not genotoxic. To determine the WEEL, consideration was given to interspecies differences, differences in route of exposure, extrapolation from subchronic data and variability in worker susceptibility, resulting in a total uncertainty factor of 40.

Using the male rat kidney tumor data from the NTP (2006) study, Michigan DEQ calculated an inhalation unit risk factor using EPA benchmark dose software and the latest guidance provided by EPA (2012b). In Table 9, that unit risk factor has been adjusted for occupational exposure and 1/1000 risk. EFSA (2009) noted that strictly speaking, the p-value for the null model of the rat kidney tumor data (linear response not different from zero) did not support a dose-response trend ($p = 0.057$).

Table 9: Health assessments of benzophenone based on sub-chronic rat feeding studies (Table 3).

| Agency/Organization | End-point | Health Assessment |
|--------------------------------------|--|--|
| European Food Safety Authority, 2009 | Non-neoplastic kidney effects | <p>Rat dose (BMDL₁₀) scaled to human equivalent with body weight scaling ((BW_a/BW_h)^{0.25}):</p> <p>(BMDL₁₀HUMAN = 3.1 mg/kg x (0.47 kg/70 kg)^{0.25}. (EPA, 2011) = 0.887 mg/kg Rfd = 0.89 ÷ 3 ÷ 10 = 0.03 mg/kg</p> <p>Where 3 is UF_{interspecies} and 10 is UF_{intraspecies}</p> <p>Converted to 8–hr air, assuming 100% absorption and 10 m³:</p> <p style="text-align: center;">0.03 mg/kg x 70 kg/10m³ = 0.21 mg/m³</p> |
| AIHA – WEEL, 2003 | Increased liver and kidney weights; histopathology | <p>NOAEL = 20 mg/kg/day. To determine OEL, consideration was given to interspecies differences, differences in route of exposure, extrapolation from subchronic data and variability in worker susceptibility; total UF = 40, specific uncertainty values not reported.</p> <p style="text-align: center;">20 mg/kg ÷ 40 = 0.5 mg/m³</p> |

| Agency/Organization | End-point | Health Assessment |
|---------------------|------------------------|--|
| Michigan DEQ, 2015 | Male Rat kidney tumors | <p>Using EPA Benchmark Dose Software (2012a) a cancer slope factor for male rat kidney adenoma/carcinoma incidence was determined and converted to human equivalent with body weight scaling $(BWh/BWa)^{0.25}$. Assuming 100% inhalation absorption, the oral slope factor was adjusted to inhalation exposure ($20 \text{ m}^3/70 \text{ kg}$) to yield the integrated unit risk, the incremental 1 per million risk of lifetime exposure to benzophenone, $0.2 \text{ ug}/\text{m}^3$.*</p> <p>The IUR can be adjusted for worker exposure (8-hr day, 5 day week, 50 week year, 45 years working) and a 1/1000 cancer risk as follows:</p> $\begin{aligned} \text{Worker exposure} &= \text{Working lifetime exposure} / \text{lifetime exposure} \\ &= 45/70 \times 50/52 \times 5/7 \times 10/20 \\ &= 0.221 \end{aligned}$ $\begin{aligned} \text{PEL} &= \text{Excess working lifetime cancer risk} \\ &= \text{URL} \times \text{Worker exposure factors} \\ &= 0.001/(4.79 \times 10^{-6}) \times 0.221 \\ &= 9459 \text{ } \mu\text{g}/\text{m}^3 = \mathbf{0.95 \text{ mg}/\text{m}^3} \end{aligned}$ |

*Calculation from Michigan DEQ, 2015:

From Table 2, Michigan DEQ, 2015

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 $\mu\text{g}/\text{m}^3$ | Candidate IRSL $\mu\text{g}/\text{m}^3$ (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 |

Recommendation

A PEL of $0.25 \text{ mg}/\text{m}^3$ based on kidney effects is recommended for discussion. The key target endpoint for the human hazard assessment of benzophenone are kidney and liver effects. Non-neoplastic and neoplastic effects were observed in both these organs in chronic feeding studies in two species. Alpha-2-globulin has not been implicated in the kidney lesions observed in male rats so it is appropriate to use the male rat kidney data for hazard assessment. Liver hypertrophy has been attributed to p450 induction (see EFSA). Benzophenone has been shown to be non-genotoxic and not or weakly endocrine-active in numerous assays.

Benzophenone induced cancer on multiple sites in both rats and mice in chronic feeding studies. However, the mode of action of carcinogenicity of benzophenone in the oral studies is uncertain. Given the results of the NTP bioassay, mutagenicity assays (negative) and the evidence of effects on the endocrine system, IARC (2013) suspected that multiple mechanisms, such as the generation of reactive oxygen species and interference with endocrine system via multiple receptors, might be involved in the carcinogenicity of benzophenone. In addition, the pathogenesis of benzophenone-induced renal tubule cancer has not been determined by NTP (2006). While IARC (2013) considered that the short survival of high-dose male rats was attributable to the increased severity of chronic progressive nephropathy (CPN), it did not conclude that CPN was a mechanism for renal tumor development. IARC concluded that benzophenone is possibly carcinogenic to humans (2B).

Benzophenone has also been associated with endocrine effects in several *in vivo* studies. Benzophenone produced no endocrine effects in 2-generation chronic feeding studies (REFs). The likely toxic molecule is a metabolite of benzophenone, 4-OPH- benzophenone. A range of *in vitro* studies and QSAR predictions indicates that benzophenone itself does not bind and activate the estrogen receptors, whereas 4-OH BP does. (Schultz et al. (2000), Nishihara et al. 2000, Nakagawa et al., 2000; Yamasaki et al., 2002; Suzuki et al 2005; Hayashi et al., 2006; Kerdivel et al 2013).

A skin notation is recommended for benzophenone. Benzophenone is well-absorbed through skin and exposure assessments for it estimate significant uptake.

Usage Information

CERS data pending approval.

Measurement Information

OSHA Method: OSHA PV2130.

The detection limit of the overall procedure is 0.27 µg and the reliable quantitation limit is 0.89 µg. The equivalent air concentrations are 5.63 µg/m³ and 18.5 µg/m³ respectively based on the recommended sampling parameter of 240 min at 0.2L/min (48 L).

Based on this information, there are no anticipated concerns with analytical feasibility.

Recommended Workplace Controls and Feasibility Issues

The Division is seeking stakeholder input on these subjects.

