Australian Government
Department of Health, Disability and Ageing
Australian Industrial Chemicals Introduction Scheme

Methanone, [1,1′-biphenyl]-4-ylphenyl- (4-Phenylbenzophenone)

Evaluation statement (EVA00201)

26 June 2026

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AICIS evaluation statement (EVA00201)

Subject of the evaluation

Methanone, [1,1′-biphenyl]-4-ylphenyl- (4-Phenylbenzophenone)

Chemical in this evaluation

CAS name	CAS number
Methanone, [1,1′-biphenyl]-4-ylphenyl-	2128-93-0

Reason for the evaluation

New information is available about human health risks.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation statement includes a human health risk assessment for all identified industrial uses of methanone, [1,1′-biphenyl]-4-ylphenyl- (4-phenylbenzophenone).

The chemical was assessed as a new industrial chemical under section 23 of the *Industrial Chemicals Notification and Assessment (ICNA) Act 1989*. The assessment report cannot be linked to this report due to confidentiality provisions under the *Industrial Chemicals Act 2019.* New toxicological data are available for multiple endpoints.

Summary of evaluation

Summary of introduction, use and end use

Based on Australian and international use information, the chemical has site-limited and commercial uses with functional use as a chemical reaction regulator including in:

- ink, toner and colourant products
- paints and coatings
- the manufacture of chemicals (including plastic and polymer products)
- adhesives and sealants.

Reported end use concentrations are typically less than 5%. International data indicated use at > 90% concentration in the manufacturing of adhesives and paints, with reformulation to lower working concentrations expected.

Although some domestic use of the chemical in inks and coatings may be possible, this is not expected to be widespread. Domestic use of the chemical has not been reported to AICIS.

The chemical has use in inks and coatings used for food contact materials.

Human health

Summary of health hazards

The identified health hazards are based on available data for the chemical. Based on the physicochemical properties the chemical is expected to be readily absorbed following oral, dermal and inhalation exposure.

Based on the available data, the chemical:

- has low acute oral and dermal toxicity
- is not irritating to skin or eyes
- is not expected to cause serious systemic health effects following repeated oral or dermal exposure.

Based on available data including positive results in a mouse local lymph node assay (LLNA), and an *in vitro* luciferase KeratinoSens™ test, the chemical is a weak skin sensitiser. A dose-dependent increase in local lymphocyte proliferation was seen in a LLNA with the SI value reaching close to 3 at the maximum concentration tested (25%), indicating higher concentrations of the chemical are likely to cause skin sensitisation.

Based on the available data, there is clear evidence of specific adverse effects on fertility and foetal development in animals. In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test, the chemical caused a significant reduction in the number of implantation sites (at 1,000 mg/kg bw day), reduced post-implantation survival of pups and reduced live litter size (at all doses tested). The study also provides evidence of altered pup growth at 300 mg/kg bw/day. The no observed adverse effect level (NOAEL) was 300 mg/kg bw/day for reproductive toxicity and < 100 mg/kg bw/day for developmental toxicity.

There is not sufficient data to conclude on the genotoxicity potential of the chemical. The chemical caused frameshift mutations in 2 bacterial reverse mutation assays. However, in the absence of *in vivo* data, conclusions cannot be drawn and classification is not possible.

There are no experimental data available for the chemical on inhalation toxicity or carcinogenicity.

For further details of the health hazard information see **Supporting information.**

Hazard classifications relevant for worker health and safety

The chemical satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Skin Sensitisation	Skin Sens. 1B	H317: May cause an allergic skin reaction
Reproductive toxicity	Repr. 1B	H360FD: May damage fertility; May damage the unborn child

Summary of health risk

Public

Based on the available use information, public exposure to the chemical is expected to be minimal.

Consumer end uses for the chemical (except in articles) has not been identified in Australia. The public could potentially be exposed to the chemical through migration from food contact materials into food. A previous survey conducted by FSANZ in Australia did not detect the chemical in food. Consequently, dietary exposure among Australian consumers is expected to be minimal and considered unlikely to pose a health risk to consumers. However, given the uncertainty regarding potential genotoxicity of the chemical, monitoring for the chemical in the Australian food supply may be appropriate to identify any potential human exposure from food packaging (see **proposed means for managing risk).**

Workers

During product formulation and packaging, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and in the cleaning and maintaining of equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the sensitisation potential and critical systemic health effects, the chemical could pose a risk to workers unless adequate control measures to minimise dermal and inhalation exposure are implemented (see **Proposed means for managing risk** section). Controls in place due to the reproductive and developmental toxicity classification should also minimise any risks relating to potential genotoxicity at the concentrations likely to be used by workers.

