

BENZOPHENONE

1. Exposure Data

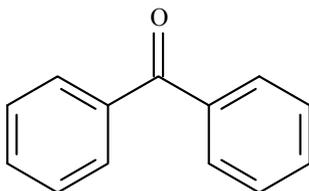
1.1 Chemical and physical data

From [IUCLID \(2000\)](#), [IPCS-CEC \(2005\)](#), [NTP \(2006\)](#), [GESTIS \(2010\)](#), and [Repertoire Toxicologique \(2010\)](#), unless otherwise specified

1.1.1 Nomenclature

Chem. Abstr. Services Reg. No.: 119-61-9
Chem. Abstr. Name: Benzene, benzoyl-; benzoylbenzene, phenyl ketone; diphenylketone; diphenyl ketone; diphenylmethanone; ketone, diphenyl; methanone, diphenyl-; α -oxodiphenylmethane; α -oxoditane
RTECS No.: DI9950000
EINECS No.: 204-337-6

1.1.2 Structural and molecular formulae and relative molecular mass



$C_{13}H_{10}O$

Relative molecular mass: 182.22

1.1.3 Chemical and physical properties of the pure substance

Description: Colourless crystalline solid with geranium- or rose-like odour

Boiling-point: 305.4 °C

Melting-point: 48.5 °C (α form) and 26 °C (β form)

Density: 1.111 at 18 °C

Vapour pressure: 1.93×10^{-3} mm Hg at 25 °C

Refractive index: 1.6077 at 19 °C

Solubility: Practically insoluble in water, but soluble in organic solvents such as alcohol, acetone, ether, acetic acid, chloroform and benzene.

Flash-point: > 110 °C

Stability: Decomposes on heating to produce toxic gases; reacts with strong oxidants.

Octanol/water partition coefficient: $\log K_{ow}$, 3.18 ([LOGKOW, 2010](#))

Henry's law constant: 1.9×10^{-6} atm.m³/mol at 25 °C

1.1.4 Technical products and impurities

No data were available to the Working Group.

1.1.5 Analysis

(a) Air

One method has been reported by the Occupational Safety and Health Administration of the United States of America (OSHA PV2130) regarding the possibility of measuring benzophenone in air using a tube filled with chromosorb 106 (100/50-mg sections, 60/80 mesh) at a recommended maximum volume of 48 L and a maximum flow rate of 0.2 L/min. An analytical solvent (99:1 carbon disulfide:*N,N*-dimethylformamide) is used to desorb the chromosorb, and the substance is then measured by gas chromatography with flame ionization detection.

(b) Food

Analysis of benzophenone in breakfast cereals has been reported using ultrasonic extraction in combination with gas chromatography-tandem mass spectrometry ([Van Hoeck *et al.*, 2010](#)).

1.2 Production and use

1.2.1 Production

A 66% yield of benzophenone can be obtained by Friedel-Crafts acylation of benzoyl chloride with an excess of benzene in the presence of anhydrous aluminium chloride ([NTP, 2006](#)). Benzophenone is also produced by atmospheric oxidation of diphenylmethane in the presence of metal catalysts, such as copper naphthenate ([HSDB, 2010](#)).

According to the US Environmental Protection Agency, it was classified in 2003 as a high volume chemical, with an annual production exceeding 1 million pounds [453 000 kg], in the USA ([NTP, 2006](#)).

1.2.2 Use

Benzophenone is used as a flavour ingredient, a fragrance enhancer, a perfume fixative and an additive for plastics, coatings and adhesive formulations; it is also used in the manufacture of insecticides, agricultural chemicals, hypnotic drugs, antihistamines and other pharmaceuticals ([HSDB, 2010](#)). Benzophenone is used as an ultraviolet (UV)-curing agent in sunglasses, and to prevent UV light from damaging scents and colours in products such as perfumes and soaps. Moreover, it can be added to plastic packaging as a UV blocker, which allows manufacturers to package their products in clear glass or plastic rather than opaque or dark packaging. It is also used in laundry and household cleaning products ([NTP, 2006](#); [HSDB, 2010](#)).

Benzophenone is widely used as a photoinitiator for inks and varnishes that are cured with UV light. In addition to being a drying catalyst, benzophenone is an excellent wetting agent for pigments; it can also be used in printing to improve the rheological properties and increase the flow of inks by acting as a reactive solvent.

[No data were available to the Working Group on the use of benzophenone in sunscreens, whereas data were available on the use of one of its derivatives (3-benzophenone, 2-hydroxy-4-methoxybenzophenone) in such products.]

1.3 Occurrence

1.3.1 Natural occurrence

Benzophenone has been reported to occur naturally in food (see Section 1.3.3).

1.3.2 Occupational exposure

Benzophenone can be absorbed into the body by inhalation, through the skin and by ingestion ([IPCS-CEC, 2005](#)).

Industrial sectors that entail risks of occupational exposure are painting (paints,

varnishes and lacquers), the manufacture of plastic composites and the manufacture and use of glues and adhesives. The National Institute for Occupational Safety and Health conducted the National Occupational Exposure Survey in 1981–1983, which estimated that, among the 4490 establishments surveyed in the USA (522 industry types, employing approximately 1 800 000 workers), 41 516 workers (18 162 women) were potentially exposed to benzophenone (NIOSH, 1990).

1.3.3 Occurrence in food and dietary exposure

Dietary sources of exposure to benzophenone include its natural occurrence in food, its presence as a contaminant in drinking-water, its migration from food packaging and its addition to food as a flavouring.

(a) Food

Benzophenone was reported to occur naturally in wine grapes (*Vitis vinifera* L.) at concentrations of 0.08–0.13 ppm [mg/kg] (TNO, 2010). According to the Council of Europe (2000), it mainly occurs in muscat grapes. Benzophenone has been detected quantitatively in passiflora species at 0.045 ppm (TNO, 2010) and qualitatively in black tea, cherimoya (*Annona cherimola*), mountain papaya (*Carica pubescens*) and soursop (*Annona muricata* L.) (Burdock, 2005). Concentrations in mountain papaya (*C. pubescens* and *C. candamarcensis*) were reported to be lower than 0.01 ppm (TNO, 2010).

Based on its concentration in muscat grapes, the Working Group estimated that consumption of 200 g grapes would result in exposure to approximately 20 µg benzophenone, i.e. 0.3 µg/kg body weight (bw) for a 60-kg adult.

(b) Drinking-water

The data on benzophenone in drinking-water are limited. Levels of 8.8 ppb [µg/L] were found in tap-water in Japan (Shinohara *et al.*, 1981) and

0.26 µg/L in finished drinking-water in a water filtration plant in the USA in 2001–02 (Loraine & Pettigrove, 2006, see Section 1.3.4).

To assess exposure to contaminants through drinking-water, the WHO uses a default consumption value of 2 L of drinking-water per capita per day for a typical adult of 60-kg bw (WHO, 2008), based on the assumption that total water consumption is 3 L per capita per day, including water present in food, which represents a conservative estimate (WHO, 2003). However, such a default assumption is not appropriate for all populations and climates. Reference hydration values under average conditions are 0.75 L in infants (5 kg), but, for physically active persons in areas with higher temperatures, could reach 4.5 L for men, women and children, 4.8 L for pregnant women and 5.5 L for lactating women (WHO, 2003).

The available data on concentrations of benzophenone in drinking-water were used by the Working Group to assess dietary exposure in adults and infants (60-kg and 5-kg bw, respectively), assuming a consumption of 2 and 0.75 L of drinking-water, respectively, i.e. 33 and 150 mL/kg bw, respectively. The infant scenario (in mL/kg bw) would correspond to a consumption of 9 L of drinking-water per day in a 60-kg adult and would therefore encompass any possible scenario of physically active persons in high-temperature areas. Hence, the estimated dietary exposure to benzophenone through the drinking-water of a standard 60-kg adult would range from 0.52 to 17.6 µg per day, i.e. 9–290 ng/kg bw per day, and that of a 5-kg infant would range from 0.2 to 6.6 µg per day, i.e. 40–1320 ng/kg bw per day.

(c) Migration from food packaging

The main source of exposure to benzophenone through food packaging is related to its wide use as photo-initiator in UV-cured inks on the external face of paperboard packaging. Benzophenone is neither totally exhausted during the printing process nor removed thereafter, and

is nor irreversibly bound into the print film layer (Koivikko *et al.*, 2010). It may thus migrate to food from paperboard, either by direct contact or through the vapour phase. Substances present on the external face of the packaging may contaminate the internal face when the carton is rolled and compressed, which is a common practice in the food packaging industry, and thus contaminate food through direct contact. Benzophenone may also contaminate food through the vapour phase, even from the secondary packaging. Internal plastic bags that are used as a barrier against moisture are not always effective (EFSA, 2009). Benzophenone is known to migrate easily through polypropylene film, whereas aluminium and multilayer materials inhibit migration efficiently (Nerín & Asensio, 2007; Pastorelli *et al.*, 2008).