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Appendix

Table 5: Mutagenicity Results for Benzophenone

| Assay | Study | Assay System | Experimental Conditions | Findings |
|--|--|---|---|--|
| Micronucleus assay in bone marrow | NTP 2006 | B6C3F1 male mice | IP: 00, 300, 400, 500 mg/kg bw (solvent: corn oil) | Negative |
| Micronucleus assay in peripheral blood polychromatic erythrocytes | NTP 2006 | B6C3F1 male and female mice | Oral (feed) 1,250, 2,500, 5,000, 10,000, 20,000 ppm | Negative |
| | Abramsson-Zetterberg and Svensson (2011) | Male CBA mice | IP: 500, 1,000, 2,000 mg/kg bw | Negative |
| | Abramsson-Zetterberg and Svensson (2011) | Male NMRI | 100, 250, 400, 600 mg/kg bw | Negative |
| Bacterial reverse Mutation (Ames) | Mortelmans et al. (1986) | S. Typhimurium TA97, TA98, TA100, TA1535 and TA1537 | 3–1,000 µg/plate | Negative |
| | CCRIS 2009 | S. Typhimurium TA97, TA98, TA100, TA1535 and TA1537 | 10-2000 µg/plate 3-333 µg/plate 10-1,000 µg/plate 1-166 µg/plate | Negative |
| | NTP, 2006 | S. Typhimurium TA98, TA100, TA1535 and TA1537 with and without activation | | Negative |
| | Wang 2018 | S. Typhimurium TA97, TA98, TA100, and TA102 | 0.05 – 500 µg/plate, S9- and S9+, 5 doses each, | TA97, 98 100 – negative all doses; TA102 positive at 0.05 and 5 –S9; all others negative |
| | CCRIS 2009 | L5178Y (tk+/-) mouse lymphoma cells | 33-90 µg/mL 35-145 µg/mL | Negative |

| | | | | |
|---|------------------------|-------------------------------------|--|--------------------------|
| Gene mutation in mammalian cells | Jeon 2007 | L5178Y (tk+/-) mouse lymphoma cells | 89 - 142.9 µg/mL 89 – 147.2 µg/mL | Negative |
| SOS/umu assay | Takemoto et al. (2002) | S. Typhimurium TA1535 | 0 – 1,000 µM | Positive(p450)/ negative |
| | Kotnik et al. (2016) | S. Typhimurium TA1535 | 7.8–1,000 µg/mL | positive |
| Comet Assay | Jeon 2017 | L5178Y mouse lymphoma cells | 18.0 - 72.1 µg/mL -S9 25.0 - 50.0 µg/mL +S9 | Positive Positive |

Table 6: In Vivo Studies of Endocrine Effects of Benzophenone and 4-Hydroxybenzophenone*

| Animal species | Administration method | Administration period | Dose | Results | References |
|-------------------------------------|---|---|--|---|-------------------------|
| Rat (SD, female) 6 rats/group | s.c. (Uterotrophic assay) (Ovariectomized rats, Ovariectomized at the age of 6 weeks) | BZP was administered for 7 days from the age of 8 weeks, and uterus was removed on the 8th day and weighed. | BZP 0, 5, 50, 500 mg/kg/day | Slight increase in uterine weight at 500 mg/kg/day. (estrogenic effect) | CERI, 2001b |
| | | | BZP 0, 5, 50, 500 mg/kg/day + 17 α -Ethinylestradiol 0.3 μ g/kg/day (s.c.) | Slight decrease in uterine weight at 50 mg/kg/day or above. (anti-estrogenic effect) | |
| Rat (SD, female) 6 rats/group | s.c. (Uterotrophic assay) | BZP was administered for 3 days from postnatal day 20, and the uterus was removed on the 4th day and weighed. | BZP 0, 2, 20, 200 mg/kg/day | No effect on uterine weight. | CERI, 2001a |
| Rat (SD, female) | s.c. (Uterotrophic assay) | BZP derivatives were administered for 3 days from postnatal day 21, and the uterus was removed 6 hr after the final dose and weighed. | 4-Hydroxy-BZP at 0, 100, 200 and 400 mg/kg/day | The uterine weight increased dose-dependently. (estrogenic effect) | Nakagawa & Tayama, 2001 |
| | | | Benzhydrol 400 mg/kg/day | No effect on uterine weight. | |
| Rat (SD, male) 6 rats/group | Oral gavage (Hershberger assay) (Castrated rats, castrated at the age of 6 weeks) | BZP was administered for 10 days from the age of 7 weeks, and male accessory reproductive organs were weighed on the 11th day. | BZP 0, 1, 10, 100 mg/kg/day | No effect on weights of male accessory reproductive organs. | CERI, 2001b |
| | | | BZP 0, 1, 10, 100 mg/kg/day + Testosterone propionate 0.4 mg/kg/day (s.c.) | No effect on weights of male accessory reproductive organs. | |

*Benzophenone is denoted as BZP and 4-hydroxybenzophenone as 4-Hydroxy-BZP in the table. Other chemicals are benzophenone derivatives not formed through metabolism. Estradiol, potent binder to the ER receptor is noted as E2.

Table 7: In Vitro Studies of Endocrine Effects of Benzophenone and 4-Hydroxybenzophenone*