Proposed means for managing risk

Inventory listing

The specific requirement to provide information as a term of the Inventory listing should be varied under section 86 of the *Industrial Chemicals Act 2019* (IC Act) to align the specific information requirement with the risk identified and considered in this evaluation statement as follows:

Term of listing	Details
Specific requirements to provide information to the Executive Director under section 101 of the IC Act	1. A person introducing this chemical must tell the Executive Director the volume of introduction and end use of the chemical within 20 working days of becoming aware if: • The chemical is being introduced for consumer end use, except uses in articles. • The end use of the chemical has changed or is likely to change from: ○ ink toner and colourant products ○ paints and coatings ○ the manufacture of chemicals including ○ plastic and polymer products ○ adhesives and sealants. • The introduction volume of the chemical exceeds 1 tonne per annum. • Manufacturing of the chemical has commenced in Australia. 2. A person introducing this chemical must, if information has become available to the person as to an adverse effect of the chemical on the environment, tell the Executive Director within 20 working days of becoming aware the: • information about the adverse effect of the chemical on the environment.

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety (see **Summary of Health Hazards** section).

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Recommended control measures that could be implemented to manage the risk arising from dermal or inhalation exposure to the chemical include, but are not limited to:

- using closed systems or isolating operations
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Measures required to eliminate or manage risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used.

These control measures should be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Food

Recommendation to Food Standards Australia and New Zealand (FSANZ)

It is recommended that FSANZ consider including 4-phenylbenzophenone in any future survey of food packaging chemicals in the Australian food supply to determine potential human exposure from food packaging, given the uncertainty regarding potential genotoxicity of this substance.

Conclusions

The Executive Director is satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

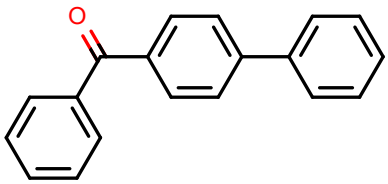
The specific requirement to provide information as a term of the Inventory listing under section 101 of the IC Act assists with managing the risks from introduction of the chemical. The information currently required to be provided is no longer aligned with the risks identified in this evaluation statement. Therefore, a variation to the specific requirement to provide information as a term of the Inventory listing is necessary to manage the risks from introduction of the chemical (see **Proposed means of managing risk** section). As this evaluation does not consider environmental risks, current information requirements relevant to environmental risks have been maintained.

Note:

1. Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.
2. A person introducing this chemical should be aware of their obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

CAS number	2128-93-0
CAS name	Methanone, [1,1′-biphenyl]-4-ylphenyl-
Molecular formula	$C_{19}H_{14}O$
Associated names	[1,1′-Biphenyl]-4-ylphenylmethanone 4-phenylbenzophenone 4-Benzoylbiphenyl
Molecular weight (g/mol)	258.31
SMILES (canonical)	O=C(C=1C=CC=CC1)C=2C=CC(=CC2)C=3C=CC=CC3
Structural formula	

Relevant physical and chemical properties

Sources: ECHA CHEM n.d. and Scifinder[n]

Physical form	Solid
Melting point	101.5°C at 1015 hPa
Boiling point	421.8°C at 1015 hPa
Vapour pressure	≤ 1.9×10^{-5} Pa at 20°C ≤ 4.3×10^{-5} Pa at 25°C
Water solubility	0.074 mg/L at 20°C
pK_a	-6.2
log K_{ow}	4.7 at 35°C

Introduction and use

Australia

Information provided to AICIS since 2020 indicate that the chemical has use as a photoinitiator in paints and coatings and in the production of polymers. The chemical was reported as used by professional workers only. Annual introduction volumes have been reported in the 1–10 tonne range.

International

The chemical is used internationally as a photoinitiator in a number of industrial applications. This includes use in adhesives and sealants, printing inks, paints, and coatings and in the manufacture of chemicals (including plastic and polymer products). While consumer use has been reported in the United States of America (US EPA 2020), in the European Union (EU), there have been no notifications of consumer use reported to the European Chemicals Agency (ECHA) (ECHA 2023a).

Concentrations in end products have been reported in the range from 1% to less than 30% (US CDR 2020; US EPA 2016); however, online websites indicate typical concentrations of up to 5%. International data indicated use at > 90% concentration in the manufacturing of adhesives and paints, with reformulation to lower working concentrations expected (US CDR 2020).

