

Dibenzoyl peroxide

MAK Value Documentation, addendum – Translation of the German version from 2024

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Keywords

dibenzoyl peroxide; irritation; eye; sensitization; developmental toxicity; MAK value; maximum workplace concentration; peak limitation; read across

Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) summarized and re-evaluated the data for dibenzoyl peroxide [94-36-0] to derive an occupational exposure limit value (maximum concentration at the workplace, MAK value) considering all toxicological end points. Relevant studies were identified from a literature search and also unpublished study reports were used. Dibenzoyl peroxide is at most mildly irritating to the skin of rabbits, but highly irritating to the rabbit eye. Eye irritation is the critical effect of the substance. Studies with repeated inhalation exposure to dibenzoyl peroxide are not available. Therefore, data for benzoic acid, the hydrolysis product of dibenzoyl peroxide, are used for the evaluation. Dibenzoyl peroxide is converted only slowly to benzoic acid, which is a much stronger eye irritant than dibenzoyl peroxide. Taking this into account as well as the maximum concentration at the workplace (MAK value) of 2 mg/m³ established for benzoic acid, a MAK value of 4 mg/m³ has been set for the inhalable fraction of dibenzoyl peroxide. Due to the immediate onset of the eye irritation, the substance has been assigned to Peak Limitation Category I. An excursion factor of 2 has been derived by analogy to benzoic acid. Again, on the basis of the data for benzoic acid, a MAK value of 1 mg/m³ has been derived for the respirable fraction and the substance has been assigned to Peak Limitation Category II with an excursion factor of 4. Damage to the embryo or foetus is unlikely if the MAK value is not exceeded. Thus, dibenzoyl peroxide has been assigned to Pregnancy Risk Group C. Studies investigating the genotoxic potential of dibenzoyl peroxide found increased levels of (oxidative) DNA damage in vitro and in vivo, but no clastogenic or mutagenic effects. The tumour-promoting effects of dibenzoyl peroxide that were observed on the skin of mice and hamsters are of no relevance for humans. There is no evidence of carcinogenic effects after oral or dermal exposure of rats and mice. Despite extensive clinical use of dibenzoyl peroxide as a topical treatment for acne, no cases of substance-related skin cancer in humans have been reported. Dermal absorption is not expected to contribute significantly to systemic toxicity. Although the results of new approach methodologies and animal studies suggest that dibenzoyl peroxide has sensitizing potential, there is still no reliable evidence of an increased risk from occupational exposure. There are no data for respiratory sensitization.

Citation Note:

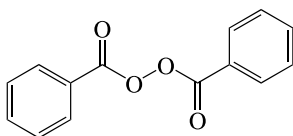
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MAK value (2023)	1 mg/m³ R (respirable fraction) 4 mg/m³ I (inhalable fraction)
Peak limitation (2023)	R fraction: category II, excursion factor 4 I fraction: category I, excursion factor 2
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2023)	Pregnancy Risk Group C
Germ cell mutagenicity	–
BAT value	–
Synonyms	benzoperoxide benzoyl superoxide diphenylglyoxal peroxide
Chemical name (IUPAC)	benzoyl benzenecarboperoxoate
CAS number	94-36-0
Structural formula	
Molecular formula	C ₁₄ H ₁₀ O ₄
Molar mass	242.23 g/mol
Melting point	104–106 °C (HCN 2012; OECD 2002)
Vapour pressure	9.29 × 10 ⁻⁵ hPa at 20 °C (calculated) (OECD 2002); 9.07 × 10 ⁻⁵ hPa at 25 °C (calculated) (ECHA 2020)
log K_{OW}	3.43 (calculated) (OECD 2002); 3.2 (experimental) (ECHA 2020)
Solubility	9.1 mg/l water at 25 °C (HCN 2012; OECD 2002); 0.35 mg/l water at 20 °C (ECHA 2020)
1 ml/m³ (ppm) ≙ 10.05 mg/m³	1 mg/m³ ≙ 0.0995 ml/m³ (ppm)
Hydrolytic stability	half-life at 25 °C determined according to OECD Test Guideline 111: 11.9 hours at pH 4, 5.2 hours at pH 7, half-life not determined at pH 9; preliminary test 5 days at 50 °C: hydrolysis of 93.5% at pH 4, 94.1% at pH 7, 94.2% at pH 9 (OECD 2002); at pH 4, 7 or 9 and 50 °C: hydrolysis of > 50% in 2.4 hours (ECHA 2020)

Production	reaction of dibenzoyl chloride with hydrogen peroxide in alkaline solution; commercialized as a solid (granules) (22%, 75% or 95%) with the corresponding residual water content (OECD 2002)
Uses	initiator for polymerization reactions (styrene polymers, acrylates and other resins) (Eben et al. 2010); as a bleaching agent for fats, oils, waxes and milk, although no longer used for bleaching flour; for preparing certain cheeses; in rubber curing; as a finishing agent for some acetate yarns; in pharmaceuticals for the topical treatment of acne in concentrations of 2.5% to 10% (HCN 2012; OECD 2002); the most widely used concentration in industry is 75%; bone cement contains between 0.5% and 2.5% dibenzoyl peroxide (Eben et al. 2010)

The documentation is largely based on the dataset publicly available through REACH (ECHA 2020), a review of genotoxicity and carcinogenicity published by the Health Council of the Netherlands (HCN 2012), an evaluation published by the International Agency for Research on Cancer (IARC 1999) and an evaluation prepared under the ICCA/HPV programme (OECD 2002). In addition, documentation for dibenzoyl peroxide was published in 1999 (Greim 1999, available in German only). Unpublished toxicological studies from companies were made available to the Commission.

Benzoic acid may form either via spontaneous degradation, which is dependent on temperature and pH, or by photolytic degradation of dibenzoyl peroxide (Zaman et al. 2001). This process may be facilitated by the presence of iron or copper ions (Binder et al. 1995; Hasegawa and Nishimura 1960).

1 Toxic Effects and Mode of Action

Dibenzoyl peroxide, applied in granule form, did not cause skin irritation in rabbits after exposure for 4 hours, but slight irritation after 24 hours. Dibenzoyl peroxide dissolved in propylene glycol or soft paraffin causes irritation of the skin of rabbits. Dibenzoyl peroxide induces marked irritation in the eyes of rabbits.

In a combined study of the toxic effects of repeated oral doses and a screening test for reproductive and developmental toxicity in Sprague Dawley rats, degeneration of the testes and the epididymis was observed in the male animals and slight increases in the absolute and relative kidney weights in the females at 1000 mg/kg body weight and day.

Dibenzoyl peroxide caused oxidative DNA damage in the form of increased levels of 8-oxo-2'-deoxyguanosine (8-oxodG) in mouse keratinocytes and in the mouse skin in vitro and in vivo and an increased incidence of DNA strand breaks in vitro. Sister chromatid exchange (SCE) was observed in vitro at cytotoxic concentrations. However, dibenzoyl peroxide was not mutagenic in bacteria and mouse lymphoma cells. Negative results were likewise obtained by in vitro tests screening for clastogenic effects and a micronucleus test and a dominant lethal test in mice. There was no increase in the induction of H-ras mutations in the skin of Sencar mice.