Under low-temperature conditions (-20 °C), benzophenone migrates from cartonboard to food during frozen storage, even when there is no direct contact between the packaging and the food or when the packaging is polyethylene-coated (Johns *et al.*, 2000). Moreover, the most commonly used raw material for paperboard is recycled, and the product therefore often contains photo-initiators, including benzophenone. Recycled board is commonly used in direct contact with dry foodstuffs, such as flour and pasta, but also with fast-food items, i.e. foodstuffs with a short duration of contact, such as pizzas. Normally, a functional barrier, e.g. plastic or aluminium foil, is used between fatty or aqueous foodstuffs and the recycled material to avoid direct contact.

Analytical data are available on the concentrations of benzophenone in food packagings and in foods. In particular, in a comprehensive survey performed by the United Kingdom Food Standards Agency (UK FSA, 2006), benzophenone was detected in four of 115 samples of foodstuff packaged in printed plastic (maximum concentration, 0.15 mg/kg), in 60/296 samples packaged directly or indirectly in printed paper

or board that contained 0.05–3.3 mg benzophenone/dm² at a concentration of 0.035–4.5 mg/kg (mean concentration, 0.9 mg/kg) and in one of 54 foodstuffs to which a printed sticky label had been attached (at 0.029 mg/kg). In this survey, a high percentage of products tested positive for benzophenone among the categories of frozen foods (18/35), ‘jelly’ (3/5) and ‘savoury snacks’ (15/40). A lower percentage of products tested positive in the categories of ‘sweets, chocolate biscuits and crisps’ (5/35), ‘bakery products’ (8/35) and ‘cereals’ (4/25). Only one ‘ready meal’ of 20 and none of 10 ‘desserts’ tested positive.

According to the United Kingdom Food Standards Agency (UK FSA, 2006), potential dietary exposure to benzophenone in high-level consumers is 1.2–1.5 µg/kg bw for adults. These estimates were calculated by combining a high level of consumption of foods that may contain benzophenone (449 g/day, the 97.5th percentile in the United Kingdom national survey of adults) with two average levels of its occurrence therein (160 and 200 µg/kg), depending on different assumptions of the values below the limit of quantification (45 µg/kg), for a 60-kg bw adult.

More recent but limited data on benzophenone concentrations in food products are available in other countries.

Samples of milk packaged in cartons on the market in the People’s Republic of China were tested: skimmed milk, whole milk and partially skimmed milk. Benzophenone was detected in the packaging of all products at a concentration of 0.94–1.37 µg/dm², and in five of six of the milk products. Higher levels were found in milk with a higher fat content and ranged from 2.84 to 18.35 µg/kg (Shen *et al.*, 2009).

The migration of benzophenone into five selected dry foods (cake, bread, cereals, rice and pasta) sampled in a supermarket in Spain was assessed by Rodríguez-Bernaldo de Quirós *et al.* (2009). The highest concentration of benzophenone was found in cake (12 mg/kg). Migration levels were positively correlated with both

porosity and fat content. These results correlated well with those reported by [Anderson & Castle \(2003\)](#), who analysed 71 food samples selected at random from a total of 143 items packaged in printed cartonboard, in which benzophenone had been detected. The highest value (7.3 mg/kg) was found in a high-fat chocolate packaged in direct contact with cartonboard.

In a study by [Sanches-Silva et al. \(2008\)](#), samples of 36 commercial beverages (fruit and vegetable juices, wine and soft drinks) were collected in Italy, Portugal and Spain in 2005 and 2006, all of which were packaged in multi-material multilayer boxes or aluminium cans. Benzophenone was detected in four samples of packaging (one under the limit of quantification of 1.7 µg/dm² and three ranging from 3.6 to 12.3 µg/dm²), and samples of the beverages contained therein were analysed. None of the extracts yielded positive results. However, according to the authors, although fruit juices contain low amounts of fat, photo-initiators can migrate and be adsorbed by juice fibres (fibre content, 0.2%) and thus contaminate the beverage.

In a study conducted by [Koivikko et al. \(2010\)](#) in the European Union (EU), samples of printed board used for secondary packaging were collected from supermarkets, together with the food contained therein ($n = 22$), and some were acquired from industrial production lines before the introduction of foodstuffs ($n = 24$). In addition, samples were taken of recycled paperboard collected from a supplier to evaluate the background level of benzophenone and other derivatives therein ($n = 19$). The most abundant photo-initiator found in the non-recycled products was benzophenone, which was detected in 61% of samples. Traces of the compound were also found in 42% of the samples of recycled unprinted board. The content of benzophenone in these samples varied from 0.57 to 3.99 mg/m².

Benzophenone migrated into 95% ethanol from recycled paperboard used for contact

with food in Japan, but not from virgin paper. Migration ranged from 1.0 to 18.9 ng/mL in eight of the 21 samples of recycled paperboard collected ([Ozaki et al., 2006](#)).

In 2009, high levels of 4-methylbenzophenone (another photo-initiator) detected in some breakfast cereal products (chocolate crunch muesli) were notified under the EU Rapid Alert System for Food and Feed (RASFF) ([European Commission, 2009](#)). Further analysis performed by the producer demonstrated high concentrations of this substance and up to 4210 µg/kg benzophenone in these products ([CS AFSCA Belgium, 2009](#)).

(d) Addition to foods as a flavouring

In the USA, the average reported levels of use of benzophenone as an additive range from 0.57 ppm [mg/kg] in non-alcoholic beverages to 1.57 ppm in baked goods, and maximum reported levels range from 1.28 ppm in non-alcoholic beverages to 3.27 ppm in frozen dairy products. Other reported uses are in soft candy, gelatins and puddings ([Burdock, 2005](#)).

Maximum levels reported by the Council of Europe are 0.5 mg/kg in beverages and 2 mg/kg in foods in general, with no exception ([Council of Europe, 2000](#)). Benzophenone is listed in the EU register of chemically defined flavourings. In the European Food Safety Authority (EFSA) Flavouring Group Evaluation 69 ([EFSA, 2008](#)), dietary exposure to benzophenone in the EU, based on poundage data provided by industry, was estimated to be 23 µg per capita per day, assuming that consumers represent 10% of the population. On the same basis, dietary exposure is estimated to be 11 µg per capita per day in the USA ([EFSA, 2008](#)).

As a flavouring of threshold of toxicological concern class III, evaluated by the EFSA on the basis of a Joint FAO/WHO Expert Committee on Food Additives evaluation, refined, surveyed levels of additive use were provided by industry to the European Commission ([IOFI-DG SANCO,](#)

2008). The single portion exposure technique was developed by the Joint FAO/WHO Expert Committee on Food Additives to estimate dietary exposure from the consumption of one standard portion per day of flavoured food or beverages containing the flavouring substance at its average level of use (Leclercq *et al.*, 2009). Using this technique, the Working Group calculated that estimated exposure to benzophenone is 6 µg per person per day when applied to IOFI-DG SANCO (2008) data, 40 µg per person per day when applied to data from the Council of Europe (2000) and 170 µg per person per day when applied to data from the USA reported by Burdock (2005).

1.3.4 Environmental occurrence

Benzophenone is harmful to aquatic organisms (IPCS-CEC, 2005). Benzophenones in general have the environmentally critical properties of high lipophilicity and persistence, and are known to have adverse effects on the reproduction and hormonal functions of fish (Parks, 2009). According to Brooks *et al.* (2009), benzophenone is persistent, bioaccumulative and toxic (PBT).

Because of its high octanol:water partition coefficient and its insolubility in water, benzophenone partitions in soil and sediment (US EPA, 1984, cited by NTP, 2006), and its adsorption to soil is proportional to the organic content therein (OHMTADS, 1991, cited by NTP, 2006).

(a) Water and sediments

Benzophenone is among the pharmaceuticals and personal care products that are known to occur in drinking-water and in reclaimed wastewater when water sources are impacted by sewage treatment plant effluent (Loraine & Pettigrove, 2006). The removal of these compounds during wastewater-treatment processes is not fully effective, and effluent-dominated streams represent 'worse-case scenarios' for studying personal care

products and other organic wastewater contaminants. In these streams, even compounds with relatively short environmental half-lives, such as benzophenone, may act as 'pseudo-persistent' compounds. Due to their continuous introduction from wastewater-treatment plants, these compounds are continuously released into the environment. As a result, aquatic organisms are exposed over their entire life cycle (Pedrouzo *et al.*, 2010).