The chemical has identified use in printing inks and coatings used for food contact materials (FCCdb n.d.).

Existing Australian regulatory controls

AICIS

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory) with a specific requirement to provide information as a term of the Inventory listing. This term is published as:

- *Obligations to provide information apply. You must tell us within 28 days if the circumstances of your importation or manufacture (introduction) are different to those in our assessment.*

Under section 75(2)(c) of the *Industrial Chemicals (Consequential Amendments and Transitional Provisions) Rules 2019* the notification obligations under subsections 64(1) and (2) of the old law (*Industrial Chemicals Notification and Assessment (ICNA) Act 1989* (ICNA Act)) are taken to be specific information requirements to be provided to the Executive Director.

No specific obligations under Section 64(1) were applied to the chemical.

Under section 64(2) of the ICNA Act a person who introduces an industrial chemical that has been assessed under this Act must within 28 days of becoming aware of any of the following circumstances since the assessment, notify the Executive Director in writing if:

a) the function or use of the chemical has changed, or is likely to change significantly
b) the amount of chemical being introduced has increased, or is likely to increase significantly
c) in the case of a chemical not manufactured, or proposed to be manufactured, in Australia at the time of the assessment – it has begun to be manufactured in Australia
d) the method of manufacture of the chemical in Australia has changed, or is likely to change, in a way that may result in an increased risk of an adverse effect of the chemical on occupational health and safety, public health or the environment
e) additional information has become available to the person as to an adverse effect of the chemical on public health, worker health and safety or the environment.

Public

No specific controls have been identified for this chemical.

There are no restrictions or maximum concentration levels for the chemical outlined in the Food Standards Code (FSANZ n.d.).

Workers

The chemical is not listed on the Safe Work Australia Hazardous Chemical Information System (HCIS) (SWA n.d.).

No exposure standards are available for the chemical in Australia (SWA n.d.).

International regulatory status

Canada

The chemical is on the Canadian Domestic Substances List (DSL). Significant New Activity (SNAc) provisions of the Canadian Environmental Protection Act, 1999 (CEPA) apply to the chemical, which trigger an obligation for a person to provide the Government of Canada with information about the chemical when proposing to use, import or manufacture for a significant new activity. The SNAc provisions for the chemical are currently under review (Government of Canada n.d.).

In relation to the substance methanone, [1,1'-biphenyl]-4-ylphenyl-, a SNAc is the

a) manufacture of any quantity of this substance in Canada; or
b) import of the substance into Canada in excess of 1,000 kilograms per calendar year, unless it is imported as a component of a finished ink formulation.

Europe

The chemical is listed in Annex 10 of the Ordinance of the Switzerland Federal Department of Home Affairs on materials and articles intended to come into contact with foodstuffs as a photo initiator, binder monomer or other starting substance (FSVO 2020).

The chemical has the following restrictions:

May only be used if the following 2 conditions are met:

a. *the substances must not be classified as 'mutagenic', 'carcinogenic' or 'toxic to reproduction' (CMR substances) of category 1A, 1B or 2 in accordance with the criteria set out in Art. 6 of the Ordinance on Protection against Dangerous Substances and Preparations.*
b. *no migration of the substance is authorized. Compliance shall be established using the appropriate test methods selected in accordance with Article 11 of Regulation (EC) No 882/2004 which can confirm the absence of migration beyond a specified detection limit. If specific detection limits have not been established for specific substances or groups of substances, a detection limit of 0.01 mg/kg shall apply. It applies to a group of compounds, if they are structurally and toxicologically related (in particular isomers or compounds with the same relevant functional group) or to individual substances that are not related, and includes any unwanted transfer* (FSVO 2020).

Human exposure

Public

If the chemical is used in the production of food contact materials, there is potential for public exposure through migration into food.

Internationally, migration of the chemical from food packaging into food and food simulants has been reported. The most common type of food packaging in reports of migration are plastics, followed by paper and board packaging (FCCdb n.d.). In a food surveys conducted in the UK and Germany the chemical was detected in 13/350 samples and 8/310 samples, respectively (Bradley et al. 2012; Jung et. Al 2014). In a survey in Taiwan focussing on cereal, fruit and vegetable juices and milk, the chemical had low detection rates in cereal (2/180 samples) but higher detection in fruit and vegetable juices (73/136 samples) and milk (28/46). The maximum level detected was 2.6 ng/g with means in the range (0.29–1.6 ng/g) (Chen et al 2022).