Despite the widespread use of dibenzoyl peroxide for the treatment of acne, an association between this use and skin cancer in humans has not been established. Dibenzoyl peroxide did not cause carcinogenic effects in rats and mice after oral and dermal exposure. The tumour-promoting effects in the skin of mice and hamsters are not relevant to humans.

In a developmental toxicity study with dibenzoyl peroxide in rats, feed consumption in the dams decreased with statistical significance and body weight gains were reduced at the dose of 1000 mg/kg body weight and day. Incomplete ossification was observed in the foetuses in a dose-dependent manner at doses of 300 mg/kg body weight and day

and above, but no malformations. In a combined study with repeated doses and a screening test for reproductive and developmental toxicity carried out in Sprague Dawley rats according to OECD Test Guideline 422, body weights were decreased and development of the offspring was delayed at 1000 mg/kg body weight and day.

Studies reported positive findings for the induction of contact sensitization in humans by dibenzoyl peroxide; however, only one case provides well-founded evidence involving healthy skin in an occupational setting. No publications that investigated sensitizing effects on the airways are available.

2 Mechanism of Action

2.1 Studies of the induction of DNA damage

A number of studies investigated the mechanisms underlying the induction of DNA strand breaks by dibenzoyl peroxide. In vitro, dibenzoyl peroxide induced DNA strand breaks in phiX-174 plasmid DNA in concentrations of 10 to 1000 µM. In this defined system, the induction was completely dependent on the addition of Cu(I). Other transition metals and benzoic acid had no effect. A benzoyloxy radical was identified by electron spin resonance spectroscopy as the primary free radical that forms from dibenzoyl peroxide (ECHA 2020).

Two studies investigated the binding of dibenzoyl peroxide to macromolecules. A study available only as an abstract reported that covalent bonds formed with proteins, but not with the DNA, after incubating primary epidermal keratinocytes from neonatal Sencar mice with ¹⁴C-ring-labelled dibenzoyl peroxide. No DNA adducts formed after pure calf thymus DNA was incubated with ¹⁴C-ring-labelled or ¹⁴C-carbonyl-labelled dibenzoyl peroxide in the presence of copper(I)chloride as the electron donor using a similar protocol. The limit of detection was 0.5 nmol/mg DNA. However, protein adducts were detected after the incubation of radioactively-labelled dibenzoyl peroxide with bovine serum albumin. Protein adducts were formed by carbonyl-labelled and ring-labelled dibenzoyl peroxide at a similar incidence. This shows that the benzoyloxy radical was the reactive species. Protein adducts or DNA adducts were not detectable after incubation with ¹⁴C-ring-labelled benzoic acid (ECHA 2020).

Neither CO₂ nor phenyl radicals were detected if dibenzoyl peroxide was incubated with copper but without cellular extracts. The induction of DNA strand breaks in plasmid DNA by dibenzoyl peroxide was inhibited by metal chelating agents and the hydrogen donors glutathione and ergothionein. *N*-tert-Butyl- α -phenylnitrone, an effective scavenger for the benzoyloxy radical, inhibited the induction of strand breaks by about 50%, while 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), which prefers to react with phenyl residues, did not prevent DNA strand breaks. The antioxidant enzymes catalase and superoxide dismutase and the hydroxyl radical scavengers mannitol and benzoic acid did not decrease the induction of DNA strand breaks by dibenzoyl peroxide. This last finding indicates that H₂O₂, superoxide and hydroxyl radicals are not involved in the induction of DNA strand breaks by dibenzoyl peroxide (ECHA 2020).

Other mechanistic studies of the induction of DNA strand breaks by dibenzoyl peroxide were carried out with the mouse keratinocyte cell line 308. Dibenzoyl peroxide induced DNA strand breaks in a concentration-dependent manner in the concentration range of 30 to 300 µM. Benzoic acid concentrations up to 300 µM did not have any effects. Consistent with the finding that glutathione prevents the induction of strand breaks in plasmid DNA, the scavenging of cellular glutathione after pre-treatment with *L*-buthionine-*S*-sulfoximine increases the sensitivity of the cells for the induction of DNA strand breaks by dibenzoyl peroxide. Strand breaks were reduced by 40% in cells incubated with dibenzoyl peroxide at 4°C in comparison with the number found in cells incubated at 37°C. This shows that the strand breaks are not dependent on enzymatic processes alone. Similar to the findings in plasmid DNA, *N*-tert-butyl- α -phenylnitrone reduced strand breaks by about 50%, while DMPO did not have any effects. The data from the 2 studies, the first using plasmid DNA and the second the mouse keratinocyte cell line 308, demonstrate that the benzoyloxy radical plays a central role in the induction of DNA strand breaks by dibenzoyl peroxide. However, indirect mechanisms, such as the activation of calcium-dependent endonuclease, may also be involved (ECHA 2020).

A study that investigated the generation of radicals by dibenzoyl peroxide in the presence of Cu(I) reported the formation of the benzoyloxy radical and the phenyl radical. Hydroxyl radicals were not observed. Other findings were the formation of adducts at the C5-C6 double bonds of pyrimidines and hydrogen abstraction at the sugar rings. Studies that investigated the RNA and DNA found evidence of base adducts, even though it was not possible to identify which adducts had formed. It is assumed that DNA strand breaks induced by dibenzoyl peroxide involve a hydrogen abstraction at the sugar-phosphate backbone. The benzoyloxy radical seems to be responsible for the majority of DNA strand breaks and the formation of base adducts (ECHA 2020).

A review described in detail the generation of radical intermediates and the penetration of dibenzoyl peroxide through the skin, which was substantiated by in vitro and in vivo studies: studies in mouse keratinocytes found that dibenzoyl peroxide is degraded by electron transfer with Cu(I) functioning as the electron donor. Benzoic acid is formed by hydrogen abstraction, while a relatively small fraction of the degradation process involves decarboxylation of the benzoyloxy radical, forming the phenyl radical and CO₂. Enzymes are apparently not involved in the initial cleavage of the peroxide bond; instead, this process depends on metals. Unlike the cleavage of the peroxide bond, the decarboxylation of the benzoyloxy radical is a specific enzyme-mediated process. Phenyl radical adducts were not detected if dibenzoyl peroxide was converted by cellular extracts in the presence of copper. The metabolism of dibenzoyl peroxide in rat liver microsomes and in mouse keratinocytes produced the same metabolites. The metabolism of dibenzoyl peroxide in the mitochondria seems to involve the transfer of 2 electrons, is therefore not mediated by free radicals and produces only benzoic acid (Binder et al. 1995).

A study investigated the induction of promutagenic damage in the *supF* gene of the mutation reporter plasmid pS189 by dibenzoyl peroxide. The plasmids were incubated in vitro with 0.1 to 1.0 mM of dibenzoyl peroxide in the presence and absence of CuCl, then transfected and replicated in human Ad293 cells. Dibenzoyl peroxide induced a concentration-dependent increase in this system with a maximum mutant frequency that was more than 100 times that found in the controls. Copper did not have to be present for mutations to form, but increased the effect. The majority of the sequenced mutants contained point mutations, but also large and small deletions in the *supF* gene. There was a strong preference for mutations in GC base pairs, which could be binding sites for copper on the DNA. The induction of mutations by dibenzoyl peroxide was not inhibited by free radical scavengers, but was blocked by the chelating agent EDTA. According to the authors, these data support the conclusion that copper bound to the DNA can activate dibenzoyl peroxide to a promutagenic species (ECHA 2020).