Another route by which benzophenone enters the aquatic environment is from municipal solid-waste landfill leachates. In a study by Pitarch *et al.* (2010), benzophenone was qualitatively identified in wastewater samples from the municipal solid-waste treatment plant at Reciplasa (Castellón province, Spain) between March 2007 and February 2009. Samples of water were collected before and after reverse osmosis treatment, which is performed before the release of water into the environment. Benzophenone was detected in 38% of treated samples and in 55% of raw leachates. In a study by Trzcinski and Stuckey (2010), submerged anaerobic membrane bioreactors were fed a simulated feedstock of the organic fraction of municipal solid waste, and benzophenone was found among contaminants in the permeate of the leachate.

In a study by Yoon *et al.* (2010) of surface waters from sampling sites on the river and in effluent-dominated creeks along the Han River (Seoul, Republic of Korea), benzophenone was detected (limit of detection, 50 ng/L) in two of four river samples (mean, 52 ng/L; maximum, 59 ng/L) and in all four effluent-dominated creek samples (mean, 102 ng/L; maximum, 130 ng/L) as a result of wastewater outfall. Benzophenone was detected in surface water at Ozark Plateau of northeastern Oklahoma (USA) at a site downstream from the outfall of a municipal wastewater-treatment plant and in a hydrologically linked cave (Bidwell *et al.*, 2010). It was present in wastewater effluent from the main sewer of the city of Zagreb (Croatia), which received no

treatment at the time of the survey and comprised a mixture of effluent from domestic and industrial sources ([Grung et al., 2007](#)).

Benzophenone was detected qualitatively in water from the Baltic Sea ([Ehrhardt et al., 1982](#)) and from Hamilton harbour, Bermuda ([Ehrhardt, 1987](#)), and was determined in two water samples from the Tama river in Japan at concentrations of 21.0 and 22.8 ng/L ([Kawaguchi et al., 2006](#)). It has been detected at concentrations of < 2.6–1040 ng/L in water samples from Venice lagoon and San Francisco estuary ([Oros et al., 2003](#), [Pojana et al., 2004](#); [Pojana et al., 2007](#)) and of 14–200 µg/kg in sediment samples ([Burkhardt et al., 2005](#); [Pojana et al., 2007](#)).

Benzophenone was detected in all 11 samples of bluegill fish collected from a regional effluent-dominated stream, i.e. about 650 m downstream from the effluent discharge of the Pecan Creek Water Reclamation Plant, in Denton County, TX, USA, at a mean concentration of 57 ng/g wet weight (standard deviation, 18 ng/g) and a range of 37–90 ng/g. The mean concentration in three samples of bluegill fish in Clear Creek (Denton County, TX, USA), a stream that experiences limited, if any, anthropogenic influence, was 24 ng/g ([Mottaleb et al., 2009](#)). A survey of water, sediment and biota (Mediterranean mussel, *Mytilus galloprovincialis*) in the Venice lagoon, a highly urbanized coastal water ecosystem that receives both industrial and municipal wastewater effluents, detected concentrations of benzophenone in lagoon sediments of 14–110 µg/kg ([Pojana et al., 2007](#)).

Benzophenone was detected by gas chromatography–mass spectrometry at a level of 8.8 ppb [µg/L] in tap-water from the Kitakyushu Municipal Institute in Japan ([Shinohara et al., 1981](#)). A survey of raw and treated drinking-water from four water filtration plants in San Diego County (CA, USA) conducted in 2001–02 showed large seasonal variations in benzophenone concentrations, with higher levels in the summer than in the winter, probably because

sunscreens are used more frequently during the summer months ([Loraine & Pettigrove, 2006](#)). Benzophenone was detected in one of 15 samples of finished drinking-water at a concentration of 0.26 µg/L, and in four of six samples of reclaimed wastewater at a concentration of 0.99 µg/L (range, 0.56–1.35 µg/L).

Benzophenone has been used as a model hydrophobic contaminant ([Brooks et al., 2009](#)). Due to their hydrophobic nature, PBT contaminants move out of the water phase and become associated with sediments. Animals that reside in or on these sediments are therefore at risk of bioaccumulating PBT compounds, and acting as vectors in their transfer to predators that may otherwise have limited direct contact with contaminated sediments. Predator species accumulate benzophenone from their prey, and exposure to narcotic organic contaminants, such as benzophenone, results in hypoactivity which may alter their ability to capture such animals successfully ([Brooks et al., 2009](#)).

Benzophenone was identified in surface sediment samples from the Havel and Spree Rivers (Germany), which are characterized by high inputs of anthropogenic contaminants into their eutrophic to hypertrophic riverine system with very slow flowing conditions. In the sedimentary records from 1979/80 up to 1995, benzophenone was detected and quantified in 10 out of 11 samples at concentrations ranging from 0.5 to 4 ng/g dry matter ([Ricking et al., 2003](#)).

(b) Air

Benzophenone was identified qualitatively in the atmosphere of a 45-year-old spruce forest located in North Rhine-Westfalia (Germany) in 1988 at a height of 1 m, where severe forest damage had been observed ([Helmig et al., 1989](#)). [Leary et al. \(1987\)](#) found that benzophenone was a component of emissions from a standard residential oil burner. Although benzophenone has been identified in the atmosphere, it is difficult to determine whether its presence is due to its being

a direct product of combustion or a secondary product of atmospheric degradation ([Helmig et al., 1989](#)).

Within an indoor-air monitoring survey conducted by the Japanese Ministry of Environment, benzophenone was detected in 67/68 samples analysed ([The Japanese Ministry of Environment, 2006](#)). Human exposure through inhalation should therefore be taken into account.

[The Working Group noted that there is no consensus in relation to the potential for bioaccumulation of benzophenone in the environment, nor for its persistence or pseudo-persistence.]

1.3.5 Other occurrence

Because of its use as an additive in fragrances, cosmetics, toiletries, pharmaceuticals, insecticides, and laundry and household cleaning products, exposure to benzophenone through dermal contact may be significant. The percutaneous absorption of benzophenone was determined *in vivo* in monkeys, and was approximately 70% of the dose applied to occluded skin within 24 hours. Under unoccluded conditions, skin penetration was reduced to 44%, presumably because of evaporation from the site of application ([Bronaugh et al., 1990](#)).

Many dentures are commonly prepared through a polymerization reaction that uses benzoyl peroxide as the initiator, of which benzophenone is a decomposition product that was found to be eluted in artificial saliva from four commercial soft denture liners (two plasticized acrylates and two silicone elastomers) ([Brożek et al., 2008](#)).

1.3.6 Total human exposure

Benzophenone ingested by humans is excreted in the urine as metabolites, such as benzhydrol ([Kawaguchi et al., 2009](#)), and the measurement of its derivatives in urine may therefore provide

an indication of overall human exposure to benzophenone. In a study conducted by [Ito et al. \(2009\)](#) in 14 healthy volunteers, benzophenone derivatives were detected in all urine samples. The concentration of benzhydrol ranged from 0.27 to 10.0 ng/mL, but the parent compound was not detected in any sample.

1.4 Regulations and guidelines

The current American Industrial Hygiene Association workplace environmental exposure level for benzophenone is 0.5 mg/m³ ([AIHA, 2009](#)).

The EU Standing Committee for the Food Chain and Animal Health endorsed a limit of 0.6 mg/kg for the sum of benzophenone and 4-methylbenzophenone ([European Commission, 2009](#)). In its conclusions, the Committee stated that the European Printing Ink Association, as well as the European Carton Board Manufacturers, advised their members that printing inks containing 4-methylbenzophenone and benzophenone are not suitable for printing of food packaging unless a functional barrier is present that blocks their transfer into food and also via the gas phase. Examples of functional barriers are aluminium, poly(ethylene terephthalate)/silicon oxide or an equivalent layer.

According to the EU Directive 2002/72/EC, benzophenone may be used in the EU as an additive in plastics materials, with a specific migration limit of 0.6 mg/kg ([European Commission, 2002](#)).

Benzophenone has been listed by the Council of Europe in category B (flavouring substances for which further information is required before the Committee of Experts is able to offer a firm opinion on their safety in use; these substances can be used provisionally in foodstuff) ([Council of Europe, 2000](#)).

The United Kingdom authorities have so far judged benzophenone as a 'class B volatile

organic compound' within the context of integrated pollution control ([IUCLID, 2000](#)).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

3.1 Oral administration

The results of carcinogenicity studies of oral administration of benzophenone are summarized in [Table 3.1](#).