| Item | Test methods and conditions | Results | Conclusion | References |
|------------------------|--|---|---|-------------------------|
| ER binding assay | Human ER binding assay (recombinant ER α ligand domain) | BZP: IC50 value: $>10^{-4}$ M (E2: 1.7×10^{-9} M) | BZP has no binding affinity for human ER. | CERI, 2001a |
| | | BZP derivatives (IC50 value) 4-Hydroxy-BZP: 1.3×10^{-5} M (E2: 1.4×10^{-9} M; RBA: 0.011%) 3-Hydroxy-BZP: 1.0×10^{-5} M (E2: 1.3×10^{-9} M; RBA: 0.013%) 4,4'-Dihydroxy-BZP: 7.3×10^{-6} M (E2: 1.2×10^{-9} M; RBA: 0.017%) 2,4-Dihydroxy-BZP: 8.9×10^{-6} M (E2: 1.2×10^{-9} M; RBA: 0.014%) 2,4,4'-Trihydroxy-BZP: 1.7×10^{-6} M (E2: 1.2×10^{-9} M; RBA: 0.074%) 2,3,4,4'-Tetrahydroxy-BZP: 4.3×10^{-6} M (E2: 1.1×10^{-9} M; RBA: 0.025%) 2,2',4,4'-Tetrahydroxy-BZP: 1.4×10^{-5} M (E2: 1.3×10^{-9} M; RBA: 0.093%) 4-Chloro-4'-hydroxy-BZP: 1.9×10^{-5} M (E2: 1.6×10^{-9} M; RBA: 0.0081%) 4-Fluoro-4'-hydroxy-BZP: 4.8×10^{-5} M (E2: 1.1×10^{-9} M); 2.7×10^{-5} M (E2: 1.1×10^{-9} M); RBA: 0.0031% 2,3,4-Trihydroxy-BZP: 1.8×10^{-5} M (E2: 1.6×10^{-9} M; RBA: 0.0088%) 4,4'-Dibromo-BZP: 1.7×10^{-5} M (E2: 1.4×10^{-9} M; RBA: 0.0082%) | BZP derivatives (4-hydroxy/3-hydroxy/4,4'-dihydroxy/2,4-dihydroxy/2,4,4'-trihydroxy/2,3,4,4'-tetrahydroxy/2,2',4,4'-tetrahydroxy/4-chloro-4'-hydroxy/4-fluoro-4'-hydroxy/2,3,4-trihydroxy/4,4'-dibromo derivatives of BZP) have binding affinity for ER (the binding affinities were 1/1,100 - 1/44,000 of that of E2). | |
| | | BZP IC50: $>5 \times 10^{-4}$ M | No effect | Nakagawa & Tayama, 2001 |
| | | 4-Hydroxy-BZP: 5×10^{-5} M | Binding affinity + | |
| Yeast two-hybrid assay | Cells: Yeast cells transfected with Gal4 DNA binding domain/human ER ligand binding domain genes, Gal4 activation domain/coactivator TIF2 genes and β -galactosidase reporter gene | REC10: $>3 \times 10^{-3}$ M (E2: 3×10^{-10} M) | BZP does not activate ER-mediated gene transcription. | Nishihara et al., 2000 |

*Benzophenone is denoted as BZP and 4-hydroxybenzophenone as 4-Hydroxy-BZP in the table. Other chemicals are benzophenone derivatives not formed through metabolism. Estradiol, potent binder to the ER receptor is noted as E2

Table 8: Epidemiological Studies**8.1. Urinary Concentrations of Benzophenone-type UV Filters in US Women and Their Association with Endometriosis**

| Rationale | Design | Findings | Discussion |
|---|--|--|---|
| The association of urinary concentrations of BP derivatives with an increase in the odds of a diagnosis of endometriosis was examined in 600 women who underwent laparoscopy/laparotomy (n = 473: operative cohort) or pelvic magnetic resonance imaging (n = 127: population cohort), during 2007-2009 | Urine samples were collected from 431 and 63 currently-menstruating women, aged 18-44 years, who were scheduled to undergo a diagnostic and/or therapeutic laparoscopy or laparotomy (referred to as “operative or surgical cohort”). Urine samples were collected from 131 currently-menstruating women who were matched to the operative cohort on age and residence (referred to as “population or unexposed cohort”). The intent of the population cohort was to identify women at risk for endometriosis (<i>i.e.</i> , currently menstruating) who did not seek medical care; this group served as a comparison cohort for the operative cohort and for the assessment of consistency of findings across cohorts. 4OH-BP was detected in 83.8% of the urine samples analyzed. | The strength of correlation between BP derivative concentrations was evaluated by simple regression analysis. The relation between BP derivative concentrations and odds of an incident endometriosis diagnosis was explored using multivariable logistic regression. Given the uncertain timing of endometriosis onset, we estimated the odds ratios (ORs) for diagnosis along with corresponding 95% confidence intervals (CIs) for each BP derivative, rather than estimating incident disease, <i>per se</i> . | The unadjusted and adjusted ORs were elevated for 2OH-4MeO-BP and 2,4OH-BP, particularly at the higher quartiles, but not for 4OH-BP. A significant trend was observed between 2,4OH-BP and the odds of an endometriosis diagnosis, but only in the operative cohort (OR = 1.19; 95% CI = 1.01, 1.41). A similar pattern was observed in the population cohort, but the CIs for all BP derivatives included one, denoting the absence of significance, possibly indicative of the limited number (<i>n</i> = 14) of women in the population cohort with endometriosis. CONCLUSION: No association between 4OH-BP and endometriosis. |

Odds of an endometriosis diagnosis by urinary concentrations of BP derivatives and cohort (ENDO Study)

| BP analyte (quarter ng/mL) | Operative cohort (n=473) | | Population cohort (n=127) | |
|--|---------------------------------|--------------------------------|----------------------------------|--------------------------------|
| | OR^c (95% CI) | OR^d (95% CI) | OR^c (95% CI) | OR^d (95% CI) |
| 4OH-BP | | | | |
| 1 st quartile (<0.082-0.17) | reference | reference | reference | reference |
| 2 nd quartile (0.18-0.35) | 0.87 (0.52, 1.45) | 0.92 (0.55, 1.54) | 1.08 (0.20, 5.85) | 1.51 (0.25, 9.20) |
| 3 rd quartile (0.36-0.71) | 1.02 (0.61, 1.71) | 1.03 (0.62, 1.73) | 1.24 (0.25, 6.06) | 2.20 (0.38, 12.7) |

| BP analyte | Operative cohort (n=473) | | Population cohort (n=127) | |
|---------------------------------------|--------------------------|--------------------------|---------------------------|--------------------------|
| | OR ^c (95% CI) | OR ^d (95% CI) | OR ^c (95% CI) | OR ^d (95% CI) |
| (quarter ng/mL) | | | | |
| 4 th quartile (0.71-22.40) | 0.84 (0.49, 1.42) | 0.87 (0.51, 1.48) | 1.16 (0.24, 5.66) | 1.69 (0.31, 9.21) |
| Trend test ^a | 0.97 (0.82, 1.14) | 0.97 (0.82, 1.15) | 1.06 (0.65, 1.73) | 1.19 (0.71, 1.98) |
| >Q3 versus <Q3 ^b | 0.87 (0.56, 1.36) | 0.89 (0.57, 1.38) | 1.05 (0.31, 3.58) | 1.12 (0.31, 4.01) |

^aTrend test assessed linear trends of BP derivatives across the four intervals defined by the 25th, 50th, and 75th percentiles.

^bWomen in the highest quartile for each BP derivative were compared with women in the combined first three quartiles.