All base modifications that were detected after dibenzoyl peroxide reacted with CuCl occurred spontaneously also in untreated samples. Dibenzoyl peroxide and CuCl increased modifications of adenine bases by a factor of up to 20 and modifications of guanine and cytosine bases by a factor of about 4. The most frequent base modification identified in plasmid DNA after treatment with dibenzoyl peroxide and CuCl was 8-oxodG. Dibenzoyl peroxide with Fe²⁺ was relatively ineffective, benzoic acid by itself was inactive. According to the authors, the pattern of the base changes induced by dibenzoyl peroxide and CuCl shows that dibenzoyl peroxide interacts with Cu⁺ to form hydroxyl residues or similar reactive species. A study has not been carried out to determine whether these types of base modifications occur in the DNA of epidermal keratinocytes after application of dibenzoyl peroxide to the skin (ECHA 2020).

Dibenzoyl peroxide induced the formation of 8-oxodG in the DNA of cultivated mouse keratinocytes (see Section 5.6.1), which was blocked by the addition of a copper chelating agent. The depletion of intracellular glutathione increased 8-oxodG formation, while the addition of intracellular glutathione protected the cells against DNA damage (HCN 2012).

After dermal exposure of female Sencar mice to dibenzoyl peroxide (75%), applied twice a week over a period of 4 weeks, the 8-oxodG concentration was increased with statistical significance by a factor of 2.4 at the high dose of 125 µmol/mouse (corresponds to about 30 mg/mouse) (Hanausek et al. 2004). The authors suggest that the mere presence of 8-oxodG in the DNA probably would not be sufficient in itself to induce tumour formation. There are many pathological conditions in which oxidative DNA damage is not associated with carcinogenesis (Cooke et al. 2003).

2.2 Studies of cell proliferation and lipid peroxidation

Dibenzoyl peroxide did not induce cell proliferation in primary human bronchial epithelial cells (Saladino et al. 1985).

A study with male and female Kunming mice (see [Section 5.2.2](#)) found a statistically significant increase in malondialdehyde (MDA) levels after gavage administration of dibenzoyl peroxide doses of 200 mg/kg body weight and day for 42 days; this finding is an indication of lipid peroxidation in the liver and is a biomarker of oxidative stress (Jia et al. 2011).

3 Toxicokinetics and Metabolism

Dibenzoyl peroxide is used as a bleaching agent, for example for fats, oils, waxes and milk, and for the preparation of specific types of cheese. In the pharmaceutical field, it is used for the topical treatment of acne (HCN 2012; OECD 2002). Benzoic acid is used as a preservative in foods (Hartwig and MAK Commission 2018). Background levels of both substances are therefore expected to be present in the human body.

3.1 Oral administration and inhalation exposure

There are no data for the absorption of dibenzoyl peroxide after oral and inhalation exposure. In an in vitro study carried out under abiotic conditions at a pH of 4, 7 or 9 and 50 °C, more than 50% of dibenzoyl peroxide underwent hydrolysis and was recovered as benzoic acid after 2.4 hours. As a result, dibenzoyl peroxide is expected to hydrolyse to benzoic acid in the stomach after oral administration. If residual dibenzoyl peroxide is absorbed, it is degraded by peroxidase activity in the liver (ECHA 2020).

The hydrolysis product benzoic acid is almost completely absorbed after oral uptake in humans, rats, dogs and hamsters. In humans and rats, almost 100% is excreted with the urine in the form of hippuric acid within 24 hours (ECHA 2020; Hartwig and MAK Commission 2018).

As dibenzoyl peroxide is hydrolysed to benzoic acid, it is assumed that very little of the substance would be systemically available after oral administration (ECHA 2020).

3.2 Dermal application

3.2.1 In vitro

Franz chambers were used to study the penetration and availability of dibenzoyl peroxide in human skin samples. Physiological saline was chosen as the receptor medium. ¹⁴C-Dibenzoyl peroxide was applied to the surface of the skin in concentrations of 2.5% to 10% in a lotion or in an aqueous emulsion vehicle. Within 8 hours, 2% to 3% of the applied radioactivity was recovered in the receptor fluid in the form of benzoic acid, while 2.6% to 4% remained in the skin. About half of the radioactivity recovered in the skin was in the form of unchanged dibenzoyl peroxide, the rest was in the form of benzoic acid. Under these experimental conditions, most of the applied dibenzoyl peroxide remained unchanged on the skin surface. After application of a 10% suspension of dibenzoyl peroxide in an aqueous emulsion vehicle (surface area 5.08 cm², surface dose 900 µg/cm²), the amount that penetrated the skin over a period of 8 hours was at most 4.5% of the dose (fraction in the receptor fluid and skin), which is equivalent to a flux of 5.1 µg/cm² and hour (Nacht et al. 1981; Yeung et al. 1983).

The dibenzoyl peroxide that was absorbed by the human skin was converted to benzoic acid in the dermis. Benzoic acid was the only metabolite that penetrated the skin (Morsches and Holzmann 1982).

3.2.2 In vivo

3.2.2.1 Rat

A gel containing 10% ^{14}C -dibenzoyl peroxide was applied topically to hairless Sprague Dawley rats and the animals were examined 3, 8 and 24 hours after application. Between 12% and 18% of the applied dose was found in the skin, mainly in the upper stratum corneum as dibenzoyl peroxide. While the radioactivity decreased in the deeper layers of the skin, the relative amount of benzoic acid increased from the stratum corneum to the deeper dermis. On average, benzoic acid made up about 23%, 59% and 74%, respectively, of the radioactivity detected in the stratum corneum, epidermis and dermis; the remainder was dibenzoyl peroxide (Wepierre et al. 1986).

3.2.2.2 Rabbit

Dibenzoyl peroxide was applied to the skin of New Zealand White rabbits daily for 33 days as a 10% formulation in 3 different lotion or gel vehicles. The benzoic acid levels in the plasma were determined before the experiment began, and on days 5, 12, 19, 26 and 33 both 30 minutes before application and 30 minutes and 3 hours after application. The levels peaked at 838 to 1656 ng/ml within 30 minutes of application and then decreased markedly. Low concentrations of benzoic acid were determined 30 minutes prior to the next application; however, the concentration remained higher than the background level. There was no evidence of an accumulation of benzoic acid (Sahut et al. 1985).

3.2.2.3 Monkey

An acetone solution containing 139 μg ^{14}C -dibenzoyl peroxide was applied to the lower forelimbs of rhesus monkeys ($4 \mu\text{g}/\text{cm}^2$ on a surface of 35 cm^2) and the residual test substance was washed off after 24 hours. About 45% of the applied radioactivity was detected in the urine within 6 days, 95.3% of this amount in the form of non-conjugated benzoic acid. Hippuric acid was not present in the urine. Radioactivity was no longer detectable in the urine 7 days after application. The recovery was 86.6% to 92.7%. The authors used the experiment to calculate a flux of $1.8 \mu\text{g}/\text{cm}^2$ and 24 hours (equivalent to $0.075 \mu\text{g}/\text{cm}^2$ and hour after linear conversion). Benzoic acid entered systemic circulation in the form of benzoate via the blood vessels in the dermis (Nacht et al. 1981). After 2.5% to 10% ^{14}C -dibenzoyl peroxide was topically applied to the skin of rhesus monkeys in a lotion, the radioactivity was excreted with the urine in a concentration-dependent manner. Benzoic acid made up 99.5% of the radioactivity in the urine. Hippuric acid was not detected (Yeung et al. 1983). Dibenzoyl peroxide thus metabolizes completely to benzoic acid as it passes through the skin and this is excreted by the kidneys prior to reaching the liver; otherwise, the benzoic acid would have been conjugated with glycine in the liver to form hippuric acid.

