

THE CANCER ASSOCIATION OF SOUTH AFRICA (CANSA)



Fact Sheet and Position Statement on Oxybenzone

Compound/Chemical name:

Oxybenzone

Synonyms:

Benzophenone-3; BP-3; (2-Hydroxy-4-Methoxyphenyl)Phenyl- Methanone, (2-Hydroxy-4-Methoxyphenyl) Phenylmethanone, 2-Benzoyl-5-Methoxyphenol, 2-Hydroxy-4-Methoxybenzophenone, 4-08-00-02442 (Beilstein Handbook Reference), 4-Methoxy-2-Hydroxybenzophenone, Advastab 45, Ai3-23644, Anuvex, B3, Benzophenone, 2-Hydroxy-4-Methoxy-, Brn 1913145, Ccris 1078, Chimassorb 90, Cyasorb Uv 9, Cyasorb Uv 9 Light Absorber, Durascreen, Einecs 205-031-5, Escalol 567, Hmbp, Hsdb 4503, Methanone, (2-Hydroxy-4-Methoxyphenyl)Phenyl-, Methanone, (2hydroxy4methoxyphenyl) Phenyl, Mob, Mod, Nci-C60957, Nsc 7778, Nsc-7778, Ongrostab Hmb, Oxibenzona, Oxibenzonum, Oxybenzon, Oxybenzone 6, Oxybenzonum, Solaquin, Spectra-Sorb UV 9, Sunscreen UV-15, Syntase 62, UF 3, Usaf Cy-9, UV 9, Uvinul 9, Uvinul M40, And Uvistat 24

What is it?

Oxybenzone, also known as benzophenone-3 or BP-3, is one of 16 active sunscreen ingredients approved by the U.S. Food and Drug Administration (FDA) for use in over-the-counter (OTC) sunscreens and was first approved in 1978. Although the FDA has approved the use of oxybenzone as an active ingredient in sunscreens and other personal care products as safe and effective in concentrations up to 6%, the 2005 CIR safety review indicates that according to the data voluntarily submitted to the FDA oxybenzone is typically used at concentrations <1% [1]. Active sunscreen ingredients are compounds that absorb, reflect or scatter ultraviolet (UV) radiation. As active ingredient, Oxybenzone provides broad-spectrum protection (protection against both UVA (320-400 nm) and UVB (280-320 nm) ultraviolet radiation) against the harmful effects of the sun.

The safety of oxybenzone has been and is regularly evaluated by regulatory authorities such as the FDA, Cosmetic Ingredient Review (CIR) expert panel and Scientific Committee on Consumer Products (SCCP) and is currently approved as safe and effective sunscreen ingredient in the US (FDA), Canada, Australia, the European Union and several ASEAN countries. However, in the past few years, oxybenzone has received increasing attention as a potentially harmful compound with some evidence linking oxybenzone to photoallergic reactions, skin absorption, hormone disruption and ecotoxicity. This document forms part of CANSA's larger effort to educate the public and put into perspective the scope of evidence on oxybenzone including its functions; oral and dermal toxicity; absorption, metabolism and excretion; irritancy and sensitization; reproductive and developmental toxicity; and carcinogenicity.

Functions:

Active sunscreen agent/ingredient, UV light absorber, UV filter and photostabilizer/photo-protector (because oxybenzone absorbs and dissipates UV radiation, it can also serve to protect cosmetics and personal care products from deterioration due to exposure to UV light). FDA approved indirect food additive in acrylic and modified acrylic plastics that come into contact with food.

Oral and Dermal Toxicity

For the reader, **acute toxicity** refers to the ability of a substance to cause adverse effects as result of either a single exposure or from multiple exposures to the substance in a short period of time (usually less than 24 hours). Whereas, **sub-chronic toxicity** refers to the ability of a substance to cause adverse effects after repeated or continuous administration of a substance for up to 90 days or not exceeding 10% of the animal's lifespan. **Chronic toxicity** refers to the ability of a substance to cause adverse effects as result of long-term exposure to the substance (more than 10% of animal's life-span – months or years). In toxicology, the **median lethal dose**, LD₅₀, LC₅₀ or LCt₅₀ is a measure of the lethal dose of a substance. The value of LD₅₀ for a substance is the dose required to kill half the members of a tested population after a specified test duration.