3.1.1 Mouse

In a 2-year carcinogenicity study, groups of 50 male and 50 female B6C3F₁ mice, 8 weeks of age, were fed diets containing 0, 312, 625 or 1250 ppm benzophenone (> 99.5% pure; equivalent to average daily doses of approximately 40, 80 or 160 and 35, 70 or 150 mg/kg bw for males and females, respectively) for 105 weeks. Feed consumption of exposed males and females was similar to that of controls, but 1250-ppm females weighed 14% less than controls at the end of the study. A positive trend in the incidence of hepatocellular adenoma was observed in males; the incidence in the 625- and 1250-ppm groups was significantly greater than that in controls and exceeded the historical control ranges (12–30%) for feed studies. Hepatoblastomas were also observed in treated males, and, although the incidence in the 1250-ppm group (3/50, 6%) was not statistically significant, it exceeded the historical control range for feed studies (0–2%). The incidence of hepatocellular adenoma in 625- and 1250-ppm female mice was increased, but the difference from controls was not significant. A positive trend in the incidence of histiocytic sarcoma of the liver, lung, ovary, uterus, spleen,

adrenal gland, kidney, urinary bladder and multiple lymph nodes was observed in female mice; the incidence in the 625-ppm group was significantly increased, and that in the 625- and 1250-ppm groups exceeded the historical control range for feed studies (0–2%) ([NTP, 2006](#); [Rhodes *et al.*, 2007](#)). [The Working Group noted that hepatoblastomas and histiocytic sarcomas are rare neoplasms in mice.]

3.1.2 Rat

In a 2-year carcinogenicity study, groups of 50 male and 50 female F344/N rats, 6 weeks of age, were fed diets containing 0, 312, 625 or 1250 ppm benzophenone (> 99.5% pure; equivalent to average daily doses of approximately 15, 30 or 60 and 15, 30 and 65 mg/kg bw for males and females, respectively) for 105 weeks. Feed consumption of 1250-ppm males was lower than that of controls after week 70, and that of 1250-ppm females was generally lower than that of controls throughout the study. Survival of 1250-ppm males was significantly shorter than that of control group, which was attributed to the increased severity of chronic progressive nephropathy in the kidney. In the standard (single sections) and extended (step-sections) evaluations of the kidney, the incidence of renal tubule adenoma was increased in male rats exposed to 625 or 1250 ppm, and the combined incidence (single and step-sections) of renal tubule adenoma in males was also increased in these groups; the incidence in the 1250-ppm group was significantly greater than that in controls. A renal tubule carcinoma and a transitional epithelium carcinoma of the renal pelvis also occurred in 625-ppm males. Male rats exposed to 312 or 625 ppm had a significantly increased incidence of mononuclear-cell leukaemia, whereas the incidence in 1250-ppm males was slightly decreased compared with controls. This incidence and that in all groups of treated females exceeded the range for historical controls from feed studies (30–68% for males,

Table 3.1 Carcinogenicity (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence and/or multiplicity of tumours (%)	Significance	Comments
Rat, F344 (M, F) (contd)		Kidney (transitional epithelial carcinoma of the renal pelvis): M-0/50, 0/50, 0/50, 1/50 (2%) (M) Haematopoietic (mononuclear-cell leukaemia): M ^g -27/50 (54%), 41/50 (82%), 39/50 (78%), 24/50 (48%) F ^h -19/50 (38%), 25/50 (50%), 30/50 (60%), 29/50 (58%) All organs (histiocytic sarcoma): F ^l -0/50, 0/50, 1/50 (2%), 2/50 (4%)	P = 0.003 (low-dose M) P = 0.005 (mid-dose M) P = 0.048 (mid-dose F)	
Mouse, Swiss (F) 120 wk Stenbäck & Shubik (1974)	0% (vehicle), 5%, 25% or 50% in acetone Dermal application twice/wk for 120 wk 50 animals/group	Skin (squamous-cell papilloma): 2/50 (4%), 2/50 (4%), 0/50, 0/50 Skin (squamous-cell carcinoma): 0/50, 0/50, 1/50 (2%), 0/50 Lung (adenomas): 9/50 (18%), 3/50 (6%), 3/50 (6%), 6/50 (12%) Liver (haemangioma): 2/50 (4%), 1/50 (2%), 1/50 (2%), 2/50 (4%) Haematopoietic (lymphoma): 12/50 (24%), 15/50 (30%), 11/50 (22%), 6/50 (12%) Haematopoietic (thymoma): 0/50, 1/50 (2%), 1/50 (2%), 0/50	NS	Squamous-cell papillomas in the 5% group occurred at the site of application; the squamous-cell carcinoma in the 25% group occurred on the lip; papillomas in the control occurred on the tail and ear; purity not specified.

^a Historical incidence (mean ± SD) for 2-year feed studies in mice: 90/460 (20.0 ± 7.1%), range 12–30%

^b Historical incidence (mean ± SD) for 2-year feed studies in mice: 40/457 (9.6 ± 2.4%), range 6–12%

^c Historical incidence (mean ± SD) for 2-year feed studies in mice: 1/460 (0.2 ± 0.6%), range 0–2%

^d Historical incidence (mean ± SD) for 2-year feed studies in mice: 2/459 (0.3 ± 0.8%), range 0–2%

^e Historical incidence (mean ± SD) for 2-year feed studies in rats: 1/459 (0.3 ± 0.8%), range 0–2%

^f Historical incidence (mean ± SD) for 2-year feed studies in rats: 1/460 (0.1 ± 0.4%), range 0–1%

^g Historical incidence (mean ± SD) for 2-year feed studies in rats: 231/460 (49.1 ± 11.9%), range 30–68%

^h Historical incidence (mean ± SD) for 2-year feed studies in rats: 112/460 (24.6 ± 9.5%), range 12–38%

ⁱ Historical incidence for 2-year feed studies in rats: 0/460

F, female; M, male; NS, not significant; SD, standard deviation; wk, week or weeks

12–38% for females). A low incidence of histiocytic sarcoma occurred in both 625- and 1250-ppm female rats (1/50 and 2/50, respectively). Histiocytic sarcomas have not been observed in historical controls in feed studies and in only 1/1209 historical controls in studies by all routes of administration during the time these studies were conducted ([NTP, 2006](#); [Rhodes *et al.*, 2007](#)).

3.2 Dermal application

3.2.1 Mouse

Groups of 50 female Swiss mice received dermal applications of 0, 5, 25 or 50% benzophenone [purity unspecified] dissolved in acetone twice a week for 120 weeks. Dermal application of benzophenone was not carcinogenic in the skin of mice ([Stenbäck & Shubik, 1974](#)).

4. Other Relevant Data

4.1 Absorption and metabolism

4.1.1 Humans

No data were available to the Working Group.

4.1.2 Experimental systems

After dermal application of [¹⁴C]benzophenone, approximately 70% was absorbed in rhesus monkeys within 24 hours ([Bronaugh *et al.*, 1990](#)). Benzophenone was rapidly absorbed from the gastrointestinal tract of Sprague-Dawley rats that were administered a single dose (100 mg/kg bw) by gavage in corn oil ([Jeon *et al.*, 2008](#)).

The metabolism of benzophenone in rabbits was originally shown to involve reduction of the keto group to produce benzhydrol, which was excreted in the urine as a glucuronide conjugate ([Robinson, 1958](#)). In a subsequent study, 4-hydroxybenzophenone was isolated from the urine of Sprague-Dawley rats that had been

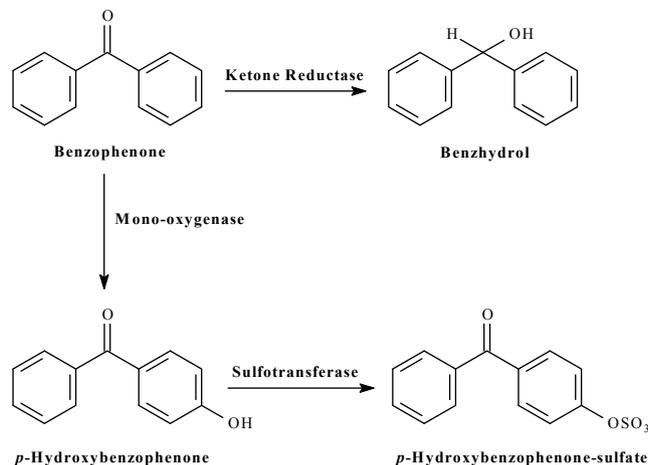
administered benzophenone in corn oil by gavage ([Stocklinski *et al.*, 1980](#)), and accounted for about 1% of the administered dose. It was isolated after treatment of the urine samples with a β -glucuronidase/aryl sulfatase preparation. A schema for the metabolism of benzophenone is shown in Fig. 4.1.

Twenty-four hour plasma time courses for benzophenone, benzhydrol and 4-hydroxybenzophenone were determined in Sprague-Dawley rats administered benzophenone by gavage in corn oil ([Jeon *et al.*, 2008](#)). 4-Hydroxybenzophenone, a product of aromatic hydroxylation, was identified after hydrolysis of the isolated metabolite with sulfatase. No dihydroxybenzophenone metabolites were identified in this study. Peak levels of benzophenone and its metabolites were reached approximately 4 hours after dosing, and the elimination half-life of the parent compound was approximately 19 hours. In toxicokinetic studies, the plasma elimination half-life of benzophenone in F344 rats was approximately 4 hours after intravenous injection and 8 hours after administration by gavage in corn oil; the plasma elimination half-life in B6C3F₁ mice was approximately 1 hour after intravenous injection and 1.5 hours after gavage in corn oil ([NTP, 2006](#)).