3.2.2.4 Humans

A study investigating percutaneous penetration in 5 patients with leg ulcers who were treated with an oil-in-water emulsion containing 20% dibenzoyl peroxide did not detect dibenzoyl peroxide in the serum (Morsches and Holzmann 1982). However, the analytical methods that were used were not sensitive enough with a limit of detection for dibenzoyl peroxide of $1 \mu\text{g}/\text{ml}$ serum (ECHA 2020).

A study used test persons to investigate the penetration of dibenzoyl peroxide into the stratum corneum from a commercial acne medication containing 10% dibenzoyl peroxide. Samples of the stratum corneum were collected at different time points by adhering and peeling off an adhesive film repeatedly at different sites. The analysis found that at least some of the dibenzoyl peroxide had been converted to benzoic acid (Seubert et al. 1984).

A comparison of the in vitro skin penetration of dibenzoyl peroxide in different species found that the substance was absorbed better through the skin of hairless SKH1 mice than through the skin of F344 rats, B6C3F1 mice or human cadaver skin (ECHA 2020).

3.2.3 Summary

After oral, inhalation or dermal exposure, dibenzoyl peroxide does not enter systemic circulation as the parent compound, but is first converted to benzoic acid. Within 24 hours, almost 100% of the hydrolytic product benzoic acid was found in the urine of humans and rats in the form of hippuric acid. After dermal application, the benzoic acid is taken up by the organism as benzoate and rapidly excreted via the kidneys without conjugation with glycine to form hippuric acid, as is assumed for oral administration.

4 Effects in Humans

4.1 Single exposures

There are no data available.

4.2 Repeated exposure

Documented studies with human subjects are available only for allergenic effects and carcinogenicity. There is also an unpublished study from 1950, which was probably used as the basis for the MAK value that was derived in 1969. The Commission adopted the value from the TLV documentation that was published in the United States without carrying out a separate evaluation. This study is described in NIOSH (1977).

Air samples were collected in a factory manufacturing a powder made up of 32% dibenzoyl peroxide and 68% unspecified amounts of potassium aluminium sulfate (alum) and magnesium carbonate that was used for bleaching flour. The samples were taken on 3 consecutive days in 6 different work areas using aqueous standard impingers (Greenburg-Smith). The sampling was performed for 20 minutes, 2 to 3 times per shift. The water from the impingers was analysed for dibenzoyl peroxide and alum using unspecified methods. The dust caused irritation of the nose, eyes and throat in the workers on all 3 days; the dibenzoyl peroxide concentrations were between 1.34 and 82.5 mg/m³ (NIOSH 1977). The study is not suitable for the derivation of a MAK value for the following reasons: samples were taken for only 20 minutes, the level of exposure may have been underestimated (impinger with water) and it is not known how peak concentrations and potassium aluminium sulfate affected irritation.

4.3 Local effects on skin and mucous membranes

Irritant skin reactions were a common finding of patch tests carried out with dibenzoyl peroxide, for example with 1% to 5% formulations in petrolatum. This is described in Section 4.4 (Greim 1999; Ockenfels et al. 2009).

4.4 Allergenic effects

4.4.1 Sensitizing effects on the skin

Dibenzoyl peroxide penetrates the skin. However, almost all of the studies found that the substance was not taken up completely by the various species (Section 3.2). Dibenzoyl peroxide is converted to benzoic acid, a certain fraction already in the stratum corneum, the largest percentage in the dermis.

A large number of studies and case reports investigated suspected allergic reactions to dibenzoyl peroxide (see Table 1 and 2). Several studies were carried out with very high concentrations of the substance. No data were given for the strength of the reaction over time and the studies do not comply with the standards that are listed in the guidelines for patch tests (AWMF 2019). These types of studies and their findings cannot be included in the evaluation, or only to

a very limited extent, due to the difficulties inherent in performing tests with dibenzoyl peroxide (see below). Furthermore, many of the case reports do not provide exact data for the critical exposure and exposure was often to a mixture of substances, which means that a clear exposure–effect relationship cannot be established.

Patch tests with dibenzoyl peroxide are usually performed with a 1% formulation in petrolatum (this formulation is included in the series “bone cement components”, “synthetic resins and adhesives” and the “dental technician – main series” of the German Contact Dermatitis Research Group (DKG)). However, the results may be affected by irritation even at this concentration. The results from these types of tests must therefore be considered critically because some of the reactions, at least the weak positive reactions, should be evaluated as false positives (Ockenfels et al. 2009). This is particularly true for patients with atopic diathesis. A descrescendo reaction is often observed in these patients, which is generally not a sign of an allergic reaction.

Comprehensive studies carried out by the Information Network of Departments of Dermatology (IVDK) likewise identified this as an issue. The objective was to determine whether carrying out additional testing with an irritant would facilitate the evaluation of the responsiveness of the skin of a patient at the time of testing and help to identify potential false positive reactions. A group of 5971 patients (3701 ♀, 2270 ♂; 66% older than 40 years) underwent patch tests with an allergen, but were simultaneously tested with an aqueous formulation of sodium lauryl sulfate. The cohort included 872 persons with occupational dermatitis and 1024 persons with known or current atopic dermatitis. The patients who produced an irritant reaction to 0.25% or 0.5% sodium lauryl sulfate in water were about twice as likely to produce a 1+ reaction or an erythematous reaction to 1% dibenzoyl peroxide than patients who did not react to sodium lauryl sulfate with irritation (Löffler et al. 2005).

Occupational exposure to dibenzoyl peroxide

Workers in plastics and adhesives production or processing may be occupationally exposed to dibenzoyl peroxide.