In 2016 Food Standards Australia New Zealand (FSANZ) published Phase 2 of the 24th Australian Total Diet Study, a comprehensive analytical food survey that investigated levels of 30 food packaging chemicals in the Australian food supply. As part of this study, foods were tested to detect any migration of printing ink chemicals including 4-phenylbenzophenone. The chemical was not detected in any of the 60 foods tested. It was concluded that there was negligible risk to consumers in Australia (FSANZ 2016).

Health hazard information

Toxicokinetics

No specific toxicokinetic data are available for the chemical.

Based on the molecular weight (258.31 g/mol), low water solubility (0.074 mg/L), and the partition coefficient (Log P_{ow} = 4.7) of the chemical, absorption via oral and dermal routes is expected. Due to the low vapour pressure (≤ 1.9 × 10^{-5} Pa at 25°C) and high boiling point (421.8°C) of the chemical (CAS n.d.; ECHA CHEM n.d.), it is expected to have minimal volatility, with inhalation only likely to arise from processes where dusts or aerosols are produced.

Acute toxicity

Oral

Based on the available information, the chemical has low acute oral toxicity.

In a GLP compliant acute oral toxicity study conducted in accordance with OECD TG 423, female Wistar rats (6/dose) were treated with a single dose of the chemical at 2,000 mg/kg bw. No mortality occurred and as such the median lethal dose (LD50) was > 2,000 mg/kg bw. Reported sublethal signs of toxicity included hunched posture in 3 of 6 animals on day 1 (ECHA CHEM n.d.).

Dermal

Based on the available information, the chemical has low acute dermal toxicity.

In a GLP compliant acute dermal toxicity study conducted in accordance with OECD TG 402, Wistar rats (5/sex/dose) were treated with a single dose of the chemical at 2,000 mg/kg bw in both sexes. No mortality occurred and as such the LD50 was > 2,000 mg/kg bw. Reported sublethal signs of toxicity included general erythema and scales of the treated area of 3 females (ECHA CHEM n.d.).

Corrosion/Irritation

Based on the available data, the chemical is not likely to be a skin or eye irritant**.**

Skin irritation

The chemical is considered to be not corrosive (based on the prediction model criteria) in an *in vitro* reconstructed human epidermis (RhE) test (OECD TG 431) using the EpiDerm™ Standard Corrosivity Test (SCT). The mean tissue viability was 99% and 94% after 3 min and 60 min exposure, respectively (ECHA CHEM n.d.).

The chemical is considered to be not irritating to skin (based on the prediction model criteria) in an *in vitro* RhE test (OECD TG 439) using the EpiSkin™ Small Model (SM). The mean tissue viability was 109% after 15 min exposure (ECHA CHEM n.d.). Based on the prediction model criteria, chemicals with > 50% viability do not meet the requirements for classification as GHS Category 1 or 2.

Eye irritation

The chemical does not require GHS classification for eye irritation or serious eye damage, based on data from the *ex vivo* bovine corneal opacity and permeability (BCOP) test (OECD TG 437) opacitometer (unspecified). The calculated *in vitro* irritancy score (IVIS) was −2.8 for

the test chemical. Based on the prediction model criteria, chemicals with IVIS values of ≤ 3 do not meet the requirements for classification as GHS Category 1 or 2 (ECHA CHEM n.d.).

Sensitisation

Skin sensitisation

Based on the available data, the chemical is a skin sensitiser warranting GHS classification.

A dose-dependent increase in local lymphocyte proliferation was seen in a local lymph node assay (LLNA) with the SI value reaching close to 3 at the maximum concentration tested (25%) indicating that the chemical is a weak sensitiser (ECETOC 2003).

The skin sensitisation potential is supported by a positive result in an *in vitro* luciferase KeratinoSens™ test. Classification using the "2 out of 3" defined approach (2o3 DA) is not possible due to the lack of conclusive data from the first Key Event (KE) assay of the Adverse Outcome Pathway (AOP) for skin sensitisation.

Overall, the available animal data support GHS classification with sub-categorisation proposed as skin sensitisation Category 1B.