Results from acute oral (substance taken in by mouth) toxicity animal studies indicate that oxybenzone are practically non-toxic, with the most recent rat oral LD₅₀ reported to be greater than 12g/kg [2–5]. The acute rat dermal (by contact with skin) LD₅₀ for oxybenzone has been reported to be greater than 16 g/kg . Naturally occurring local skin reactions consisting of mild to moderate erythema (reddening of skin caused by increased blood flow in superficial capillaries) not associated with pathology (diseases) were found in two animals at the 2 g/kg dose 24 and 48 hours following exposure to the skin [5,6].

It was found that Oxybenzone, in a study on sub-chronic oral toxicity, caused no toxic effects in rats when incorporated into their diets (up to 1%) for 27 days, while a 90 day study showed feeding rats 0.5% and 1% depressed growth, increased white blood cells (leucocytosis), decreased haemoglobin concentrations (anaemia), reduced organ weights, and kidney degeneration (nephrosis) [4–6]. the National Toxicology Programme (NTP) reported results from three studies, after two weeks oral administration liver and kidney weights were increased and microscopic changes in the kidney were found primarily in high-dose rats. In the 13 week oral study, oxybenzone administration was associated with decreased body weight gain in both female and male rats and progressed kidney lesions [7].

Absorption, Metabolism and Excretion

Both *in vitro* (studies performed with microorganisms, cells, or biological molecules outside their normal biological context) and human studies have demonstrated that oxybenzone is absorbed into the skin when applied topically. Oxybenzone is then broken down (metabolized) and excreted mainly in urine (67%) [8,9] and faeces (21%) [10,11], with a further studies reporting excretion in breast milk [12,13]. However, in 2019, the U.S. Food and Drug Administration (FDA) noted in their recommendations for future study that, "While research indicates that some topical drugs can be absorbed into the body through the skin, this does not mean these drugs are unsafe" [14] as the doses and extent of exposure will influence the safety profile. Therefore, according to their recommendations more studies on the safety of repeated use is needed.

Skin Irritancy and Sensitization

Procedures outlined by the Federal Hazardous Substances Labelling Act (FHSLA) were used in two studies to test oxybenzone for acute skin irritation, which found it to be non-irritating to both intact and abraded (scratched) skin of albino rats at concentrations from 4% to 100% [5]. Another animal study using the Kligman Maximization procedure to test the sensitizing potential of oxybenzone found that after intradermal injection of 5% oxybenzone, followed by a topical booster patch containing 10% oxybenzone administered after 7 days from injection was non-sensitizing to albino guinea pigs skin [5].

Oxybenzone has also been tested for its potential irritation and sensitization to human skin. In general, it was found to be non-irritating and non-sensitizing at concentrations higher than those found in cosmetic products. Please see below table for summarized results:

Table 1: Clinical assessment of skin irritation and sensitization of oxybenzone (Human patch test data)

Test Method	No. of subjects	Oxybenzone concentration (%)	No. of reactions	Comments	Reference
Single Insult Patch Test (SIPT)	14	16, 8 & 4	0	Non-irritating	[5]
Modified Draizel/Shelanski Repeated Insult Patch Test (Mod. D/S RIPT)	100	16, 8 & 4	0	Non-irritating/non-sensitizing	[15]
Mod. D/S RIPT	203	25	0	Non-irritating/non-sensitizing	[5]
SIPT	100	10	0	Non-irritating	[16]
Mod. D/S RIPT	150	3	Several non-specific reactions	Not a primary irritant; non-sensitizing	[16]
Mod. D/S RIPT	150	3	Mild irritation (Challenge patches)	Non-sensitizing	[16]
Mod. D/S RIPT	57	3	1 Sensitized reaction	Minimum sensitizing potential	[5]
RIPT	19570	1 to 6	48 dermal responses (0.26% of population)	Non-significant sensitization and irritation potential	[17]
SkinEthic™, human epidermis model	N/A	-	-	Negative for phototoxicity	[17]