The studies that were included in the documentation of Greim (1999) suggested that dibenzoyl peroxide may be an occupational allergen for dental assistants and technicians (Gebhardt and Geier 1996; Geier and Schnuch 1994). Subsequent evaluations of the IVDK data likewise found that dental technicians had a higher incidence of reactions to dibenzoyl peroxide (Heratizadeh et al. 2018; Ockenfels et al. 2009; Table 2), while an earlier study with dental technicians (Rustemeyer and Frosch 1996 in Greim (1999)) and a study with dentists (Kiec-Swierczyńska and Krecisz 2002) did not find an increase in the number of reactions (Table 1). A comprehensive evaluation of IVDK data from 2007 to 2016 reported that 281 (6.2%) of 4554 persons with occupational contact dermatitis reacted to dibenzoyl peroxide (no data for reaction strength) (Table 1). In the group of dental technicians, 25 produced reactions that were classified as clearly positive and 155 produced reactions that were clearly negative. A surprising finding of this evaluation was that dibenzoyl peroxide is an occupational allergen for dentists. This occupational group made up a large fraction of the cohort that produced positive reactions (8.5% [95% confidence interval (CI): 5.5–12.4]). Possible explanations suggested by the authors are that dental assistants, who were included in the occupational group of “dentists” in the IVDK documentation, actually performed the work of dental technicians or that a number of dental technicians were incorrectly documented as dentists. The evaluation did not show that dibenzoyl peroxide is an occupational allergen for mechanics and persons in related occupations. A disproportionately small number of patients in the group with occupational dermatosis who produced positive reactions were working in these occupations in comparison with the number found in the group of patients without occupational dermatosis who produced positive reactions (9.3% [95% CI: 6.1–13.3] compared with 14.8% [95% CI: 13.7–16.0]) (Geier and Schubert 2021). Furthermore, an earlier evaluation of IVDK data relating to tests carried out with plastic and glue components from 1996 to 2001 found positive reactions to dibenzoyl peroxide both in patients with occupational dermatosis (11%, 26 of 241) and in patients without occupational dermatosis (10%, 24 of 249). The incidence remained marginally higher than that of the total cohort (9%) (Hillen et al. 2007).

In addition, case reports suggest that dibenzoyl peroxide may be an occupational allergen in other occupational groups:

A 48-year-old male marbler developed workplace-related eczema on the face, particularly on the eyelids, as well as on the trunk, lower arms and hands. A patch test was carried out with a plastics and glues series and workplace-related materials. He produced a 3+ reaction to dibenzoyl peroxide (1% in petrolatum) on day 3 and to a curing agent containing

dibenzoyl peroxide, which was used for working on marble (Tsivilis et al. 2005). However, there are no data for the course of the reaction over time.

A 59-year-old male patient who worked in the manual production of electronic transformer coils and wrapped binding tape containing dibenzoyl peroxide around copper coils developed bilateral hand dermatitis with erythema, blistering and scabbing. The symptoms improved when he worked in another area of the facility. A patch test with a plastics and glues series, a metals series and the British standard series yielded a 1+ reaction to dibenzoyl peroxide (1% in petrolatum) on day 4. There are no data for the course of the reaction over time (Elangasinghe and Johnston 2012).

A 32-year-old male orthopaedic technician developed workplace-related eczema on the face, neck and arms over a period of 2 years. He reported frequent exposure to plaster dust at the workplace. He had allergic rhinitis in the spring, but not allergic asthma. The patient produced a strong positive reaction (no other data) with papulovesicles to a curing agent that contained 5% dibenzoyl peroxide and a questionable positive reaction to dibenzoyl peroxide (1% in petrolatum) in the patch test. The ingredients of the curing agent were tested again and clear positive reactions were obtained for 1% and 2.5% dibenzoyl peroxide. The patient did not react in a subsequent test to the curing agent without dibenzoyl peroxide. Furthermore, the symptoms subsided when exposure was avoided (Forschner et al. 2002). However, no further information is available for the curing agent without dibenzoyl peroxide or for the course of the reaction over time. The results of a test with 2.5% dibenzoyl peroxide were in the false positive range because of irritation and cannot be used as substantiated evidence of an allergic reaction.

Other studies that investigated suspected reactions to dibenzoyl peroxide in plastics and glues are not suitable for the evaluation of the sensitizing effects of dibenzoyl peroxide because of insufficient documentation and unclear clinical relevance in almost all of the cases (Table 1). In this context, earlier studies that tested concentrations of 0.2% to 2.2% did not find an increased incidence of reactions to dibenzoyl peroxide (Shmidt et al. 2010).

There are also studies and case reports of suspected reactions to dibenzoyl peroxide that are related to its use by bakers for the bleaching of flour. However, the evaluation must take into account that many countries have banned the use of dibenzoyl peroxide for this purpose. In some countries, this ban has been in place for more than 50 years. Furthermore, the residual amounts of dibenzoyl peroxide in bleached flour are classified as extremely low with values in the lower mg/kg range (Saiz et al. 2001).

Accordingly, an analysis of the data available to the IVDK (1992–1999) found that 19 of 283 bakers (5.5%) reacted to 1% dibenzoyl peroxide as opposed to 1558 of the total cohort tested of 17 986 (8.9%), thereby concluding that the number of reactions was not increased (Bauer et al. 2002). In a Swedish study, 4 of 45 bakers produced a positive reaction (no other details) to 1% dibenzoyl peroxide in the patch test. According to the authors, the 4 patients did not have any known exposure outside of work (Meding et al. 2003).

A 64-year-old male baker with previously diagnosed atopic dermatitis, which had been treated unsuccessfully with, among other medication, a washing solution containing dibenzoyl peroxide, developed pruriginous dermatitis on the hands, arms and trunk. According to the patient, this occurred after switching from unbleached to bleached flour. In the patch test, the patient produced a 1+ and 2+ reaction to dibenzoyl peroxide (1% in petrolatum) on days 2 and 7 and a 1+ reaction to Peru balsam on day 2. According to the authors, the symptoms improved after exposure to the allergens was avoided (no other details) (Adelman et al. 2019). If the patient had been allergic to dibenzoyl peroxide, the dermatitis would have become more severe after treatment with a washing solution containing dibenzoyl peroxide.

Non-occupational exposure to dibenzoyl peroxide

Most cases of non-occupational exposure involve the application of the substance in the form of acne formulations containing dibenzoyl peroxide. These formulations are widely prescribed in high concentrations (up to 10%) based on the calculated defined daily dose (DDD) (Günther and Fricke 2020). However, because acne formulations containing dibenzoyl peroxide are often combined with an antibiotic or retinoid, these cases usually involve exposure to a mixture of substances.

Well-documented studies and case reports are available in this context that describe patch test reactions to dibenzoyl peroxide that were interpreted as positive (Table 1 and 2). However, the number of cases is comparatively small considering the widespread use of acne treatments containing dibenzoyl peroxide, the high concentrations these contain and the frequency of exposure (Ockenfels et al. 2009). The available data show that high concentrations of dibenzoyl peroxide may have sensitizing effects after repeated to frequent contact in cases of an existing inflammatory skin disease with a disturbed skin barrier. However, this type of exposure is not comparable to the conditions at the workplace.

There are also studies that investigated dibenzoyl peroxide as a possible cause of intolerance reactions to bone and dental implants (Table 1 and 2). Most of these studies are insufficiently documented and do not specify whether the implants contained dibenzoyl peroxide. As a result, the clinical relevance of the patch test reactions is unclear. These findings are not included in the evaluation because of (possible) systemic exposure that is not relevant to workplace scenarios.