Benzophenone was metabolized to 4-hydroxybenzophenone, its sulfate conjugate, and benzhydrol in isolated F344 rat hepatocytes. Pretreatment of the hepatocyte suspension with 2,6-dichloro-4-nitrophenol, a sulfotransferase inhibitor, resulted in increased concentrations of free 4-hydroxybenzophenone ([Nakagawa *et al.*, 2000](#)).

Exposure of an aqueous solution of benzophenone to UV or sunlight irradiation produced two-ring hydroxylated derivatives — 3-hydroxybenzophenone and 4-hydroxybenzophenone — with concomitant generation of hydrogen peroxide, and the formation of 4-hydroxybenzophenone by UV irradiation was enhanced by the addition of hydrogen peroxide. The authors

Fig. 4.1 Proposed metabolism of benzophenone



Adapted from [Nakagawa & Tayama \(2001\)](#)

suggested that benzophenone might act as a photosensitizer that generates a reactive oxygen species which can cause aromatic ring hydroxylation ([Hayashi et al., 2006](#)).

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

Benzophenone was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535 or TA1537 in the presence or absence of metabolic activation systems. It did not increase the frequency of micronucleated polychromatic erythrocytes in samples of bone marrow obtained from male B6C3F₁ mice administered three intraperitoneal injections of benzophenone (200 to 500 mg/kg bw), or the frequency of micronucleated normochromatic erythrocytes in the peripheral blood of male or female B6C3F₁ mice administered benzophenone (1250 to 20 000 ppm) in the diet (estimated daily dose range, 200–4200 mg/kg bw) for 14 weeks ([NTP, 2006](#)).

Neither benzophenone nor its metabolites — benzhydrol or 4-hydroxybenzophenone — induced *umu* gene expression in *S. typhimurium* strain TA1535 in the presence or absence of rat or mouse liver microsomes. However, *umu* gene expression, which can be caused by DNA damaging agents, was elicited when *Escherichia coli* membranes expressing recombinant human cytochrome P450 (CYP) 2A6, 1A1, 1A2 or 1B1 were added to the incubation medium of *Salmonella*. The metabolite(s) responsible for this genotoxic effect were not identified ([Takemoto et al., 2002](#)).

4.3 Toxic effects

4.3.1 Humans

No data were available to the Working Group.

4.3.2 Experimental systems

In a 2-year feed study, treatment with benzophenone increased the severity of chronic nephropathy and the incidence of renal tubule hyperplasia and hepatocellular hypertrophy in rats, and the incidence of nephropathy, metaplasia of the olfactory epithelium and hyperplasia

of splenic lymphoid follicles in mice ([NTP, 2006](#)). [The animals were 6 weeks (rats) or 8 weeks (mice) of age when treatment began and, consequently, any potential endocrine-related effects associated with perinatal exposure were not captured in these studies.]

4.4 Endocrine-disrupting effects

4.4.1 *In-vitro* effects

The benzophenone metabolite, 4-hydroxybenzophenone, induced proliferation of MCF-7 cells (an estrogen-responsive human breast cancer cell line) when cultured in estradiol-free medium; this effect was also produced by 17 β -estradiol, but not by benzophenone or benzhydrol ([Nakagawa et al., 2000](#)).

4-Hydroxybenzophenone competed with 17 β -estradiol to bind to human recombinant estrogen receptor α (ER α) coated on 96-well plates (50% inhibitory concentration, $\sim 5 \times 10^{-5}$ M), but neither benzophenone nor benzhydrol demonstrated such competition ([Nakagawa & Tayama, 2001](#)). The competitive potency of 4-hydroxybenzophenone was approximately three orders of magnitude lower than that of diethylstilbestrol.

The two-ring hydroxylated compounds (3- and 4-hydroxybenzophenone) that are produced during exposure of benzophenone to sunlight competitively inhibited the binding of 17 β -estradiol to human recombinant ER α and elicited ER-mediated transcriptional activity in yeast cells ([Hayashi et al., 2006](#)).

Certain derivatives of benzophenone that have been widely used as UV screens also have estrogenic activity: benzophenone-2 (2,2',4,4'-tetrahydroxybenzophenone) also competed with 17 β -estradiol to bind to ER α and ER β ([Seidlová-Wuttke et al., 2004](#)).

Moreover, benzophenone-3 (2-hydroxy-4-methoxybenzophenone) elicited anti-androgenic activity in a human breast carcinoma cell

line (MDA-kb2) by inhibiting dihydrotestosterone-induced activation of androgen receptor, but showed no evidence of agonistic activity for this nuclear receptor ([Ma et al., 2003](#)). It transcriptionally activated human ER α and ER β in transfected human embryonic kidney cells (HEK293) and was antagonistic to the transcriptional activation of the androgen receptor by dihydrotestosterone and the progesterone receptor by a synthetic progestin (ORG 2058) in a transfected human osteosarcoma cell line (U2-OS) ([Schreurs et al., 2005](#)).

Benzophenone and its metabolite, 4-hydroxybenzophenone, elicited estrogenic activity in MCF-7 cells and anti-androgenic activity in transfected rat fibroblast NIH3T3 cells. In both assays, 4-hydroxybenzophenone was more potent than benzophenone but less potent than benzophenone-2 ([Suzuki et al., 2005](#)).

4.4.2 *In-vivo* effects

The *in-vivo* estrogenic activity of benzophenone was confirmed in the uterotrophic assay. Subcutaneous injection of 4-hydroxybenzophenone (once a day for 3 days at doses of 100, 200 or 400 mg/kg bw) to immature (21-day-old) female Sprague-Dawley rats produced a dose-related increase in absolute and relative uterine weights ([Nakagawa & Tayama, 2001](#)). Morphological evaluation showed that the treatment increased the luminal epithelial height and the thickness of the stromal layer of the uterus due to proliferation of uterine luminal epithelial cells, and increased the thickness and induced cornification of the vaginal epithelium. The same uterotrophic effects were observed in ovariectomized Sprague-Dawley rats administered benzophenone at doses of 100 and 400 mg/kg bw for 3 consecutive days by gavage in corn oil ([Nakagawa & Tayama, 2002](#)). Uterine weights were also increased in ovariectomized female F344 rats that received intraperitoneal injections of benzophenone (300 mg/kg bw) for 3 days

(Suzuki *et al.*, 2005). [The estrogen-like effects of benzophenone in the female reproductive tract appear to be due to metabolism to 4-hydroxybenzophenone, which binds to ER α .]

3- and 4-Hydroxybenzophenone induced increases in uterine weights in immature female Sprague-Dawley rats exposed subcutaneously for 3 consecutive days (Hayashi *et al.*, 2006). The effect on uterine weight was suppressed by pretreatment with the anti-estrogen ICI 182 780 (Faslodex). Thus, estrogenic products of benzophenone can also be generated by photochemical activation. [This observation is important because benzophenone has been used as a UV filter in cosmetics.]

The same uterotrophic effects as those described for 4-hydroxybenzophenone were observed in ovariectomized Sprague-Dawley rats fed benzophenone-2 in the diet for 3 months (Seidlová-Wuttke *et al.*, 2004). In addition to uterotrophic effects, the expression of ER-related receptor 1 in the uterus and ER β expression in the thyroid was increased and ER α expression in the uterus was decreased in ovariectomized Sprague-Dawley rats administered benzophenone-2 by gavage in olive oil for 5 days (Schlecht *et al.*, 2004). At similar exposures, benzophenone-3 did not increase uterine weight, but did decrease ER α expression in the pituitary and ER β expression in the uterus. Apart from the induction of estrogen-like effects by benzophenone-2 in multiple organs (including increased expression of insulin growth factor 1 in the vagina, decreased expression of insulin growth factor 1 in the liver, reduced luteinizing hormone synthesis by the pituitary gland, and a reduction of serum cholesterol high- and low- density lipoproteins), the 5-day treatment caused a reduction in serum thyroxine and triiodothyronine levels through a non-ER-mediated process (Jarry *et al.*, 2004). The latter effect of benzophenone-2 appears to be due to interference of thyroid hormone biosynthesis by inhibiting or inactivating thyroid peroxidase (Schmutzler *et al.*, 2007).

Among 17 benzophenone derivatives that were evaluated for anti-androgenic activity *in vitro*, the most potent (2,4,4'-trihydroxybenzophenone) also significantly suppressed the effect of testosterone on the weight gains of prostate and seminal vesicle in castrated male F344 rats (Hershberger assay), confirming the *in-vivo* anti-androgenic effect of this chemical (Suzuki *et al.*, 2005). Benzophenone-2 — an estrogenic chemical — also induced hypospadias in male C57BL/6 mice that were treated by gavage from gestational day 12 through to gestational day 17 (Hsieh *et al.*, 2007). The authors concluded that this effect was dependent on ER signalling because co-administration with an ER antagonist (EM-800) prevented the induction of hypospadias by benzophenone-2.