Reproductive and Developmental Toxicity

A study by Schlumpf *et al.* [18], has studied the oestrogenic (estrogen – American spelling) effects (ability to act as the hormone oestrogen) of oxybenzone and found stimulation breast cancer cell (MCF-7) growth and increase of uterine weight by oxybenzone, however it should be noted that the oestrogenic effect of oxybenzone is proven here to be weak as the **detected stimulation was 1 millionth-fold less than that of oestrogen**, the positive control. In fact, a study by Wang *et al.* [19], with the aim to place into perspective the doses of oxybenzone used by Schlumpf *et al.* [18], conservatively estimated that it would take up to

277 years of daily application (at generous in-use dose of 1 mg/cm²) of a sunscreen containing 6% oxybenzone on 25% of the body (face, neck, hands, and arms) to attain a comparable level of exposure in humans as used in the study of Schlumpf *et al* [18], whereas for 100% body coverage with the same applied daily dose it would take up to 69.3 years. It should be noted that this estimation is deemed as conservative as it does not take into account the excretion (amount or rate) of oxybenzone. Furthermore, a NTP study found that oxybenzone did not cause an uterotrophic response (effect on the uterus) in ovariectomised (surgical removal of both ovaries) rats when tested up to 1 g/kg [20].

With regards to animal studies, both 2- and 13-week dosed feed studies from the NTP, rats and mice in the highest dose group (receiving a diet with 50000 ppm oxybenzone) exhibited a decrease in epididymal sperm density (27%) and an increase in length of the estrous cycle. Their 2-week dermal study in mice also supported these findings. However, a reproductive assessment by continuous breeding study in mice at the same concentrations used in previously mentioned study showed that oxybenzone had no effect on the fertility of the F₀ (parental) group as no changes in sperm density or oestrogen cycles were found. Furthermore, minimal effects of fertility was found in the F1 (first new generation) and it was concluded that oxybenzone had minimal effects on fertility and reproduction at the exposure concentrations [21]. Another study assessing the effects of maternal and lactational exposure to Oxybenzone on development and reproductive organs in rat offspring, found that at the highest dose (50 000ppm), spermatocyte development was impaired and ovarian follicular development was delayed, while concentrations of 10 000ppm and less showed no adverse effects on the reproductive system in rats [21]. It is important to note that the high doses at which adverse events occurred are much higher than usual human exposure levels.

One maternal exposure study in humans has found that oxybenzone is associated with lower birth weight, while another has shown a positive correlation between oxybenzone concentration and body weight [22,23]. It has been postulated that oxybenzone is involved in the development of Hirschsprung's disease, as one study estimated that odds ratio of having a child with Hirschsprung's disease is slightly increased (2.4:1 increased to 2.6:1) in pregnant women with high oxybenzone concentrations in their urine [24]. Another study by Janjua *et al.* [25], reported that when oxybenzone was repeatedly applied to the entire body of human volunteers, no biologically significant alterations in reproductive hormones (testosterone, follicle-stimulating hormone, luteinizing hormone, or oestradiol) were detectable. These findings were supported by a similar study assessing the potential effect of oxybenzone dermal application on serum hormone changes in young men and postmenopausal women, which concluded that the amount of oxybenzone absorbed did not alter the endogenous (produced within the body) reproductive hormone homeostasis [24].

Carcinogenicity (ability to cause cancer):

A recent study by the NTP found equivocal (ambiguous/unclear) evidence of carcinogenic activity when fed to Hsd:Sprague Dawley® SD® Rats, while oxybenzone was found to not have carcinogenic activity when fed to B6C3F1/N Mice even at the highest exposure concentration, 10 000ppm [20]. No further literature was found on carcinogenicity of oxybenzone.

Genotoxicity:

Oxybenzone was found to be negative in tests screening for mutagenic agents in sunscreen [26,27]. Oxybenzone was found to be non-mutagenic when mixed with 10% hamster liver S9 feed, however when

mixed with 30% hamster liver S9 feed it showed weak mutagenic effects [7]. Also oxybenzone was positive for induction of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells when testing occurred in the presence of rat liver S9 mix [7]. *In vivo* studies (animal studies) utilising *Drosophila*, male Sprague Dawley rats and mice to assess oxybenzone's genotoxic potential, found no mutagenic effects [7,28]. The main metabolite of oxybenzone, DHB, was also found to be non-mutagenic [29,30].