^cOdds ratios from unadjusted logistic regressions

^dOdds ratios from multivariable logistic regressions adjusting for site (Utah, California) and hair color (red, blonde, brown/black)

8.2. Urinary Concentrations of Benzophenone-Type Ultraviolet Radiation Filters and Couples' Fecundity

| Rationale | Design | Findings | Discussion |
|---|--|---|--|
| 501 couples who were discontinuing use of contraceptives in order to become pregnant recruited for the Longitudinal Investigation of Fertility and the Environment (LIFE) Study. Couples provided urine specimens and completed daily journals until they either achieved pregnancy or had tried for 12 months. Multiple BP derivatives measured in urine including 4OH-BP. | Fecundability odds ratios (FORs) and 95% confidence intervals were estimated for each UV filter, modeling each partner's concentrations individually and then modeling both partners' concentrations. UV filter concentrations were dichotomized at the 75th percentile to assess more-exposed persons versus less-exposed persons relative to couple fecundity. FOR estimates the odds of becoming pregnant for partners/couples above the 75th exposure percentile relative to those | When FORs were estimated for each partner separately, 2 UV filters were significantly associated with FORs below 1, indicative of diminished fecundity or a longer time to pregnancy. Specifically, BP-2 was associated with an approximately 31% reduction in fecundity (FOR = 0.69, 95% confidence interval (CI): 0.50, 0.95), and 4-OH-BP was associated with a 26% reduction (FOR = 0.74, 95% CI: 0.54, 1.00). None of the UV filters measured in females were associated with fecundability, with the exception of BP-8, but only in the creatinine- and age-adjusted model (FOR = 1.34, 95% CI: 1.02, 1.78) | The strongest signal was for males' concentrations of BP-2, which reflected a consistent reduction in fecundability when partners' concentrations were modeled individually or jointly. In addition, when only males' 4-OH-BP concentrations were modeled, 4-OH-BP was negatively associated with fecundability. CONCLUSION: 4-OH-BP was associated with a 26% reduction (FOR = 0.74, 95% CI: 0.54, 1.00). |

| | | | |
|--|----------------------------|--|--|
| | below the 75th percentile. | | |
|--|----------------------------|--|--|

Table 3. Fecundability Odds Ratios According to Urinary Concentrations of Benzophenone-Type Ultraviolet Radiation Filters, by Partner Sex and Model, LIFE Study, 2005–2009^a

| UV Filter | Female Partners (n = 454) | | | | | | Male Partners (n = 439) | | | | | |
|-------------------------|-------------------------------|------------|-------------------------------|------------|-------------------------------|------------|-------------------------------|------------|-------------------------------|------------|-------------------------------|------------|
| | Unadjusted Model ^b | | Adjusted Model 1 ^c | | Adjusted Model 2 ^d | | Unadjusted Model ^b | | Adjusted Model 1 ^c | | Adjusted Model 2 ^d | |
| | FOR | 95% CI | FOR | 95% CI | FOR | 95% CI | FOR | 95% CI | FOR | 95% CI | FOR | 95% CI |
| BP-1 (2,4-OH-BP) | 1.06 | 0.80, 1.40 | 1.13 | 0.85, 1.49 | 1.02 | 0.76, 1.37 | 1.06 | 0.79, 1.42 | 1.06 | 0.79, 1.43 | 0.97 | 0.71, 1.32 |
| BP-2 (2,2',4,4'-OH-BP) | 0.77 | 0.57, 1.04 | 0.81 | 0.60, 1.10 | 0.82 | 0.60, 1.12 | 0.66 ^e | 0.48, 0.90 | 0.70 ^f | 0.51, 0.95 | 0.69 ^f | 0.50, 0.95 |
| BP-3 (2-OH-4-MeO-BP) | 1.11 | 0.83, 1.47 | 1.21 | 0.91, 1.62 | 1.12 | 0.83, 1.53 | 1.20 | 0.90, 1.59 | 1.20 | 0.90, 1.59 | 1.10 | 0.81, 1.49 |
| BP-8 (2,2'-OH-4-MeO-BP) | 1.25 | 0.95, 1.65 | 1.34 ^f | 1.02, 1.78 | 1.20 | 0.89, 1.63 | 1.39 ^f | 1.04, 1.86 | 1.43 ^f | 1.07, 1.91 | 1.34 | 0.98, 1.83 |
| 4-OH-BP | 0.83 | 0.61, 1.12 | 0.86 | 0.63, 1.16 | 0.77 | 0.56, 1.06 | 0.84 | 0.64, 1.11 | 0.85 | 0.65, 1.12 | 0.74 ^f | 0.54, 1.00 |

Abbreviations: CI, confidence interval; FOR, fecundability odds ratio; LIFE, Longitudinal Investigation of Fertility and the Environment; 4-OH-BP, 4-hydroxybenzophenone; 2,4-OH-BP, 2,4-dihydroxybenzophenone; 2,2',4,4'-OH-BP, 2,2',4,4'-tetrahydroxybenzophenone; 2-OH-4-MeO-BP, 2-hydroxy-4-methoxybenzophenone; 2,2'-OH-4-MeO-BP, 2,2'-dihydroxy-4-methoxybenzophenone; UV, ultraviolet.

^a Separate models were fitted for each UV filter and partner. Concentrations of UV filters were dichotomized at the 75th percentile, with the group corresponding to lower values serving as the referent. All models accounted for left-truncation or time off contraception.

^b Adjusted for each partner's UV filter concentration (ng/mL; dichotomized) and urinary creatinine concentration (mg/dL; continuous).

^c Adjusted for each partner's UV filter concentration (ng/mL; dichotomized), urinary creatinine concentration (mg/dL; continuous), and age (years; continuous).

^d Adjusted for each partner's UV filter concentration (ng/mL; dichotomized), urinary creatinine concentration (mg/dL; continuous), age (years; continuous), body mass index (categorical; see Table 1), smoking status as defined by serum cotinine level (active exposure, passive exposure, or no exposure; see Table 1), season (winter, spring, summer, or fall), and research site (Michigan or Texas).

^e P < 0.01 (ttest).

^f P < 0.05.