In vivo

In a LLNA conducted in accordance with OECD TG 429, 5 female CBA/J mice received topical applications of 5, 10 or 25% w/w of the chemical (99.74% purity) in N,N-dimethylformamide for 3 consecutive days. The highest concentration of 25% deviated from the standard 50% used in TG 429 due to poor solubility of the chemical at this concentration. A dose-dependent increase in local lymphocyte proliferation was observed demonstrating that 4-phenylbenzophenone has skin sensitising potential. The reported stimulation indices (SI) were 1.3, 2.3 and 2.9 for concentrations of 5, 10 or 25%, respectively. The highest concentration tested (25%) produced close to a 3-fold increase in lymphocyte proliferation (EC3) with a mean SI value of 2.9 suggesting the chemical is a skin sensitiser at higher concentrations. The SI for individual animals was > 3 for 3 out of the 5 animals and > 2 for one animal. On animal had a low SI value, which had a large influence on the arithmetic mean. The median SI is 3.8 (ECHA 2023a; ECHA 2023b; ECHA CHEM n.d.).

In vitro/In chemico

The chemical was reported negative in the first KE assay in the AOP for skin sensitisation. In a GLP-compliant direct peptide reactivity assay (DPRA) conducted in accordance with OECD TG 442C, using defined ratios of peptide to test item (1:10 cysteine peptide, 1:50 lysine peptide) in acetonitrile, mean cysteine and lysine depletion by the chemical was 1.5%, indicating minimal activity. Precipitation of the chemical during the assay, due to low solubility, meant that the available concentration of the chemical remaining in solution was uncertain. Therefore, the negative result is uncertain as the cysteine and lysine depletion may have been underestimated (ECHA 2023a; ECHA 2023b; ECHA CHEM n.d.).

The chemical was reported positive in the second KE assays in the AOP for skin sensitisation. In a GLP-compliant keratinocyte activation test (KeratinoSens™ assay, OECD TG 442D) it was reported that up to 125 µM, the chemical induced significant luciferase activity indicating keratinocyte activation, with a 1.5−fold induction at a concentration of 0.64µM (ECHA 2023a; ECHA 2023b; ECHA CHEM n.d.).

In silico

The chemical and its metabolites using the skin metabolism simulator have no structural alerts for protein binding based on the mechanistic profiling functionality of the Organisation for Economic Co-operation and Development (OECD) QSAR Application Toolbox (OECD QSAR Toolbox v4.5).

The chemical was predicted to be non-sensitising to skin using the knowledge−based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.1 (Lhasa Limited). Predictions using OASIS–TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator; version 2.31.2) were out of domain.

Repeat dose toxicity

Based on the available data, the chemical is not expected to cause serious systemic health effects following repeated oral exposure. Although there was some evidence of effects on the thyroid and adrenal glands, observed effects occurred mainly at high doses and were not severe enough to warrant hazard classification.

Oral

In a GLP-compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted in accordance with OECD TG 422, Han Wistar rats (10/sex/dose) were administered the chemical (purity 99.74%) by gavage at 0, 100, 300 or 1,000 mg/kg bw/day in propylene glycol once daily, 7 days a week. All animals were treated for 14 days before mating. Males were treated for a total of 29 days. Females that delivered pups were treated for a total of 50–56 days (one female was treated for 64 days), corresponding to 2 weeks prior to mating, conception, and the duration of pregnancy, and 13–15 days post-delivery, up to necroscopy. Females that did not deliver or had total litter loss were treated for 39–54 days.

Histological changes in the thyroid gland (follicular cell hypertrophy) were observed in all animals including controls but there was increased incidence in both the number of animals effected and severity (up to slight) in males and females at 1,000 mg/kg bw/day. Increased thyroid stimulating hormone (TSH) levels (with no apparent dose response) were reported in males of all dose groups, without a corresponding increase in thyroxine (T4) levels. Infiltration of inflammatory cells (predominantly lymphocytes) in the *zona fasciculata* and *zona reticularis* of the adrenal cortex were noted to a minimal degree in the females treated with 1,000 mg/kg bw/day.

No adverse effects were observed in parental males and females at the highest dose tested. Effects on clinical biochemistry were observed without corresponding adverse pathology changes. This included statistically significantly lower activity for alkaline phosphatase and higher level of chloride in males of the highest dose group. Non-dose related changes to serum glucose and sodium (lower and higher respectively) were observed in lactating females of the 300 mg/kg bw/day group (and 100 mg/kg bw day group for glucose). These

changes were considered to be unrelated to treatment with the chemical. The no observed adverse effect level (NOAEL) was set as 300 mg/kg bw/day for both sexes (ECHA 2023a).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

There is not sufficient data to conclude on the genotoxicity potential of the chemical. The chemical caused frameshift mutations in 2 bacterial reverse mutation assays. However, in the absence of *in vivo* data, conclusions cannot be drawn and hazard classification is not possible.