Benzophenone was also shown to induce an interaction between the pregnane X receptor and the steroid receptor coactivator 1 *in vitro*, and to induce the expression of *CYP2B1/2*, *-2C11* and *-3A1* genes in the liver of male Sprague-Dawley rats that had been administered intraperitoneal doses of 50, 100 or 250 mg/kg bw per day for 3 days (Mikamo *et al.*, 2003). [The increased expression of *CYP2B1* suggests the involvement of the constitutive androstane receptor.] Thus, benzophenone can also disrupt normal endocrine function by transcriptionally activating the pregnane X receptor and upregulating the expression of genes that code for enzymes involved in the metabolism of endogenous steroid hormones.

The above studies indicate that endocrine-active, benzophenone-derived chemicals may alter normal development and affect endocrine regulation in multiple organs by multiple mechanisms.

4.5 Mechanisms of carcinogenesis

Although the mechanisms of tumour induction by benzophenone are not fully known, they may be complex. The effects may include the generation of reactive oxygen species, or

endocrine disruption through multiple receptors, which include the induction of estrogen-like effects as a result of binding of benzophenone to ER α , alteration of the metabolism of endogenous steroid hormones, antagonism of transcriptional activation of the androgen receptor, and possible activation of nuclear constitutive androstane and pregnane X receptors. [The Working Group noted that aromatic hydroxylation of benzophenone to a transcriptionally active metabolite is likely to occur in humans.]

5. Summary of Data Reported

5.1 Exposure data

Benzophenone is produced by the acylation of benzoyl chloride with an excess of benzene. It may also be formed by atmospheric oxidation of diphenylmethane. Benzophenone is used as an ultraviolet curing agent, flavour ingredient, fragrance enhancer and perfume fixative, and as an additive for plastics, coatings and adhesive formulations. Benzophenone is also used as a screen to prevent ultraviolet light-induced damage to cosmetics. It is used in laundry and household cleaning products, and in the manufacture of pharmaceuticals, insecticides and agricultural chemicals. Benzophenone enters the environment after having been washed from skin and clothes through wastewater and from municipal solid-waste landfill leachates, and is ubiquitous in water, sediment and biota.

Occupational exposure may occur through inhalation and dermal contact in the manufacture of products that contain benzophenone. Dietary exposure to benzophenone occurs as a result of its natural occurrence in food or addition to food as a flavouring agent, its presence in drinking-water as a contaminant, and through its migration from food packaging, printing inks or recycled paperboard. Exposure may also occur through the inhalation of fragrances used

in indoor air and dermal contact with household cleaning and personal care products.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Benzophenone was tested for carcinogenicity by oral administration in the diet in one study in mice and rats and by dermal application in one study in mice. Oral administration of benzophenone significantly increased the incidence of hepatocellular adenoma, and hepatocellular adenoma, hepatocellular carcinoma and hepatoblastoma (combined) in male mice and histiocytic sarcoma in female mice. It increased the incidence of mononuclear-cell leukaemia in male and female rats (not statistically significant in females), renal tubule adenoma in male rats and histiocytic sarcoma in female rats (not statistically significant). Dermal application of benzophenone did not induce tumours in mice.

Tumours of the kidney, histiocytic sarcomas and hepatoblastomas are rare spontaneous neoplasms in experimental animals.

5.4 Other relevant data

No data were available on the toxicokinetics of benzophenone in humans. Benzophenone is absorbed in monkeys after dermal application, and is rapidly absorbed from the gastrointestinal tract of rodents. It is metabolized by reduction to benzhydrol or by oxidation to 4-hydroxybenzophenone. The latter compound can also be formed by ultraviolet or sunlight irradiation of benzophenone.

Benzophenone was not mutagenic in *Salmonella* and did not induce micronuclei in mice. Benzophenone and its metabolites induced *umu* gene expression, an indication of

DNA damage, in *Salmonella* in the presence of *Escherichia coli* membranes expressing recombinant human cytochrome P450s.

The benzophenone metabolite, 4-hydroxybenzophenone, elicits estrogenic activity and anti-androgenic activity *in vitro*, and the *in-vivo* estrogenic activity of benzophenone has been confirmed in multiple uterotrophic assays. Benzophenone may alter endocrine signalling through multiple effects on receptors.

The mechanistic evidence for tumour induction by benzophenone is weak, but the relevance of the tumour response in experimental animals to humans cannot be excluded.

6. Evaluation

6.1 Cancer in humans

No data were available to the Working Group.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of benzophenone.

6.3 Overall evaluation

Benzophenone is *possibly carcinogenic to humans (Group 2B)*.

References

- AIHA (2009). American Industrial Hygiene Association. Available at: www.aiha.org/foundations/GuidelineDevelopment/weel/Documents/weel-levels.pdf
- Anderson WA & Castle L (2003). Benzophenone in cartonboard packaging materials and the factors that influence its migration into food. *Food Addit Contam*, 20: 607–618. doi:10.1080/0265203031000109486 PMID:12881135
- Bidwell JR, Becker C, Hensley S *et al.* (2010). Occurrence of organic wastewater and other contaminants in cave streams in northeastern Oklahoma and northwestern Arkansas. *Arch Environ Contam Toxicol*, 58: 286–298. doi:10.1007/s00244-009-9388-6 PMID:19763679
- Bronaugh RL, Wester RC, Bucks D *et al.* (1990). *In vivo* percutaneous absorption of fragrance ingredients in rhesus monkeys and humans. *Food Chem Toxicol*, 28: 369–373. doi:10.1016/0278-6915(90)90111-Y PMID:2379896
- Brooks AC, Gaskell PN, Maltby LL (2009). Importance of prey and predator feeding behaviors for trophic transfer and secondary poisoning. *Environ Sci Technol*, 43: 7916–7923. doi:10.1021/es900747n PMID:19921914
- Brożek R, Rogalewicz R, Koczorowski R, Voelkel A (2008). The influence of denture cleansers on the release of organic compounds from soft lining materials. *J Environ Monit*, 10: 770–774. doi:10.1039/b719825f PMID:18528545
- Burdock GA (2005) *Fenaroli's Handbook of Flavor Ingredients*, 5th ed. Boca Raton, FL: CRC Press.
- Burkhardt MR, Revello R, Smith S, Zaugg S (2005). Pressurized liquid extraction using water/isopropanol coupled with solid-phase extraction cleanup for industrial and anthropogenic waste-indicator compounds in sediment. *Anal Chim Acta*, 534: 89–100. doi:10.1016/j.aca.2004.11.023
- Council of Europe (2000). *Chemically-defined Flavouring Substances*. Strasbourg, France: Council of Europe Publishing.
- CS AFSCA Belgium (2009). *Comité Scientifique de l'Agence Fédérale pour la Sécurité de la Chaîne Alimentaire. Migration de 4-méthylbenzophénone de l'emballage en carton imprimé vers les céréales de petit déjeuner (dossier 2009/05)*. 16/02/2009.
- EFSA (2008). Flavouring Group Evaluation 69 (FGE.69). *Consideration of aromatic substituted secondary alcohols, ketones and related esters evaluated by JECFA (57th meeting) structurally related to aromatic ketones from chemical group 21 evaluated by EFSA in FGE.16* (2006). Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (EFSA-Q-2008–053). Adopted on 31 January 2008. European Food Safety Authority. The EFSA Journal 869:1–35. Available at: http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902172504.htm
- EFSA (2009). (European Food Safety Authority) *Toxicological evaluation of benzophenone. Scientific Opinion of the Panel on food contact materials, enzymes, flavourings and processing aids (CEF)*. Question N° EFSA-Q-2009–411. Adopted on 14 May 2009. *The European Food safety Authority Journal*, 1104: 1–30.
- Ehrhardt M (1987). Photo-oxidation products of fossil fuel components in the water of Hamilton