Tab. 1 Studies with patch tests carried out with dibenzoyl peroxide in patients with suspected contact allergy (data from 1998 onwards published after the collection of data for Greim (1999) had been completed)

Concentration, Test persons in petrolatum	Reaction (allergy + irritation)	Comments	References
Suspected contact allergy related to occupational exposure			
1%	199	Reaction: 19 + 4 (9.5% + 2.0%) Test period: 2001–2015 Cohort: IVDK study Total cohort of 163 261 test persons, 399 of the persons were working as dental technicians, 226 of the technicians had occupational contact dermatitis and 199 were tested with DBPO. 11 × ?+, 14 × 1+, 3 × 2+, 2 × 3+, 4 × irritation; Reading time: day 3 (in exceptional cases day 4)	Heratizadeh et al. 2018 ^{a)}
1%	29 758	Reaction: 2316 + 619 (7.8% + 2.1%) Test period: 1992–2007 Cohort: IVDK study Total cohort of 144 814 patients, 29 758 of these patients (60% ♀, 40% ♂) were tested with DBPO. 2270 × ?+, 1931 × 1+, 326 × 2+, 59 × 3+, 619 × irritation; Percentage of positive [questionable and irritant] reactions 1992–1995: 8.2% [11.5%], 1996–1999: 8.8% [10.6%], 2000–2003: 7.8% [7.9%], 2004–2007: 5.8% [7.2%]; Percentage of positive [questionable and irritant] reactions in 576 dental technicians over the entire period: 10.1% [11.1%], 21.3% [no data] of the 29 758 patients had occupational dermatitis. Reading time: day 3 (in exceptional cases day 4), possible overlapping with the cohort of Heratizadeh et al. 2018	Ockenfels et al. 2009 ^{a)}
1%	925 in total, of these 118 cutting metalworkers 704 mechanics 103 other metalworkers	Reaction: 7 (6.0%) Test period: 2010–2018 Cohort: IVDK study Total cohort of 3356 metalworkers (349 ♀, 3007 ♂, average age 45 years) Reading time: day 3 (in exceptional cases day 4), possible overlapping with the cohort of Heratizadeh et al. 2018	Schubert et al. 2020 ^{a)}
1%	22 750 in total, of these 15 771 4554	Reaction: 1331 + 408 (5.8% + 1.8%) Test period: 2007–2016 Cohort: IVDK study Possible overlapping with the cohort of Heratizadeh et al. 2018; Schubert et al. 2020 15 771 patients with non-occupational contact dermatitis 4554 patients with occupational contact dermatitis, in addition, probably 408 questionable (erythematous) follicular or irritant reactions; Reading time: day 3 (in exceptional cases day 4)	Geier and Schubert 2021 ^{a)}

Tab. 1 (continued)

Concentration, Test persons in petrolatum	Reaction (allergy + irritation)	Comments	References
1% 57	2	Test period: 2002–2005 Cohort: 57 mechanics and machinists with occupational hand dermatitis for 2 to 3 years and suspected allergic contact dermatitis; of these: 33 mechanics (average age 46 years), 2 with positive reactions (no data for reaction strength), no data for possible exposure; both had multiple reactions to preservatives and thiuram mix, carba mix, potassium dichromate, cobalt chloride and epoxy resin (length of employment 15 and 30 years), 24 machinists (average age 41 years), none produced a positive reaction; Reading time: not specified	Donovan et al. 2007
1% 40 10	8 1	Test period: not specified Cohort: 40 dentistry students (21 ♀, 19 ♂, average age 25 years); control group: 10 dental patients without occupational exposure (6 ♀, 4 ♂, average age 48 years), no data for possible exposure; Reading time: days 2 and 3	Lyapina et al. 2017
Suspected contact allergy related to plastics and glues			
1% 593	59 (9.9%)	Test period: 1996–2001 Cohort: 829 patients (310 ♀, 519 ♂) with suspected contact allergy against glues, 593 of the patients were tested also with DBPO; no data for exposure, reaction severity and irritant reactions; Reading time: day 3	Hillen et al. 2007
1% 79	2	Test period: 1990–2000 Cohort: 79 dentists (72 ♀, 7 ♂) with suspected occupational contact allergy; no data for exposure, reaction severity and irritant reactions; Reading time: day 3	Kiec-Swierczyńska and Krecisz 2002
1% 126	11 (9%)	Test period: 1995–1999 Cohort: 126 dental technicians (no other data) with suspected occupational contact allergy; according to the authors, only 3 of 11 cases had clinical relevance; Reading time: day 3	Peiler et al. 2000
1% 439	42 + 10 (9.8% + 2.3%)	Test period: 2000–2007 Cohort: total cohort of 444 patients (263 ♀, 181 ♂, average age 53 years), 439 of the patients tested with DBPO as part of the plastics and glues series, no data for exposure, erythematous reactions likewise evaluated as positive; however, the percentage of these reactions was not determined; total reactions: 42 (9.8%), of these: irritation: 10 (2.3%) allergic, not relevant: 2 allergic, probably relevant: 1 allergic, relevant: 9 questionably relevant: 30; Reading time: days 2–3 and days 4–7	Shmidt et al. 2010
5% 22 workers with and 7 workers without skin symptoms	5 (or 3?) 0 (or 1?)	Test period: not specified Cohort: 22 and 7 workers from a Japanese plant for fibreglass-reinforced plastics made of unsaturated polyester resin; with and without skin symptoms, respectively, no data for reaction strength and reading times; the number of positive reactions is inconsistently documented in the publication; a table with individual findings from the 22 workers shows 3 positive and 1 questionably positive reaction; the 4 reactions are interpreted as “allergic contact eczema and/or mechanical irritation” and “glass fibre (dust)” is given as the self-reported cause of the skin disorders. According to the authors, DBPO was not used as a curing agent at the time of the study. Therefore, they assume sensitization was caused by earlier exposure (no other details); Reading time: day 3	Minamoto et al. 2002

Tab. 1 (continued)

Concentration, Test persons in petrolatum	Test persons	Reaction (allergy + irritation)	Comments	References
1%	26	0	Test period: not specified Cohort: persons with a self-reported intolerance to medical adhesive bandages (18 ♀, 8 ♂, 1 person < 18 years old), no allergic reactions to DBPO, no data for the number of irritant reactions, no reactions to 10 tested adhesive bandages; Reading time: days 2 and 7	Widman et al. 2008
Suspected contact allergy related to dental, bone and joint implants				
1%	92		Test period: not specified Cohort: 92 patients with a hip or knee endoprosthesis, symptomatic group: 66 (45 ♀, 21 ♂, average age 65 years) suspected intolerance to osteosynthesis/endoprosthesis materials;	Eben et al. 2010
	of these 66 with complaints	7		
	26 control persons	0	Control group: 26 asymptomatic persons with a cemented total knee endoprosthesis (17 ♀, 9 ♂, average age 73 years); Reading time: days 2, 3 and 6	
1%	80	33	Test period: not specified Cohort: 40 atopic patients (28 ♀, 12 ♂, average age 35 years) and 40 non-atopic patients (30 ♀, 10 ♂, average age 42 years), analysis of reactions to dental materials, 12.5% (10 of 80) of the reactions interpreted as allergic: atopic persons: 22.5% (9 of 40), non-atopic persons: 2.5% (1 of 40), assessed as irritant and questionable reactions: atopic persons: 27.5% (11 of 40), non-atopic persons: 30% (12 of 40); Reading time: days 2 and 3	Rojas-Alcayaga et al. 2012
1%	54	17	Test period: 2010–2012 Cohort: patients with suspected contact dermatitis caused by a dental prosthesis (50 ♀, 4 ♂; average age 61 years); Reading time: days 2 and 4, parallel study with patients without a dental prosthesis (as the control group): 19 of 45	Yoshimura et al. 2016
1%	13	3	Test period: no data Cohort: 9 ♀, 4 ♂, average age 61 years; with suspected intolerance to knee implants, (1 × 1+; 2 × 2+), of these, 1 reaction assessed as probably allergic, 2 of unknown genesis; Reading time: days 2 and 3	Treudler and Simon 2007
1%	289	5 (1.7%)	Test period: 05/2000–04/2004 Cohort: total cohort of 331 patients (268 ♀, 63 ♂, average age 58 years) with “burning mouth” syndrome, 289 of these patients were tested, 5 (1.7%) produced positive reactions, 1 of these reactions was assessed as relevant (no other details); Reading time: days 2 and 4	Torgerson et al. 2007
1%	311		Test period: 2004–2017 Cohort: 220 ♀, 91 ♂; average age 64 years, tests performed before and after surgery (in cases of complications and a suspected metal allergy) in patients with (hip and knee) implants, osteosynthesis, unclear how many patients were tested both before and after surgery; Reading time: day 2 and once between days 3 and 6	Furrer et al. 2018
	of these pre-operative: 73	5		
	post-operative: 238	31 (13.0%)		
1%	193		Test period: 6/2009–2/2012 Cohort: total cohort of 234 persons; 163 persons with complaints were tested of a group of 187 persons (122 ♀, 65 ♂, average age 64 years) with a knee endoprosthesis. 30 of a total of 47 asymptomatic persons were tested as the control group (37 ♀, 10 ♂, average age 75 years); Reading time: days 2, 3 and 7	Thomas et al. 2013 ^{a)}
	of these 163	13 (8.0%)		
	30	2		