Positive results were reported in the following *in vitro* genotoxicity studies:

- Positive results were reported in a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 and *Escherichia coli* strain WP2 uvrA at concentrations up to 5,000 µg/plate. The chemical induced dose related increases in the number of revertant colonies with and without metabolic activation (S9) in *S. typhimurium* strains TA 98 and TA 1537. The chemical was not mutagenic in other *Salmonella* strains or in the *E. coli* strain (ECHA CHEM n.d.).
- Positive results were reported in a bacterial reverse mutation assay (OECD TG 471) in *S typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 and *E coli* strain WP2 uvrA at concentrations up to 5,000 µg/plate. The chemical induced dose related increases in the number of revertant colonies with and without metabolic activation (S9) in *S. typhimurium* strains TA1537 and TA98, and without metabolic activation in TA 1535. The chemical was not mutagenic in TA 100 or the *E. coli* strain (ECHA CHEM n.d.).

Negative results were reported in an *in vitro* mammalian chromosome aberration assay (OECD TG 473) in cultured peripheral human lymphocytes with and without metabolic activation at concentrations up to 125 µg/mL. The chemical did not induce significant chromosome aberration in 2 independent tests. In one of 2 tests there was an increase in the number of polyploid cells without S9-mix suggesting inhibition of mitotic processes (ECHA CHEM n.d.).

No experimental *in vivo* data are available for the genotoxicity of the chemical.

In silico

The available *in silico* data provide some but not conclusive evidence that that chemical may be genotoxic.

There were no alerts for the genotoxicity using the profiling functionality of the OECD QSAR Toolbox v4.5. However, predicted metabolites of the chemical using the *in vivo* rat metabolism simulator have mechanistic alerts for genotoxicity in the QSAR Toolbox. Alerts were present for:

- *in vitro* mutagenicity (1 x alpha, beta-unsaturated carbonyls; 1 x Quinones)
- micronucleus *in vivo* mutagenicity (1 x alpha,beta-unsaturated carbonyls; 2 x H-acceptor-path3-H-acceptor; 1 x Quinones)
- protein binding for chromosomal aberrations (AN2 >> Michael addition to the quinoid type structures; Hydroxylated Phenols; Substituted Phenols).

The knowledge-based expert system DEREK Nexus version 6.0.1 was utilised to estimate the genotoxicity potential of the chemical. The chemical and its metabolites generated by Nexus Meteor had no alerts for mutagenicity and were therefore predicted inactive for mutagenicity (with no misclassified or unclassified features) *in vitro* in bacterium (Ames). However, the simulated diaryl ketone metabolite of the chemical had alerts for non-genotoxic carcinogenicity (Lhasa Limited).

ChemTunes ToxGPS predicted a negative result for Ames mutagenicity, an uncertain result for *in vitro* chromosomal aberration, and a positive result for *in vivo* micronucleus (predictions were within the applicability domain of the models) (MN-AM n.d.). No mechanistic information was available for the *in vivo* micronucleus prediction.

The chemical was out of domain using OASIS−TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator).

Carcinogenicity

No data are available.

Reproductive and development toxicity

Based on the available data the chemical may cause adverse effects on fertility and development which warrants hazard classification (see **Hazard classifications relevant for worker health and safety** section).

The chemical caused a significant reduction in the number of implantation sites, reduced post-implantation survival of pups, and reduced live litter size in a reproduction/developmental toxicity screening test (OECD TG 422) in rodents. The study also provides evidence of altered pup growth. The observed adverse effects on female fertility occurred together with organ toxicity (thyroid hypertrophy and inflammatory cell infiltration in adrenal gland), but in the absence of general toxicity (see **Repeated dose toxicity** section). Survival, clinical signs, food consumption and changes in body weight or body weight gain did not indicate overt systemic toxicity. The evidence of target organ toxicity is not sufficient alone to conclude that effects on fertility and development could be a secondary non-specific consequence to other toxic effects. Therefore, a classification of Reproductive Toxicity 1B; May damage fertility and the unborn child is warranted based on clear evidence of adverse effects on sexual function and fertility and development.

Sexual function and fertility

In a GLP compliant combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test (OECD TG 422) (see **Repeat dose toxicity** section), Wistar Han rats (10/sex/group) were administered the chemical (in polyethylene glycol) via gavage at 0, 100, 300 or 1,000 mg/kg bw/day. All animals were dosed prior to mating (14 days), throughout mating, and until termination for male rats, or throughout gestation and to 13–15 days post-delivery for female rats (see **Repeated dose toxicity** section).