- harbour, Bermuda. *Mar Chem*, 22: 85–94. doi:10.1016/0304-4203(87)90050-8
- Ehrhardt M, Bouchertall F, Hopf H-P (1982). Aromatic ketones concentrated from Baltic sea water. *Mar Chem*, 11: 449–461. doi:10.1016/0304-4203(82)90010-X
- European Commission (2002). *Directive 2002/72/EC of 6th August 2002 relating to plastic materials and articles intended to come into contact with food-stuff*. Official Journal of the European Communities 15.8.2002. L220/18. Available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:220:0018:0018:EN:PDF>
- European Commission (2009). *Health and Consumers Directorate General. Standing Committee on the Food Chain and Animal Health. Section Toxicological Safety Conclusions of the meeting of 06 March 2009*. Bruxelles. Available at : http://ec.europa.eu/food/fs/rc/scfcah/index_en.html
- GESTIS (2010). *Benzophenone*. GESTIS international limit values. Available at: <http://www.dguv.de/ifa/en/gestis/index.jsp>
- Grung M, Lichtenhaler R, Ahel M *et al.* (2007). Effects-directed analysis of organic toxicants in wastewater effluent from Zagreb, Croatia. *Chemosphere*, 67: 108–120. doi:10.1016/j.chemosphere.2006.09.021 PMID:17166550
- Hayashi T, Okamoto Y, Ueda K, Kojima N (2006). Formation of estrogenic products from benzophenone after exposure to sunlight. *Toxicol Lett*, 167: 1–7. doi:10.1016/j.toxlet.2006.08.001 PMID:17010539
- Helmig D, Müller J, Klein W (1989). Volatile organic substances in a forest atmosphere. *Chemosphere*, 19: 1399–1412. doi:10.1016/0045-6535(89)90088-X
- HSDB (2010). *Benzophenone*. Hazardous substance database. Available at: <http://toxnet.nlm.nih.gov/>
- Hsieh MH, Grantham EC, Liu B *et al.* (2007). In utero exposure to benzophenone-2 causes hypospadias through an estrogen receptor dependent mechanism. *J Urol*, 178: 1637–1642. doi:10.1016/j.juro.2007.03.190 PMID:17707034
- IOFI-DG SANCO (2008). *Focused Survey of the Global Flavour Industry on Added Use Levels for Class III. Flavouring Substances: Background and Methodology*. Reported submitted by IOFI, EFFA, FEMA, JFFMA to DG SANCO, European Commission.
- IPCS-CEC (2005). *Benzophenone*. CAS No. 119–61–9. ICSC (International Chemical Safety Cards): 0389 Peer reviewed 2010. International Programme on Food Safety-Commission of the European Communities. Available at: <http://www.inchem.org/documents/icsc/icsc/eics0389.htm>
- Ito R, Kawaguchi M, Koganei Y *et al.* (2009). Development of miniaturized hollow-fiber assisted liquid-phase microextraction with in situ acyl derivatization followed by GC-MS for the determination of benzophenones in human urine samples. *Anal Sci*, 25: 1033–1037. doi:10.2116/analsci.25.1033 PMID:19667483
- IUCLID (2000). *IUCLID dataset created by European Commission – European Chemical Bureau. Substance ID: 119–61–9*. Available at: http://esis.jrc.ec.europa.eu/doc/IUCLID/data_sheets/119619.pdf
- Jarry H, Christoffel J, Rimoldi G *et al.* (2004). Multi-organic endocrine disrupting activity of the UV screen benzophenone 2 (BP2) in ovariectomized adult rats after 5 days treatment. *Toxicology*, 205: 87–93. doi:10.1016/j.tox.2004.06.040 PMID:15458793
- Jeon HK, Sarma SN, Kim YJ, Ryu JC (2008). Toxicokinetics and metabolisms of benzophenone-type UV filters in rats. *Toxicology*, 248: 89–95. doi:10.1016/j.tox.2008.02.009 PMID:18448226
- Johns SM, Jickells SM, Read WA, Castle L (2000). Studies on functional barriers to migration. 3. Migration of benzophenone and model ink components from cartonboard to food during frozen storage and microwave heating. *Packag. Technol. Sci.*, 13: 99–104. doi:10.1002/1099-1522(200005)13:3<99::AID-PTS499>3.0.CO;2-K
- Kawaguchi M, Ito R, Endo N *et al.* (2006). Stir bar sorptive extraction and thermal desorption-gas chromatography-mass spectrometry for trace analysis of benzophenone and its derivatives in water sample. *Anal Chim Acta*, 557: 272–277. doi:10.1016/j.aca.2005.08.087
- Kawaguchi M, Ito R, Honda H, Kawaguchi *et al.* (2009). Miniaturized hollow fiber assisted liquid-phase microextraction and gas chromatography-mass spectrometry for determination of benzophenone and derivatives in human urine sample. *J Chromatogr B Analyt Technol Biomed Life Sci*, 877: 298–302. doi:10.1016/j.jchromb.2008.12.021 PMID:19117809
- Koivikko R, Pastorelli S, Rodríguez-Bernaldo de Quirós A *et al.* (2010). Rapid multi-analyte quantification of benzophenone, 4-methylbenzophenone and related derivatives from paperboard food packaging. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*, 27: 1478–1486. doi:10.1080/19440049.2010.502130 PMID:20640959
- Leary JA, Biemann K, Lafleur AL *et al.* (1987). Chemical and toxicological characterization of residential oil burner emissions: I. Yields and chemical characterization of extractables from combustion of No. 2 fuel oil at different Bacharach Smoke Numbers and firing cycles. *Environ Health Perspect*, 73: 223–234. doi:10.1289/ehp.8773223 PMID:3665865
- Leclercq C, Charrondière UR, Di Novi M *et al.* (2009). *Dietary exposure assessment of flavouring agents: incorporation of the Single Portion Exposure Technique (SPET) into the procedure for the safety evaluation of flavouring agents*. In: *IPCS, ed. Safety evaluation of certain food additives. Prepared by the sixty ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)*. Geneva: WHO Food Additives

- Series: 60:267–289. Available at: http://whqlibdoc.who.int/publications/2009/9789241660600_eng.pdf
- LOGKOW (2010). *Benzophenone*. A databank of evaluated octanol-water partition coefficient, ICSU-CODATA. Available at: <http://logkow.cisti.nrc.ca/logkow/>
- Lorraine GA & Pettigrove ME (2006). Seasonal variations in concentrations of pharmaceuticals and personal care products in drinking water and reclaimed wastewater in southern California. *Environ Sci Technol*, 40: 687–695. doi:10.1021/es051380x PMID:16509304
- Ma R, Cotton B, Lichtensteiger W, Schlumpf M (2003). UV filters with antagonistic action at androgen receptors in the MDA-kb2 cell transcriptional-activation assay. *Toxicol Sci*, 74: 43–50. doi:10.1093/toxsci/kfg102 PMID:12730620
- Mikamo E, Harada S, Nishikawa J, Nishihara T (2003). Endocrine disruptors induce cytochrome P450 by affecting transcriptional regulation via pregnane X receptor. *Toxicol Appl Pharmacol*, 193: 66–72. doi:10.1016/j.taap.2003.08.001 PMID:14613717
- Mottaleb MA, Usenko S, O'Donnell JG *et al.* (2009). Gas chromatography-mass spectrometry screening methods for select UV filters, synthetic musks, alkylphenols, an antimicrobial agent, and an insect repellent in fish. *J Chromatogr A*, 1216: 815–823. doi:10.1016/j.chroma.2008.11.072 PMID:19100555
- Nakagawa Y, Suzuki T, Tayama S (2000). Metabolism and toxicity of benzophenone in isolated rat hepatocytes and estrogenic activity of its metabolites in MCF-7 cells. *Toxicology*, 156: 27–36. doi:10.1016/S0300-483X(00)00329-2 PMID:11162873
- Nakagawa Y & Tayama K (2001). Estrogenic potency of benzophenone and its metabolites in juvenile female rats. *Arch Toxicol*, 75: 74–79. doi:10.1007/s002040100225 PMID:11354909
- Nakagawa Y & Tayama K (2002). Benzophenone-induced estrogenic potency in ovariectomized rats. *Arch Toxicol*, 76: 727–731. doi:10.1007/s00204-002-0401-3 PMID:12451449
- Nerín C & Asensio E (2007). Migration of organic compounds from a multilayer plastic-paper material intended for food packaging. *Anal Bioanal Chem*, 389: 589–596. doi:10.1007/s00216-007-1462-1 PMID:17680237
- NIOSH (National Institute for Occupational Safety and Health) (1990). *National Occupational Exposure Survey 1981–83*. Cincinnati, OH: United States Department of Health and Human Services. Available at: <http://www.cdc.gov/noes/noes3/empl0003.html>
- NTP (2006). Toxicology and carcinogenesis studies of benzophenone (CAS No. 119–61–9) in F344/N rats and B6C3F₁ mice (feed studies). *Natl Toxicol Program Tech Rep Ser*, 5331–264. PMID:16741556
- OHMTADS (Oil and Hazardous Materials/Technical Assistance Data System) (1991). *On-line database created by the Environmental Protection Agency; maintained by the National Information Services Corporation (NISC)*. Baltimore, MD. Available at: <http://www.ovid.com/site/products/fieldguide/CHEMBANK/omtd.htm#searchexp>
- Oros DR, Jarman WM, Lowe T *et al.* (2003). Surveillance for previously unmonitored organic contaminants in the San Francisco Estuary. *Mar Pollut Bull*, 46: 1102–1110. doi:10.1016/S0025-326X(03)00248-0 PMID:12932491
- Ozaki A, Kawasaki C, Kawamura Y, Tanamoto K (2006). [Migration of bisphenol A and benzophenones from paper and paperboard products used in contact with food] *Shokuhin Eiseigaku Zasshi*, 47: 99–104. doi:10.3358/shokueishi.47.99 PMID:16862986
- Parks N (2009). UV-stabilizing chemicals contaminating Japan's marine environment. *Environ Sci Technol*, 43: 6896–6897. doi:10.1021/es902293a PMID:19806714
- Pastorelli S, Sanches-Silva A, Cruz JM *et al.* (2008). Study of the migration of benzophenone from printed paperboard packages to cakes through different plastic films. *Eur Food Res Technol*, 227: 1585–1590. doi:10.1007/s00217-008-0882-2
- Pedrouzo M, Borrull F, Marcé RM, Pocurull E (2010). Stir-bar-sorptive extraction and ultra-high-performance liquid chromatography-tandem mass spectrometry for simultaneous analysis of UV filters and antimicrobial agents in water samples. *Anal Bioanal Chem*, 397: 2833–2839. doi:10.1007/s00216-010-3743-3 PMID:20428847
- Pitarch E, Portolés T, Marín JM *et al.* (2010). Analytical strategy based on the use of liquid chromatography and gas chromatography with triple-quadrupole and time-of-flight MS analyzers for investigating organic contaminants in wastewater. *Anal Bioanal Chem*, 397: 2763–2776. doi:10.1007/s00216-010-3692-x PMID:20428853
- Pojana G, Bonfà A, Busetti F *et al.* (2004). Estrogenic potential of the Venice, Italy, lagoon waters. *Environ Toxicol Chem*, 23: 1874–1880. doi:10.1897/03-222 PMID:15352475
- Pojana G, Gomiero A, Jonkers N, Marcomini A (2007). Natural and synthetic endocrine disrupting compounds (EDCs) in water, sediment and biota of a coastal lagoon. *Environ Int*, 33: 929–936. doi:10.1016/j.envint.2007.05.003 PMID:17559935
- Repertoire Toxicologique (2010). *Benzophenone*. Québec, Canada: repertoire toxicologique de la commission de la santé et sécurité du travail (CSST).
- Rhodes MC, Bucher JR, Peckham JC *et al.* (2007). Carcinogenesis studies of benzophenone in rats and mice. *Food Chem Toxicol*, 45: 843–851. doi:10.1016/j.fct.2006.11.003 PMID:17187913
- Ricking M, Schwarzbauer J, Franke S (2003). Molecular markers of anthropogenic activity in sediments of the Havel and Spree Rivers (Germany). *Water Res*, 37: 2607–2617. doi:10.1016/S0043-1354(03)00078-2 PMID:12753838