8.3. Bisphenol A, benzophenone-type ultraviolet filters, and phthalates in relation to uterine leiomyoma

| Rationale | Design | Findings | Discussion |
|--|--|--|---|
| Utilized the Endometriosis, Natural history, Diagnosis, and Outcomes (ENDO) Study in which all women underwent either a diagnostic and/or therapeutic laparoscopy or laparotomy allowing for the detection of uterine fibroids. 5 benzophenone-type ultraviolet (UV) filter metabolites were measured 2OH-4MeO-BP, 2,4OH-BP, 2,2',4,4'OH-BP, and 4OH-BP in spot urine samples. | Women with and without fibroids were compared by various characteristics using the Chi-square statistics or nonparametric Wilcoxon rank sum test for categorical and continuous, respectively. Geometric mean urinary concentrations and accompanying 95% confidence intervals (CIs) for all chemicals were compared by fibroid status using the Wilcoxon test for assessing significance. Logistic regression was used to estimate the odds of fibroids along with 95% CIs. Separate models were run for each chemical generating both unadjusted and adjusted odds ratios (OR) and | Significantly higher geometric mean creatinine-corrected concentrations of BPA, 2,4OH-BP, and 2OH-4MeO-BP were observed in women with than without fibroids [BPA: 2.09 µg/g vs. 1.46 µg/g p=0.004; 2,4OH-BP: 11.10 µg/g vs. 6.71 µg/g p=0.01; 2OH-4MeO-BP: 11.31 µg/g vs. 6.10 µg/g p=0.01]. | CONCLUSION: No association between urinary 4OH-BP levels and presence of fibroids |

| | | | |
|--|---|--|--|
| | corresponding 95% confidence interval (CI). | | |
|--|---|--|--|

Geometric mean (95% confidence interval) comparison of chemicals by fibroid status (n=473)

| Chemicals (µg/g) | Fibroids (n=99) Geometric Mean (95% CI) | No Fibroids (n=374) Geometric Mean (95% CI) | LOQ value (ng/mL) | % above LOQ/L OD | % of negative & zero values |
|---------------------------------|---|---|-------------------|------------------|-----------------------------|
| Benzophenone derivatives | | | | | |
| 2,4OH-BP | 11.1 (7.1, 17.4) | 6.7 (5.4, 8.3) ^a | 0.08 | 99 | 0 |
| 4OH-BP | 0.2 (0.2, 0.3) | 0.3 (0.2, 0.3) | 0.08 | 83 | 0 |
| 2OH-4MeO-BP | 11.3 (6.4, 20.1) | 6.1 (4.6, 8.0) ^a | 0.28 | 91 | 0 |

^a p<0.05

^b p<0.005

NOTE: All chemicals were creatinine (mg/dL) standardized using the following formula: $100 \times \text{chemical (ng/ml)} / \text{creatinine (mg/dL)}$. Nonparametric Wilcoxon rank sum test was used to compare chemical concentrations between those with and without fibroids.

8.4. Urinary Concentrations of Benzophenone-Type Ultra Violet Light Filters and Semen Quality

| Rationale | Design | Findings | Discussion |
|---|---|--|---|
| 413 men provided semen and urine samples, 2005–2009. Five UV filters were quantified in urine: BP-1, BP-2, BP-3, and 4-OH-BP. | Using linear regression, beta coefficients (β) and 95% CIs for each chemical dichotomized at the 75 th percentile and Box-Cox transformed semen endpoint were estimated, after adjusting for age, BMI, cotinine, season, and site. | BP-2 associated with diminished sperm concentration ($\beta=-0.74$; CI $-1.41, -0.08$), straight ($\beta=-4.57$; 95% CI $-8.95, -0.18$) and linear movement ($\beta=-3.15$; CI $-6.01, -0.30$), more immature ($\beta=0.38$; CI $0.15, 0.62$) sperm, and a decreased percentage of other tail abnormalities ($\beta=-0.16$; CI $-0.31, -0.01$). No associations were observed for BP-1, BP-3 or 4OH-BP. | CONCLUSION: No association between 4OH-BP and semen quality |

| Semen Quality Endpoint | BP-1 | | BP-2 | | BP-3 | | BP-8 | | 4OH-BP | |
|---|---------|-------------|--------------|---------------------|---------|-------------|--------------|---------------------|---------|-------------|
| | β | 95% CI | β | 95% CI | β | 95% CI | β | 95% CI | β | 95% CI |
| <i>General Characteristics</i> | | | | | | | | | | |
| Volume (mL) | 0.13 | -0.04, 0.29 | 0.04 | -0.13, 0.22 | 0.12 | -0.04, 0.28 | 0.09 | -0.08, 0.26 | 0.04 | -0.13, 0.21 |
| Sperm concentration ($\times 10^6$ /mL) | -0.05 | -0.69, 0.59 | -0.74 | -1.41, -0.08 | 0.11 | -0.53, 0.74 | -0.03 | -0.68, 0.61 | -0.49 | -1.16, 0.18 |
| Total sperm count ($\times 10^6$ /ejaculate) | 0.41 | -0.55, 1.36 | -0.91 | -1.91, 0.09 | 0.59 | -0.36, 1.55 | 0.22 | -0.75, 1.18 | -0.40 | -1.40, 0.61 |
| Hypo-osmotic swollen (%) | 0.22 | -2.05, 2.50 | -1.75 | -4.14, 0.63 | -0.13 | -2.40, 2.14 | -2.57 | -4.86, -0.29 | -0.34 | -2.73, 2.05 |
| Straw distance (mm) | 0.01 | -0.13, 0.15 | 0.02 | -0.13, 0.17 | 0.00 | -0.13, 0.14 | -0.06 | -0.20, 0.08 | -0.01 | -0.15, 0.14 |
| <i>Sperm Motility (24 hour)</i> | | | | | | | | | | |
| Average path velocity ($\mu\text{m}/\text{sec}$) | 0.72 | -2.05, 3.49 | -0.62 | -3.53, 2.30 | 0.33 | -2.44, 3.10 | -0.63 | -3.43, 2.16 | 1.29 | -1.63, 4.20 |
| Straight line velocity ($\mu\text{m}/\text{sec}$) | 0.12 | -2.15, 2.40 | -0.71 | -3.10, 1.69 | -0.37 | -2.64, 1.91 | -1.00 | -3.30, 1.30 | 0.78 | -1.61, 3.18 |
| Curvilinear velocity ($\mu\text{m}/\text{sec}$) | 1.92 | -2.91, 6.75 | -0.27 | -5.35, 4.80 | 1.10 | -3.73, 5.93 | -1.18 | -6.06, 3.70 | 3.83 | -1.24, 8.90 |
| Amplitude head displacement (μm) | 0.01 | -0.29, 0.32 | 0.03 | -0.29, 0.35 | 0.04 | 1.29, -1.63 | -0.02 | -0.33, 0.29 | 0.29 | -0.03, 0.61 |
| Beat cross frequency (Hz) | 1.01 | -0.52, 2.54 | -0.47 | -2.08, 1.14 | 0.67 | -0.86, 2.20 | -0.98 | -2.52, 0.56 | 0.50 | -1.11, 2.11 |
| Straightness (%) | 0.30 | -3.89, 4.50 | -4.57 | -8.95, -0.18 | -0.19 | 1.29, -1.63 | -3.51 | -7.72, 0.71 | -0.89 | -5.29, 3.52 |
| Linearity (%) | 0.05 | -2.68, 2.78 | -3.15 | -6.01, -0.30 | -0.19 | -2.92, 2.54 | -2.25 | -4.99, 0.49 | -1.56 | -4.42, 1.30 |
| Percent motility (%) | -0.23 | -0.87, 0.40 | -0.31 | -0.98, 0.36 | -0.36 | -1.00, 0.27 | -0.37 | -1.01, 0.27 | -0.30 | -0.97, 0.37 |
| <i>Sperm Head Measurements</i> | | | | | | | | | | |
| Length (μm) | -0.01 | -0.02, 0.01 | 0.01 | -0.01, 0.02 | -0.01 | -0.02, 0.00 | 0.00 | -0.01, 0.02 | 0.00 | -0.02, 0.01 |
| Area (μm^2) | -0.12 | -0.32, 0.08 | -0.07 | -0.28, 0.14 | -0.13 | -0.33, 0.07 | -0.04 | -0.24, 0.16 | -0.06 | -0.27, 0.15 |
| Width (μm) | -0.02 | -0.06, 0.02 | -0.04 | -0.08, 0.00 | -0.01 | -0.05, 0.03 | -0.03 | -0.08, 0.01 | 0.00 | -0.05, 0.04 |
| Elongation factor (%) | -0.02 | -1.27, 1.23 | -1.29 | -2.60, 0.01 | 0.41 | -0.84, 1.66 | -1.13 | -2.39, 0.14 | 0.00 | -1.32, 1.32 |
| Perimeter (μm) | -0.07 | -0.19, 0.05 | 0.02 | -0.10, 0.15 | -0.08 | -0.20, 0.03 | 0.01 | -0.10, 0.13 | -0.04 | -0.16, 0.08 |
| Acrosome area of head (%) | 0.59 | -0.53, 1.70 | -0.82 | -1.99, 0.35 | 0.88 | -0.24, 1.99 | 1.14 | 0.01, 2.26 | -0.01 | -1.19, 1.17 |
| <i>Morphology</i> | | | | | | | | | | |
| Strict criteria (%) ^a | 0.59 | -0.47, 1.64 | -0.85 | -1.99, 0.30 | 0.40 | -0.66, 1.45 | -0.08 | -1.16, 1.00 | 0.72 | -0.41, 1.86 |