The total number of implantation sites per dose group were reduced by 18.46%, 16.92% and 41.54% compared to the controls at 100, 300, and 1,000 mg/kg bw/day, respectively. The mean number of implantation sites per pregnant female were significantly reduced at 1,000 mg/kg bw/day (26.9%). *Corpora lutea* were counted only for females with zero implantation sites. Therefore, the evidence of pre-implantation loss cannot be clearly assessed. There was evidence of pregnancy in 8/10 females but only one of these produced offspring (see **developmental toxicity)**. In these 7, small and aged implantation were sighted and noted, with minimal to no development of the mammary glands. Increased relative and absolute ovary weight was observed in females at the highest dose. However, there were no abnormal histological findings in the assessed ovaries. No treatment-related effect on oestrus cycle, sperm parameters, and morphology of the reproductive organs of both sexes was reported in all dosed groups. No significant changes in anogenital distance (AGD) or nipple retention were reported at 100 and 300 mg/kg bw/day. The NOAEL was 300 mg/kg bw/day for reproductive toxicity, based on the significant reduction in the number of implantation sites at 1,000 mg/kg bw day (ECHA 2023a; ECHA 2023b; ECHA CHEM n.d.).

Developmental toxicity

A dose-dependent reduction in post-implantation survival indices was observed, with survival indices of 82%, 78%, 3% for the 100, 300 and 1,000 mg/kg bw/day dose groups, respectively. The indices were lower than the control (89%) and available historical control data (HCD) for all dose groups. At 1,000 mg/kg bw/day, no live pups were born. Out of 8 pregnant dams 7 had implantation sites only and the remaining dam gave birth to 2 stillborn pups. A dose related but not statistically significant decrease in litter size was observed (11.4, 9.8, 9.2, 0 at 0, 100, 300 and 1,000 mg/kg bw/day, respectively)

The full assessment of the developmental toxicity could not be evaluated in this study as no live pups were born at highest dose. A statistically significant increase in postnatal deaths of pups was noted in the 300 mg/kg bw/day group. The viability index on postnatal day (PND) 4 was 95% which was below the mean HCD value.

Mean body weights of male and female pups in the 300 mg/kg bw/day dose group were lower compared with controls on PND4 by 9%. This trend continued until the end of the lactation period (PND 13), where there was a 17% difference compared to controls. From PND 7 onwards, the lower mean body weights were statistically significant. For male pups, mean birth weight was also reduced (8%), for female pups the reduction was less severe (5%).

No other effects on clinical chemistry, gross pathology, or clinical signs were evident in the pups at any dose tested. The developmental toxicity NOAEL was determined as < 100 mg/kg bw/day due to the reduced post-implantation survival of pups and reduced live litter size (ECHA 2023a; ECHA 2023b; ECHA CHEM n.d.).

Endocrine effects

Limited data are available on the endocrine effects of the chemical. Although some endocrine activity has been observed *in vitro*, the available data do not provide sufficient evidence of an adverse effect from an endocrine mode of action.

Endocrine activity

In the available OECD TG 422 study, increased thyroid stimulating hormone (TSH) levels (with no apparent dose response) were reported in males of all dose groups, without a corresponding increase in thyroxine (T4) levels (see **Repeat dose toxicity** section).

In vitro cell-based assays were used to determine the activation or inhibition of steroid and non-steroid hormone receptors by 4-phenylbenzophenone at concentrations of 1 µM, 10 µM, 100 µM and 1 mM. The chemical had agonistic activity in the µM range activating oestrogen receptors 1 and 2 (ER1, ER2). Receptor activation corresponding to 10–50% of the reference ligand response was classified as weak to moderate activity (+), while responses exceeding 50% were classified as strong activity (++). While ER1 and ER2 were activated by 4-phenylbenzophenone to relatively strong (++) and weak/moderate (+) levels, respectively when tested in the µM range, in comparison the endogenous ligand oestradiol is active in the pM range, indicating much higher endogenous potency. Quantitative activity values such as EC50 were not reported in this publication. The chemical caused antagonistic effects in ER2 assays, reducing the response of the reference oestrogen ligand when present at µM levels. There was also activation of thyroid hormone receptor beta (TRβ), suggesting 4-phenylbenzphenone may have the potential to affect thyroid regulation (Simon et al 2016).

Adverse effects

In the available OECD TG 422 study no treatment-related effects on oestrus cycle, sperm parameters, and morphology of the reproductive organs of both sexes were reported in all dosed groups. No significant changes in anogenital distance (AGD) or nipple retention were observed. Histopathological changes observed in the thyroid and adrenal glands at 1,000 mg/kg bw/day were minimal to slight in severity. The chemical caused adverse effects on fertility and foetal development in this study, but no mode of action has been established (ECHA 2023a; ECHA 2024b).