Government Restrictions:

Restricted to concentrations up to 6% by the FDA for over the counter sunscreen products and other personal care products.

CANSA Position Statement

The CANSA Seal of Recognition, known by consumers as the CANSA Smart Choice Seal, is an educational initiative of the Cancer Association of South Africa (CANSA) aimed at reducing consumer's risk of developing cancer. Scientists estimate that between 30-50% of all cancer cases are preventable if exposure to cancer risk factors is reduced and consumers adopt healthier lifestyles particularly pertaining to their diet [31–34]. The CANSA Seal is awarded to products that may aid in reducing consumer's risk of developing cancer and promotes healthy lifestyle choices.

As ultraviolet (UV) radiation, and in particular solar radiation, has been proven to be carcinogenic to humans, causing all major types of skin cancer, such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma, CANSA awards its Seal to products that reduce consumers exposure to UV radiation, such as sunscreen and protective clothing and apparel per condition that the product complies with CANSA's stringent evidence based criteria, National Standards (SANS) and International Standards (ISO) and have been tested by an independent laboratory for effectiveness. Thus, the CANSA Seal serves as a tool for consumers to easily identify safe and effective sun protection products.

On the basis of the data available on oxybenzone in literature, the majority of research studies support that oxybenzone is safe for topical application to humans in the present practices of use and concentration and that more research is needed to support the recent, equivocal evidence on oxybenzone as potentially harmful substance. However, CANSA's Research and Operations Committee (ROC) has decided to steer on the side of caution and has added oxybenzone to CANSA's unacceptable list of ingredients, which forms part of our requirements for sunscreen and personal care products to be awarded the CANSA Seal of Recognition, until indisputable/ conclusive evidence comes to light. In light of this decision CANSA has given notice to all Seal bearing sunscreen manufacturers to remove oxybenzone from their formulation, all of whom have agreed to remove oxybenzone from their sunscreen, which is currently being implemented within the agreed period for old products to exit circulation.

Resources:

- [1] Cosmetic Ingredient Review Expert Panel, Annual Review of Cosmetic Ingredient Safety Assessments - 2002/2003, *Int. J. Toxicol.* 24 (2005) 1–102. doi:10.1080/10915810590918625.
- [2] By Submission of data, CTFA., INDUSTRIAL BIOLOGY AND RESEARCH TESTING LABS (IBRTL), 1960.
- [3] S. Homrowski, Studies on the toxicity of additives applied in the domestic production of plastics. 3. Acute and subacute toxicity of some benzophenone derivatives., *Rocz. Panstw. Zakl. Hig.* 19 (1968) 179–87. <http://www.ncbi.nlm.nih.gov/pubmed/5662410> (accessed January 28, 2020).