| Semen Quality Endpoint | BP-1 | | BP-2 | | BP-3 | | BP-8 | | 4OH-BP | |
|--|---------|-------------|---------|--------------|---------|-------------|---------|-------------|---------|-------------|
| | β | 95% CI | β | 95% CI | β | 95% CI | β | 95% CI | β | 95% CI |
| Traditional normal (%) ^a | 1.92 | -1.18, 5.02 | -2.64 | -6.00, 0.71 | 1.46 | -1.63, 4.56 | -0.14 | -3.31, 3.03 | 1.35 | -1.98, 4.68 |
| Amorphous (%) | -0.13 | -0.37, 0.12 | 0.23 | -0.04, 0.50 | -0.15 | -0.40, 0.09 | -0.06 | -0.32, 0.19 | 0.02 | -0.25, 0.28 |
| Round (%) | -0.02 | -0.15, 0.11 | 0.09 | -0.05, 0.23 | 0.02 | -0.11, 0.15 | -0.01 | -0.15, 0.12 | -0.04 | -0.18, 0.10 |
| Pyriiform (%) | 0.03 | -0.17, 0.22 | 0.11 | -0.10, 0.32 | -0.02 | -0.22, 0.17 | 0.15 | -0.05, 0.35 | -0.01 | -0.23, 0.20 |
| Bicephalic (%) | -0.04 | -0.17, 0.10 | 0.12 | -0.03, 0.27 | -0.04 | -0.17, 0.10 | 0.00 | -0.14, 0.13 | -0.03 | -0.18, 0.11 |
| Taper (%) | -0.06 | -0.22, 0.11 | 0.09 | -0.09, 0.26 | -0.09 | -0.25, 0.07 | 0.05 | -0.11, 0.22 | -0.01 | -0.18, 0.17 |
| Megalo head (%) | 0.02 | -0.10, 0.14 | 0.11 | -0.02, 0.24 | -0.02 | -0.14, 0.10 | 0.03 | -0.09, 0.15 | 0.07 | -0.06, 0.19 |
| Micro head (%) | -0.02 | -0.13, 0.09 | 0.00 | -0.12, 0.12 | -0.03 | -0.14, 0.08 | 0.05 | -0.06, 0.17 | -0.04 | -0.16, 0.08 |
| Neck/mid-piece abnormalities (%) | -0.05 | -0.14, 0.04 | 0.05 | -0.04, 0.15 | -0.02 | -0.11, 0.06 | 0.00 | -0.09, 0.09 | -0.05 | -0.15, 0.05 |
| Coiled tail (%) | 0.05 | -0.06, 0.15 | -0.01 | -0.12, 0.11 | 0.02 | -0.09, 0.13 | -0.01 | -0.12, 0.10 | -0.02 | -0.13, 0.10 |
| Other tail abnormalities (%) | -0.11 | -0.24, 0.03 | -0.16 | -0.31, -0.01 | -0.08 | -0.22, 0.06 | -0.03 | -0.17, 0.11 | -0.07 | -0.21, 0.08 |
| Cytoplasmic droplet (%) | 0.09 | -0.17, 0.35 | 0.09 | -0.19, 0.37 | 0.07 | -0.19, 0.33 | -0.03 | -0.29, 0.24 | 0.10 | -0.18, 0.38 |
| Immature sperm (#) | 0.08 | -0.14, 0.30 | 0.38 | 0.15, 0.62 | 0.05 | -0.17, 0.27 | 0.01 | -0.21, 0.24 | 0.16 | -0.08, 0.40 |
| <i>Sperm Chromatin Stability Assay</i> | | | | | | | | | | |
| DNA fragmentation index (%) | -0.02 | -0.15, 0.11 | -0.01 | -0.14, 0.13 | 0.00 | -0.13, 0.12 | 0.09 | -0.04, 0.22 | -0.04 | -0.18, 0.09 |
| High DNA stainability (%) | -0.08 | -0.21, 0.06 | 0.13 | -0.01, 0.27 | -0.09 | -0.22, 0.04 | -0.09 | -0.23, 0.04 | 0.01 | -0.13, 0.15 |