References

Bradley EL, Stratton JS, Leak J, Lister L, Castle L (2013) Printing ink compounds in foods: UK survey results. Food Addit Contam Part B Surveill. 6(2):73-83. doi:10.1080/19393210.2012.725774

CAS (Chemical Abstracts Service) (n.d.) *CAS SciFinder*^{n}, CAS website, assessed 22 August 2025.

Chen ML, Chen CH, Huang YF, Chen HC, Chang JW (2022) Cumulative Dietary Risk Assessment of Benzophenone-Type Photoinitiators from Packaged Foodstuffs. Foods. 2022;11(2):152, doi:10.3390/foods11020152

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (2003) Technical Report No. 87 Contact Sensitisation: Classification According to Potency. ISSN-0773-8072-87.

ECHA European Chemicals Agency Committee for Risk Assessment (2023a), *CLH report: Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Chemical name: 4-Phenylbenzophenone*, ECHA website, accessed 22 August 2024.

ECHA European Chemicals Agency Committee for Risk Assessment (2023b), *Opinion: proposing harmonised classification and labelling at EU level of 4-phenylbenzophenone*, ECHA website, accessed 22 August 2024.

FCCdb (Food Contact Chemicals database) (n.d.) *FCCmigex database A systematic evidence map to explore migrating and extractable food contact chemicals - version 5*, accessed 9 March 2026.

FSANZ (Food Standards Australia New Zealand) (2016) *The 24th Australian Total Diet Study (ATDS), Phase 2*, FSANZ website, accessed 9 March 2026.

FSANZ (Food Standards Australia New Zealand) (n.d.) *Food Standards Code legislation*, FSANZ website, accessed 01 August 2025.

FSVO (Switzerland Federal Food Safety and Veterinary Office) (2020) *Annex 10 of the Ordinance of the FDHA on materials and articles intended to come into contact with foodstuffs - List of permitted substances for the production of packaging inks, and related requirements*, FSVO website, accessed 01 August 2025.

Government of Canada (n.d.) *Methanone, [1,1'-biphenyl]-4-ylphenyl- Significant New Activity (SNAc) Orders and Notices*, Government of Canada website, accessed 9 March 2026.

Jung T, Simat TJ, Altkofer W, Fügel D (2013) Survey on the occurrence of photo-initiators and amine synergists in cartonboard packaging on the German market and their migration into the packaged foodstuffs. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 30(11):1993-2016. doi:10.1080/19440049.2013.837586

Lhasa Limited (2018) Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus (Version 6.0.1), [Computer software], Lhasa Limited, accessed 22 August 2025.

MN-AM (Molecular Networks GmbH Altamira LLC) (n.d.) ChemTunes·ToxGPS®, [Computer software], MN-AM, accessed 17 March 2026.

OASIS LMC (Laboratory of Mathematical Chemistry) Optimised Approach based on Structural Indices Set–TIssue MEtabolism Simulator (OASIS–TIMES) (Version 2.31.2), [Computer software], LMC, accessed 22 August 2025.

OECD (Organisation for Economic Co-operation and Development) (2024) Quantitative Structure Activity Relationship Toolbox (Version 4.5) [Computer software], OECD website, accessed 22 August 2025.

ECHA (European Chemicals Agency) CHEM (n.d.), REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) registered dossier for 4-phenylbenzophenone, CAS No. 2128-93-0, dossier registration date: 26 April 2018, *European Chemicals Agency website*, accessed 16 August 2026.

Simon C, Onghena M, Covaci A, Van Hoeck E, Van Loco J, Vandermarken T, Van Langenhove K, Demaegdt K, Mertens B, Vandermeiren K, Scippo ML, Elskens M (2016) Screening of endocrine activity of compounds migrating from plastic baby bottles using a multi-receptor panel of in vitro bioassays,Toxicology in Vitro, Volume 37, 121-133, https://doi.org/10.1016/j.tiv.2016.09.008.

SWA (Safe Work Australia) (n.d.) *Hazardous Chemical Information System*, SWA website, accessed 01 August 2025.

US EPA (United States Environmental Protection Agency) (2016) *2016 CDR Data*, US EPA website, accessed 30 July 2025.

US EPA (United States Environmental Protection Agency) (2020) *2020 CDR Data*, US EPA website, accessed 30 July 2025.