- [4] H.J. Lewerenz, G. Lewerenz, R. Plass, Acute and subacute toxicity studies of the UV absorber MOB in rats, *Food Cosmet. Toxicol.* 10 (1972) 41–50. doi:10.1016/S0015-6264(72)80045-2.
- [5] Cosmetics Ingredient Review Expert panel (CIR), Final Report on the Safety Assessment of Benzophenones-1, 3, 4, 5, 9, and 11, *J. Am. Coll. Toxicol.* 2 (1983) 35–77. doi:10.3109/10915818309140714.
- [6] Submission of data by CTFA., HAZELTON LABS, 1953.
- [7] J.E. French, NTP technical report on the toxicity studies of 2-Hydroxy-4-methoxybenzophenone (CAS No. 131-57-7) Administered Topically and in Dosed Feed to F344/N Rats and B6C3F1 Mice., *Toxic. Rep. Ser.* 21 (1992) 1-E14. <http://www.ncbi.nlm.nih.gov/pubmed/12209185> (accessed January 28, 2020).
- [8] C. Han, Y.H. Lim, Y.C. Hong, Ten-year trends in urinary concentrations of triclosan and benzophenone-3 in the general U.S. population from 2003 to 2012, *Environ. Pollut.* 208 (2016) 803–810. doi:10.1016/j.envpol.2015.11.002.
- [9] L. Wang, K. Kannan, Characteristic profiles of benzophenone-3 and its derivatives in urine of children and adults from the United States and China, *Environ. Sci. Technol.* 47 (2013) 12532–12538. doi:10.1021/es4032908.
- [10] M. Okereke, CS and Abdel-Rahman, Species differences in the disposition of benzophenone-3 after oral administration in rat and mouse, *TOXIC SUBST. J.* 13 (1994) 239–251.
- [11] S.M. El Dareer, J.R. Kalin, K.F. Tillery, D.L. Hill, Disposition of 2-hydroxy-4-methoxybenzophenone in rats dosed orally, intravenously, or topically, *J. Toxicol. Environ. Health.* 19 (1986) 491–502. doi:10.1080/15287398609530947.
- [12] M. Schlumpf, S. Durrer, O. Faass, C. Ehnes, M. Fuetsch, C. Gaille, M. Henseler, L. Hofkamp, K. Maerkel, S. Reolon, B. Timms, J.A.F. Tresguerres, W. Lichtensteiger, Developmental toxicity of UV filters and environmental exposure: A review, in: *Int. J. Androl.*, 2008: pp. 144–150. doi:10.1111/j.1365-2605.2007.00856.x.
- [13] E.P. Hines, P. Mendola, O.S. von Ehrenstein, X. Ye, A.M. Calafat, S.E. Fenton, Concentrations of environmental phenols and parabens in milk, urine and serum of lactating North Carolina women, *Reprod. Toxicol.* 54 (2015) 120–128. doi:10.1016/j.reprotox.2014.11.006.
- [14] FDA finalizes recommendations for studying absorption of active ingredients in topically-applied OTC monograph drugs | FDA, (n.d.). <https://www.fda.gov/news-events/fda-brief/fda-finalizes-recommendations-studying-absorption-active-ingredients-topically-applied-otc-monograph> (accessed January 27, 2020).
- [15] H. Wolska, H. Wolska, A. Langner, F.N. Marzulli, P. D, The hairless mouse as an experimental model for evaluating the effectiveness of sunscreen preparations, *J. SOC. COSMET. CHEM.* (n.d.) 974. <http://citeseerx.ist.psu.edu/viewdoc/summary?doi=10.1.1.624.3723> (accessed January 30, 2020).
- [16] FDA, Report on Sunscreen Drug Products for Over-the-Counter Human Drugs., 1978.
- [17] P.P. Agin, K. Ruble, S.J. Hermansky, T.J. McCarthy, Rates of allergic sensitization and irritation to oxybenzone-containing sunscreen products: A quantitative meta-analysis of 64 exaggerated use studies, *Photodermatol. Photoimmunol. Photomed.* 24 (2008) 211–217. doi:10.1111/j.1600-0781.2008.00363.x.