Tab. 1 (continued)

Concentration, Test persons in petrolatum	Reaction (allergy + irritation)	Comments	References
1% 250	23 (9.2%)	Test period: 08/2010–09/2013 Cohort: 250 patients (164 ♀, 86 ♂, average age 65 years) with arthroplasty and a suspected allergic reaction to the implant; Reading time (number of positive reactions): day 2 (0), day 3 (23) and day 6 (10); however, none of the patients produced a reaction only on day 6; cohort probably overlaps with that of Thomas et al. 2013	Thomas et al. 2015 ^{a)}
Suspected contact allergy related to acne treatments			
1% 20	17	Test period: 2015–2018 Cohort: 24 female patients (average age 24 years) with dermatitis after applying an acne gel containing DBPO, 2 of the patients with irritant contact dermatitis; tests with the gel produced no reaction in 1 patient, 1 patient refused to undergo patch testing; all patients produced also 1+ (11 ×) or 2+ (9 ×) reactions to a 2.5% DBPO gel on day 3; according to the authors, a total of 286 patients, including 13 of the 20 tested patients, were prescribed a DBPO gel in a clinic; this was used to calculate a percentage of sensitization of 4.5%, 3 × ?, 14 × 1+, 3 × 2+ (on day 3); Reading time: days 2, 3 and 7	Iijima and Tsunoda 2019
Others			
1% 1968	72 (3.7%)	Test period: 1990–2014 Cohort: total cohort of 14 911 patients, 2600 of these patients were diagnosed with contact dermatitis caused by topical formulations. 1968 patients of the total cohort were tested also with DBPO; however, the indication for testing was not documented. No data for exposure, reaction severity and irritant reactions; Reading time: day 2 (or day 3) and day 4	Gilissen and Goossens 2016
1% 1524	24 (1.6%)	Test period: 1995–2010 Cohort: total cohort of 2088 patients was tested with a standard series, 1524 of these patients were tested also with DBPO; the authors regarded 87.5% of the reactions as relevant. No data for exposure, reaction severity and irritant reactions; Reading time: days 2 and 4	Patel and Belsito 2012
1% 285 children 2175 adolescents 7904 adults	47 (16.5%) 174 (8%) about 616 (7.8%)	Test period: 1995–2002 Cohort: IVDK study 285 children (153 ♀, 132 ♂, 6–12 years) and 2175 adolescents (1559 ♀, 616 ♂, 13–18 years), 7904 adults were used as the control group (4874 ♀, 3030 ♂, 60–66 years); the authors interpreted most of the reactions produced by the children as false positive because of a lack of clinical relevance, reactions produced by adolescents and adults may have been caused also by irritation; Reading time: day 1 or day 2, day 3 (the results of day 3 were used)	Heine et al. 2004 ^{a)}
1% 1168	11 (0.9%)	Test period: 1990–2002 Cohort: a total cohort of 8543 patients, 1168 of these patients had foot dermatitis, DBPO was included in what was known at this time as the “shoe series”. Other allergens tested included potassium dichromate, cobalt chloride and <i>p</i> -phenylenediamine, no data for possible exposure; Reading time: day 2 (in exceptional cases day 3), day 4 and, if necessary, later	Nardelli et al. 2005

^{a)} possible overlapping of the cohorts

?: questionable; DBPO: dibenzoyl peroxide

Tab. 2 Individual findings from patch tests with dibenzoyl peroxide in patients with a suspected contact allergy (data from 1998 onwards published after the collection of data for Greim (1999) had been completed)

Concentration, in petrolatum	Reaction	Comments	References
Suspected contact allergy related to occupational exposure			
1%	3+ (day 3)	48-year-old male patient, worked for 30 years as a marbler, non-atopic, eczema on the face, particularly on the eyelids, and on the trunk, lower arms and hands. Positive reactions also to thiurams and a curing agent containing DBPO, which was mixed with glue and used for marble processing (grinding)	Tsovilis et al. 2005
1%	?	32-year-old male orthopaedic technician with occupational eczema on the face, neck and arms for more than 2 years, frequent exposure to plaster dust, allergic rhinitis in the spring, but no allergic asthma.	Forschner et al. 2002
1%	“positive”		
2.5%	“positive”	Positive reactions to several types of pollen; strong initial reaction with papulovesicles to a curing agent (5% DBPO), questionable positive reaction to DBPO (1%); components of the curing agent were then tested again and clear positive reactions were observed for 1% and 2.5% DBPO, but no reactions when the curing agent was tested without DBPO; symptoms subsided when exposure was avoided	
1%	1+ (day 4)	59-year-old male patient with bilateral hand dermatitis with erythema, blistering and scabbing. Patient worked in the manual production of electronic transformer coils, wrapping binding tape containing DBPO around Cu coils; symptoms improved when he worked in a different area of the factory; patient was likewise tested with components of the glues, plastics and metals series; there are no data for other positive results; according to the authors, DBPO has irritant potential	Elangasinghe and Johnston 2012
1%	1+ (day 2) 2+ (day 7)	64-year-old male baker who developed pruriginous dermatitis on the hands, arms and trunk which, according to the patient, was caused by switching from unbleached to bleached flour. Anamnesis: atopic dermatitis treated with, among other medication, a washing solution containing DBPO, no improvement of the symptoms; also a positive reaction to Peru balsam; according to the authors, marked improvement of the symptoms after the allergens were avoided	Adelman et al. 2019
no data	“positive”	48-year-old female baker with an intolerance to a knee implant, strong positive test results with ulcers under the patch. The patient had developed symptoms in the past when handling flour containing DBPO	Edwards and Gardiner 2007
Suspected contact allergy related to plastics and glues			
1%	1+ (days 2, 4)	73-year-old female patient who had developed eczematous pruritic reactions on the wrist twice, probably caused by patient ID bands made of PVC that were worn during hospital stays. Additionally 2+ reactions to the band and to resorcin monobenzoate; manufacturer did not confirm that the band contained any of the allergens	Tung and Taylor 1998
1%	+/- (day 2) 1+ (days 4/5)	14-year-old female patient with a rash probably caused by shin guards (football), reactions to, among other substances, fragrance mix, gold sodium thiosulfate, thimerosal, abitol. 1+ (day 2) and 2+ (days 4/5) reactions to the shin guard; no data whether the shin guards contained DBPO; report includes another 9 patients who were probably tested with DBPO, but did not produce a reaction	Powell and Ahmed 2010
1%	2+ (day 2) 3+ (day 3)	80-year-old male patient who was described by the authors as having non-allergic dermatitis on the stump of his amputated leg for more than 6 months (amputation had been performed decades ago). Testing to identify the cause of the dermatitis led to reactions to the adhesive tape used for the patch test; positive reaction to DBPO in a second patch test; negative results were obtained with all other allergens tested including colophonium, abietic acid and abitol; manufacturer of the adhesive tape confirmed that it contained DBPO (probably in the polyester film of the tape; acrylates were apparently not tested as a possible ingredient of the adhesive glue)	Greiner et al. 1999