- Robinson D (1958). Studies in detoxication. 74. The metabolism of benzhydrol, benzophenone and p-hydroxybenzophenone. *Biochem J*, 68: 584–586. PMID:13522664
- Rodríguez-Bernaldo de Quirós A, Paseiro-Cerrato R, Pastorelli S *et al.* (2009). Migration of photoinitiators by gas phase into dry foods. *J Agric Food Chem*, 57: 10211–10215. doi:10.1021/jf9026603 PMID:19839623
- Sanches-Silva A, Pastorelli S, Cruz JM *et al.* (2008). Development of a multimethod for the determination of photoinitiators in beverage packaging. *J Food Sci*, 73: C92–C99. doi:10.1111/j.1750-3841.2007.00642.x PMID:18298722
- Slecht C, Klammer H, Jarry H, Wuttke W (2004). Effects of estradiol, benzophenone-2 and benzophenone-3 on the expression pattern of the estrogen receptors (ER) alpha and beta, the estrogen receptor-related receptor 1 (ERR1) and the aryl hydrocarbon receptor (AhR) in adult ovariectomized rats. *Toxicology*, 205: 123–130. doi:10.1016/j.tox.2004.06.044 PMID:15458797
- Schmutzler C, Bacinski A, Gotthardt I *et al.* (2007). The ultraviolet filter benzophenone 2 interferes with the thyroid hormone axis in rats and is a potent in vitro inhibitor of human recombinant thyroid peroxidase. *Endocrinology*, 148: 2835–2844. doi:10.1210/en.2006-1280 PMID:17379648
- Schreurs RH, Sonneveld E, Jansen JH *et al.* (2005). Interaction of polycyclic musks and UV filters with the estrogen receptor (ER), androgen receptor (AR), and progesterone receptor (PR) in reporter gene bioassays. *Toxicol Sci*, 83: 264–272. doi:10.1093/toxsci/kfi035 PMID:15537743
- Seidlová-Wuttke D, Jarry H, Wuttke W (2004). Pure estrogenic effect of benzophenone-2 (BP2) but not of bisphenol A (BPA) and dibutylphtalate (DBP) in uterus, vagina and bone. *Toxicology*, 205: 103–112. doi:10.1016/j.tox.2004.06.042 PMID:15458795
- Shen DX, Lian HZ, Ding T *et al.* (2009). Determination of low-level ink photoinitiator residues in packaged milk by solid-phase extraction and LC-ESI/MS/MS using triple-quadrupole mass analyzer. *Anal Bioanal Chem*, 395: 2359–2370. doi:10.1007/s00216-009-3115-z PMID:19784638
- Shinohara R, Kido A, Eto S *et al.* (1981). Identification and determination of trace organic substances in tap water by computerized gas chromatography-mass spectrometry and mass fragmentography. *Water Res*, 15: 535–542. doi:10.1016/0043-1354(81)90016-6
- Stenbäck F & Shubik P (1974). Lack of Toxicity and Carcinogenicity of Some Commonly Used Cutaneous Agents. *Toxicol Appl Pharmacol*, 30: 7–13. doi:10.1016/0041-008X(74)90242-7
- Stocklinski AW, Ware OB, Oberst TJ (1980). Benzophenone metabolism. I. Isolation of p-hydroxybenzophenone from rat urine. *Life Sci*, 26: 365–369. doi:10.1016/0024-3205(80)90152-6 PMID:7378157
- Suzuki T, Kitamura S, Khota R *et al.* (2005). Estrogenic and antiandrogenic activities of 17 benzophenone derivatives used as UV stabilizers and sunscreens. *Toxicol Appl Pharmacol*, 203: 9–17. doi:10.1016/j.taap.2004.07.005 PMID:15694459
- Takemoto K, Yamazaki H, Nakajima M, Yokoi T (2002). Genotoxic activation of benzophenone and its two metabolites by human cytochrome P450s in SOS/umu assay. *Mutat Res*, 519: 199–204. PMID:12160905
- The Japanese Ministry of Environment (2006). Available at: <http://www.env.go.jp/chemi/kurohon/2005/http2005/30furoku/313.pdf>
- TNO (2010). *Volatile Compounds in Food Database*. Release 12.1. Available at: <http://www.vcf-online.nl/VcfHome.cfm>
- Trzcinski AP & Stuckey DC (2010). Treatment of municipal solid waste leachate using a submerged anaerobic membrane bioreactor at mesophilic and psychrophilic temperatures: analysis of recalcitrants in the permeate using GC-MS. *Water Res*, 44: 671–680. doi:10.1016/j.watres.2009.09.043 PMID:19822341
- UKFSA; UK Food Standards Agency (2006). *Benzophenone and 4-hydroxybenzophenone migration from food packaging into foodstuffs*. Food Survey Information Sheet. Available at: <http://www.food.gov.uk/science/surveillance/fsisbranch2006/fsis1806>
- US EPA; United States Environmental Protection Agency (1984). Information Review: *Benzophenone*. Rockville, Maryland: Submitted by CRCS, Inc. in Collaboration with Dynamac Corporation Enviro Control Division, TSCA Interagency Testing Committee.
- Van Hoeck E, De Schaetzen T, Pacquet C *et al.* (2010). Analysis of benzophenone and 4-methylbenzophenone in breakfast cereals using ultrasonic extraction in combination with gas chromatography-tandem mass spectrometry (GC-MS(n)). *Anal Chim Acta*, 663: 55–59. doi:10.1016/j.aca.2010.01.044 PMID:20172097
- WHO (2003). *Domestic water quantity, service level and health*. Geneva: World Health Organization (WHO/SDE/WSH/3.02). Available at: http://www.who.int/water_sanitation_health/diseases/wsh0302/en/index.html
- WHO (2008). *Guidelines for drinking-water quality*. 3rd ed, incorporating first and second addenda. Vol. 1. Recommendations. Geneva: World Health Organization. Available at: http://www.who.int/water_sanitation_health/dwq/gdwq3rev/en/
- Yoon Y, Ryu J, Oh J *et al.* (2010). Occurrence of endocrine disrupting compounds, pharmaceuticals, and personal care products in the Han River (Seoul, South Korea). *Sci Total Environ*, 408: 636–643. doi:10.1016/j.scitotenv.2009.10.049 PMID:19900699