- [18] M. Schlumpf, B. Cotton, M. Conscience, V. Haller, B. Steinmann, W. Lichtensteiger, In vitro and in vivo oestrogenicity of UV screens, *Environ. Health Perspect.* 109 (2001) 239–244. doi:10.1289/ehp.01109239.
- [19] S.Q. Wang, M.E. Burnett, H.W. Lim, Safety of oxybenzone: Putting numbers into perspective, *Arch. Dermatol.* 147 (2011) 865–866. doi:10.1001/archdermatol.2011.173.
- [20] National Toxicology Program (NTP), NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2-Hydroxy-4-methoxybenzophenone (CAS No. 131-57-7) Administered in Feed to Sprague Dawley (Hsd:Sprague Dawley® SD®) Rats and B6C3F1/N Mice, (2019). <http://ntp.niehs.nih.gov> (accessed January 29, 2020).
- [21] J.E. French, National Toxicology Program Toxicity Report Series Number 21 NTP Technical Report on Toxicity Studies of 2-Hydroxy-4-methoxybenzophenone (CAS Number: 131-57-7) Administered Topically and in Dosed Feed to F344/N Rats and B6C3F1 Mice, 1992.
- [22] C. Philippat, M. Mortamais, C. Chevrier, C. Petit, A.M. Calafat, X. Ye, M.J. Silva, C. Brambilla, I. Pin, M.A. Charles, S. Cordier, R. Slama, Exposure to phthalates and phenols during pregnancy and offspring size at birth, *Environ. Health Perspect.* 120 (2012) 464–470. doi:10.1289/ehp.1103634.
- [23] M.S. Wolff, S.M. Engel, G.S. Berkowitz, X. Ye, M.J. Silva, C. Zhu, J. Wetmur, A.M. Calafat, Prenatal phenol and phthalate exposures and birth outcomes, *Environ. Health Perspect.* 116 (2008) 1092–1097. doi:10.1289/ehp.11007.
- [24] W. Huo, P. Cai, M. Chen, H. Li, J. Tang, C. Xu, D. Zhu, W. Tang, Y. Xia, The relationship between prenatal exposure to BP-3 and Hirschsprung's disease, *Chemosphere.* 144 (2016) 1091–1097. doi:10.1016/j.chemosphere.2015.09.019.
- [25] N.R. Janjua, B. Mogensen, A.M. Andersson, J.H. Petersen, M. Henriksen, N.E. Skakkebaek, H.C. Wulf, Systemic absorption of the sunscreens benzophenone-3, octyl- methoxycinnamate, and 3-(4-methyl-benzylidene) camphor after whole-body topical application and reproductive hormone levels in humans, *J. Invest. Dermatol.* 123 (2004) 57–61. doi:10.1111/j.0022-202X.2004.22725.x.
- [26] A.M. Bonin, A.P. Arlauskas, D.S. Angus, R.S.U. Baker, C.H. Gallagher, G. Greenoak, M.M.L. Brown, K.M. Meher-Homji, V. Reeve, UV-absorbing and other sun-protecting substances: genotoxicity of 2-ethylhexyl P-methoxycinnamate, *Mutat. Res. Lett.* 105 (1982) 303–308. doi:10.1016/0165-7992(82)90097-5.
- [27] K. Morita, M. Ishigaki, T. Abe, Mutagenicity of Materials related with Cosmetics, *J. Soc. Cosmet. Chem. Japan.* 15 (1981) 243–253. doi:10.5107/sccj.15.3_243.
- [28] S.H. Robison, M.R. Odio, E.D. Thompson, M.J. Aardema, A.L. Kraus, Assessment of the in vivo genotoxicity of 2-hydroxy 4-methoxybenzophenone, *Environ. Mol. Mutagen.* 23 (1994) 312–317. doi:10.1002/em.2850230409.
- [29] Hazardous Substances Data Bank. 2,4-Dihydroxybenzophenone. National Library of Medicine (US), Division of Specialized Information Services, 2-HYDROXY-4-METHOXYBENZOPHENONE. (n.d.). <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+131-57-7> (accessed January 27, 2020).
- [30] V. Sarveiya, S. Risk, H.A.E. Benson, Liquid chromatographic assay for common sunscreen agents: Application to in vivo assessment of skin penetration and systemic absorption in human volunteers, *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 803 (2004) 225–231.

doi:10.1016/j.jchromb.2003.12.022.

- [31] K.F. Brown, H. Rumgay, C. Dunlop, M. Ryan, F. Quartly, A. Cox, A. Deas, L. Elliss-Brookes, A. Gavin, L. Hounsome, D. Huws, N. Ormiston-Smith, J. Shelton, C. White, D.M. Parkin, The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015, *Br. J. Cancer*. 118 (2018) 1130–1141. doi:10.1038/s41416-018-0029-6.
- [32] Nearly 40% of Cancer Deaths Are Preventable With Lifestyle Changes, Says Study, (n.d.). <https://www.sciencealert.com/lifestyle-changes-could-stop-40-of-cancer-deaths> (accessed January 30, 2020).
- [33] L.F. Wilson, A. Antonsson, A.C. Green, S.J. Jordan, B.J. Kendall, C.M. Nagle, R.E. Neale, C.M. Olsen, P.M. Webb, D.C. Whiteman, How many cancer cases and deaths are potentially preventable? Estimates for Australia in 2013, *Int. J. Cancer*. 142 (2018) 691–701. doi:10.1002/ijc.31088.
- [34] WHO | Cancer prevention, (n.d.). <https://www.who.int/cancer/prevention/en/> (accessed January 30, 2020).