8.5. Preconception seminal plasma concentrations of endocrine disrupting chemicals in relation to semen quality parameters among male partners planning for pregnancy

| Rationale | Design | Findings | Discussion |
|--|---|--|---|
| 5 UV filters (BP-1, BP-2, BP-3, BP-8, and 4-OH-BP) were quantified in seminal plasma from 339 male partners who participated in a prospective pregnancy study. Semen samples underwent next day analysis using a standardized protocol for the quantification of 35 endpoints. | Linear mixed-effects models of EDCs that were log transformed and rescaled by their standard deviations or dichotomized at the 75th percentile for each exposure and outcomes with covariate adjustment were performed. EDCs in seminal plasma were also assessed relative to clinical reference values of semen quality endpoints using logistic regression or generalized estimating equations. | BP-2 was associated with a 5% reduction in straightness and a 3% reduction in linearity, when measured in both urine and seminal plasma. No association between semen quality and 4OH-BP | CONCLUSION: No association between 4OH-BP and semen quality |

Odds Ratios (95% CI) for seminal plasma chemicals and semen quality parameters ^a.

| | <u>Volume</u> | | <u>Sperm Concentration</u> | | <u>Total Count</u> | | <u>Sperm Viability</u> | | <u>WHO Normal</u> | | <u>Strict Normal</u> | | <u>DNA Fragmentation</u> | |
|---------------------|----------------------------------|----------------|--|----------------|---|----------------|---------------------------------|----------------|---------------------------------|----------------|---------------------------------|----------------|---------------------------------|----------------|
| | (mL) ^c OR (95% CI) | FDR p-value | (x 10 ⁶ /m) ^c OR (95% CI) | FDR p-value | (per ejaculate) ^c OR (95% CI) | FDR p-value | (%) ^c OR (95% CI) | FDR p-value | (%) ^b OR (95% CI) | FDR p-value | (%) ^b OR (95% CI) | FDR p-value | (%) ^c OR (95% CI) | FDR p-value |
| Bisphenols | | | | | | | | | | | | | | |
| BPA | 0.71 (0.51, 0.99) | 0.33 | 0.97 (0.73, 1.27) | 0.95 | 0.75 (0.61, 0.91) | 0.07 | 0.91 (0.75, 1.10) | 0.67 | 0.94 (0.74, 1.19) | 0.94 | 6.29 (1.12, 35.5) | 0.76 | 0.85 (0.46, 1.57) | 0.80 |
| BPF | 0.77 (0.53, 1.10) | 0.47 | 1.32 (0.83, 2.09) | 0.63 | 1.23 (0.83, 1.84) | 0.67 | 1.01 (0.81, 1.25) | 0.99 | 0.89 (0.70, 1.13) | 0.80 | 2.60 (0.78, 8.68) | 0.76 | 0.99 (0.63, 1.56) | 0.99 |
| BPS | 0.80 (0.60, 1.07) | 0.47 | 1.16 (0.73, 1.83) | 0.78 | 1.03 (0.61, 1.75) | 0.99 | 1.11 (0.89, 1.38) | 0.67 | 0.77 (0.60, 0.98) | 0.76 | 1.85 (0.78, 4.35) | 0.76 | 0.89 (0.59, 1.34) | 0.79 |
| UV Filters | | | | | | | | | | | | | | |
| BP – 1 | 0.63 (0.24, 1.65) | 0.60 | 0.70 (0.28, 1.75) | 0.55 | 1.01 (0.41, 2.51) | 0.81 | 1.08 (0.63, 1.86) | 0.97 | 1.19 (0.70, 2.03) | 0.88 | 3.21 (0.39, 26.1) | 0.69 | 0.63 (0.25, 1.56) | 0.55 |
| BP – 2 | 2.89 (1.29, 6.49) | 0.37 | 1.12 (0.49, 2.54) | 0.97 | 1.19 (0.50, 2.82) | 0.97 | 1.62 (0.98, 2.66) | 0.37 | 0.95 (0.55, 1.64) | 0.95 | – ^a | – | 1.28 (0.42, 3.88) | 0.84 |
| BP – 3 | 0.55 (0.21, 1.48) | 0.55 | 0.71 (0.29, 1.76) | 0.55 | 0.88 (0.35, 2.24) | 0.72 | 1.13 (0.66, 1.94) | 0.91 | 1.23 (0.72, 2.10) | 0.88 | 3.27 (0.40, 26.6) | 0.69 | 0.63 (0.26, 1.56) | 0.55 |
| BP – g ^f | | | | | | | | | | | | | | |
| 4-OH-BP | 1.36 (0.59, 3.15) | 0.72 | 1.53 (0.67, 3.49) | 0.60 | 1.96 (0.84, 4.58) | 0.55 | 1.77 (1.05, 2.99) | 0.37 | 1.60 (0.92, 2.78) | 0.69 | 3.66 (0.45, 29.8) | 0.69 | 1.26 (0.42, 3.74) | 0.91 |

8.6. Maternal urinary benzophenones and infant birth size: Identifying critical windows of exposure

| Rationale | Design | Findings | Discussion |
|---|--|---|---|
| <p>BP-1, BP-3 and 4-OH-BP were measured in maternal urine from first, second, and third trimester (847). Birth weight and length were measured at time of delivery. Information on maternal age, parity, weight at delivery, birth date, infant sex, and gestational age at delivery were collected. Information on maternal demographic characteristics (age, educational levels, and ethnicity), socioeconomic factors (annual family income) and lifestyle (consumption of tobacco and alcohol) was collected.</p> | <p>Birth weight and length were continuous variables in the generalized estimating equation (GEE) models with a linear function. In the final multiple linear regression model, the following potential confounders were included: gestational age, pregnancy weight gain (kg), prepregnancy body mass index, parity, maternal education, passive smoking, paternal height (cm), and infant sex (except in models stratified by sex). In a stratified analysis by infant sex, the interaction term between infant sex and exposure to BPs was added into the model to assess the potential modification effects of infant sex.</p> | <p>No significant association was found between maternal urinary levels of BPs with birth weight in all newborns, and also in boys after stratification by infant sex. In girls, each log unit increase in maternal urinary BP-1 and BP-3 concentrations in the 3rd trimester were associated with decreases in birth weight by 27.99 g (95% CI: -50.66, -5.31), and 19.75 g (95% CI: -37.31, -2.19), respectively.</p> | <p>CONCLUSION: No association between 4OH-BP urinary levels and birth weight and length.</p> |

Table 3Regression coefficients [β (95% CI)] for associations of ln-transformed SG-adjusted concentrations of benzophenones (ng/mL) in three trimesters with birth weight.

| Birth Weight | All (n = 847) | Boys (n = 445) | Girls (n = 402) | p^c -value |
|------------------|-----------------------------|-----------------------------|-----------------------------|--------------|
| | Adjusted β^a (95% CI) | Adjusted β^b (95% CI) | Adjusted β^b (95% CI) | |
| lnBP-1 | | | | |
| 1st trimester | -13.19 (-26.58, 0.20) | -16.82 (-36.99, 3.35) | -10.88 (-28.71, 6.95) | 0.64 |
| 2nd trimester | -6.77 (-21.44, 7.90) | -3.34 (-23.94, 17.26) | -10.15 (-31.00, 10.70) | 0.72 |
| 3rd trimester | -11.37 (-26.46, 3.71) | 1.40 (-18.82, 21.62) | -27.99 (-50.66, -5.31)* | 0.07 |
| p^d -value | 0.81 | 0.43 | 0.43 | |
| lnBP-3 | | | | |
| 1st trimester | -7.79 (-19.23, 3.66) | -8.77 (-25.45, 7.91) | -7.37 (-23.06, 8.33) | 0.91 |
| 2nd trimester | -4.98 (-16.86, 6.91) | -5.92 (-22.52, 10.68) | -4.84 (-21.86, 12.18) | 0.78 |
| 3rd trimester | -9.48 (-21.48, 2.52) | -2.18 (-18.64, 14.28) | -19.75 (-37.31, -2.19)* | 0.17 |
| p^d -value | 0.87 | 0.86 | 0.52 | |
| ln4-OH-BP | | | | |
| 1st trimester | -13.97 (-32.94, 5.00) | -9.90 (-37.05, 17.24) | -17.84 (-44.32, 8.64) | 0.68 |
| 2nd trimester | -17.85 (-37.14, 1.44) | -12.70 (-39.72, 14.33) | -22.22 (-49.74, 5.30) | 0.71 |
| 3rd trimester | -14.14 (-33.18, 4.89) | -2.76 (-29.59, 24.07) | -26.16 (-53.12, 0.79) | 0.31 |
| p^d -value | 0.95 | 0.87 | 0.91 | |
| lnBP sum | | | | |
| 1st trimester | -7.19 (-24.80, 10.42) | -12.58 (-39.03, 13.86) | -7.25 (-30.85, 16.35) | 0.90 |
| 2nd trimester | -5.70 (-34.31, 22.91) | -11.43 (-61.77, 38.91) | -4.23 (-38.76, 30.29) | 0.90 |
| 3rd trimester | 14.95 (-21.00, 50.90) | 46.95 (-30.93, 124.83) | 5.98 (-34.16, 46.11) | 0.37 |
| p^d -value | 0.55 | 0.36 | 0.86 | |

Table 4Regression coefficients [β (95% CI)] for associations of ln-transformed SG-adjusted concentrations of benzophenones (ng/mL) in three trimesters with birth length.

| Birth length | All (n = 847) | Boys (n = 445) | Girls (n = 402) | p^c -value |
|------------------|-----------------------------|-----------------------------|-----------------------------|--------------|
| | Adjusted β^a (95% CI) | Adjusted β^b (95% CI) | Adjusted β^b (95% CI) | |
| lnBP-1 | | | | |
| 1st trimester | -0.06 (-0.11, -0.01)* | -0.10 (-0.17, -0.03)** | -0.03 (-0.09, 0.04) | 0.11 |
| 2nd trimester | -0.01 (-0.07, 0.04) | -0.02 (-0.10, 0.06) | 0.00 (-0.07, 0.08) | 0.67 |
| 3rd trimester | -0.04 (-0.10, 0.01) | 0.00 (-0.08, 0.07) | -0.08 (-0.17, 0.00)* | 0.20 |
| p^d -value | 0.42 | 0.13 | 0.38 | |
| lnBP-3 | | | | |
| 1st trimester | -0.03 (-0.08, 0.01) | -0.05 (-0.11, 0.01) | -0.02 (-0.07, 0.04) | 0.35 |
| 2nd trimester | -0.02 (-0.06, 0.02) | -0.01 (-0.07, 0.05) | -0.03 (-0.09, 0.03) | 0.76 |
| 3rd trimester | -0.03 (-0.08, 0.01) | 0.02 (-0.05, 0.08) | -0.08 (-0.15, -0.02)* | 0.04 |
| p^d -value | 0.93 | 0.29 | 0.50 | |
| ln4-OH-BP | | | | |
| 1st trimester | -0.08 (-0.15, -0.01)* | -0.09 (-0.19, 0.01) | -0.05 (-0.15, 0.05) | 0.51 |
| 2nd trimester | -0.06 (-0.13, 0.01) | -0.09 (-0.19, 0.01) | -0.03 (-0.13, 0.07) | 0.50 |
| 3rd trimester | -0.05 (-0.12, 0.02) | -0.02 (-0.12, 0.08) | -0.07 (-0.16, 0.03) | 0.59 |
| p^d -value | 0.83 | 0.53 | 0.85 | |
| lnBP sum | | | | |
| 1st trimester | 0.02 (-0.04, 0.09) | 0.02 (-0.08, 0.12) | 0.02 (-0.07, 0.10) | 0.84 |
| 2nd trimester | 0.03 (-0.07, 0.14) | 0.01 (-0.17, 0.20) | 0.03 (-0.09, 0.16) | 0.96 |
| 3rd trimester | 0.08 (-0.06, 0.21) | 0.13 (-0.16, 0.41) | 0.07 (-0.08, 0.21) | 0.75 |
| p^d -value | 0.74 | 0.76 | 0.84 | |

Abbreviation: CI, confidence interval.

* p -value < 0.05, ** p -value < 0.01.^a Adjusted for pre-pregnancy body mass index, pregnancy weight gain, gestational age, parity, maternal education, paternal height, passive smoking, and infant sex.^b Adjusted as model A expect for infant sex.^c p values for interaction between ln-transformed specific gravity adjusted urinary benzophenones concentrations and infant sex.^d Score test of homogeneity of estimates in three trimesters.