Tab. 2 (continued)

Concentration, in petrolatum	Reaction	Comments	References
Suspected contact allergy related to dental and bone implants			
no data	"positive"	63-year-old male patient with intolerance to an implant. Tests with metals yielded negative results	Gothner et al. 2011
1%	4 × 2+ 1 × 1+	5 patients aged between 39 and 71 years with orthopaedic implants, tested because of an intolerance to the implants. None of the patients were atopic or had known allergies to jewellery or other metals; the findings were difficult to interpret because of irritation; data are unclear whether the implants contained DBPO	Bircher et al. 2012
no data	4 × 1+ (day 3) 2 × 2+ (day 3)	6 patients aged between 54 and 82 years (3 ♀, 3 ♂, average age 65 years), with total knee arthroplasty. Data are unclear whether implants contained DBPO; 3 patients reacted also to other allergens (including nickel sulfate)	Fröschen et al. 2019
1%	– (day 2) 2+ (day 3) – (day 2) 1+ (day 3)	2 female patients (29 and 43 years) with a dental prosthesis developed erythema, oedema and pain in the oral cavity while wearing the prosthesis (containing DBPO), improvement of the symptoms when not worn. Patient 1 reacted also to nickel sulfate, cobalt chloride, colophonium; patient 2 did not produce any other positive reactions	Dejobert et al. 2002
Suspected contact allergy related to acne treatments			
1%	3+ (days 2, 4)	26-year-old female patient with dermatitis on the face after applying an acne formulation containing DBPO and clindamycin (5% DBPO). Vesicular reaction to DBPO; the vesicles and bullae spread to adjacent application sites on day 4; positive reactions also to clindamycin and nickel sulfate	Holden et al. 2014
2%	3+ (day 4)	32-year-old male patient with pruriginous, erythematous dermatitis on the genitals after self-prescribed application of a cream containing DBPO. 2+ reaction to the cream	Corazza et al. 2018
1%	2 × 1+ 4 × 2+ 1 × 3+ (in each case on days 2 and 4)	7 female patients; 6 women had eczema on the face after applying an acne formulation containing 2.5% DBPO; 1 woman had eczema on the chest even though only her partner had used a cream containing DBPO. All patients produced positive reactions to the formulation	Bulinckx et al. 2012
1%	2+ (day 4)	20-year-old female patient with acute erythema and oedema on the face 2 weeks after beginning treatment with an acne formulation that contained DBPO (5% DBPO). Patient produced a 3+ reaction also to the formulation containing DBPO; 5 control persons did not react to the formulation	Felton et al. 2013
1%	2+ (day 4)	42-year-old female patient with skin irritation, erythema and desquamation after applying 2 acne formulations that contained DBPO (10% DBPO). Patient had reacted to cosmetic products in the past (for example sunscreen, plasters); besides DBPO, positive reactions to colophonium, phenyl salicylate and the 2 previously applied acne formulations	Felton et al. 2013
1%	3+ (day 2)	26-year-old female patient with pruriginous erythema after applying an acne formulation containing 10% DBPO. In addition, positive reactions in the patch test to the acne formulation (2+), nickel sulfate, Peru balsam	Minciullo et al. 2006
1%	2+ (days 2, 4)	39-year-old female patient known to have an intolerance to costume jewellery and who had used acne formulations as an adolescent, at the time without complications, developed dermatitis on the face. This was believed to have been caused by close skin contact with her son, who was using an acne formulation containing 10% DBPO	Hernández-Núñez et al. 2002

Tab. 2 (continued)

Concentration, in petrolatum	Reaction	Comments	References
1%	1+	17-year-old male patient with a suspected allergy to acne formulations containing 2.5% DBPO. Reaction to DBPO and quaternium-15 (1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride, formaldehyde releaser); no data for the reading times	Kim et al. 2015
1%	+/- (day 2) 1+ (day 3)	10-year-old female patient with suspected allergic contact dermatitis caused by an acne formulation containing 5% DBPO. 2+ reaction to the formulation on days 2 and 3	Sandre and Skotnicki-Grant 2018

DBPO: dibenzoyl peroxide

4.4.2 Sensitizing effects on the airways

There are no data available.

4.5 Reproductive and developmental toxicity

Long-term clinical use in the form of topical acne treatment did not lead to any evidence of teratogenic effects (Schäfer et al. 2011).

4.6 Genotoxicity

There are no data available.

4.7 Carcinogenicity

In the US and the EU, dibenzoyl peroxide is the most widely used active ingredient in topical acne formulations. It is used in prescription and over-the-counter creams, solutions, soaps, cleansers and shaving creams. Its keratolytic and antibacterial properties make it effective in the treatment of acne. Dibenzoyl peroxide is generally used in concentrations of 2.5% to 10%, but may be formulated in higher concentrations for the treatment of stasis ulcers (ECHA 2020).

4.7.1 Case reports

Two cases of lung cancer were reported in men (a 40-year-old smoker and a 35-year-old non-smoker) who worked mainly in the production of dibenzoyl peroxide, but were exposed also to dibenzoyl chloride and other chemicals (Sakabe and Fukuda 1977). The study cannot be used to evaluate dibenzoyl peroxide because the workers were exposed to a mixture of substances.

4.7.2 Case-control studies

Two case-control studies were carried out to evaluate the risk of developing skin cancer through the use of dibenzoyl peroxide for the treatment of acne:

A pilot case-control study in England investigated malignant melanomas in patients who had used dibenzoyl peroxide for the treatment of acne. The study included all 159 cases of a malignant melanoma that were detected in patients younger than 45 years between 1984 and 1986. The cases were obtained from the regional Yorkshire Specialist Register of Cancer. The study was based only on case files from hospitals and general practitioners. The control group was made up of 213 persons who were matched by sex and age. The medical records of both groups were examined for details about acne, prescribed skin medications and longer periods of sun exposure. The odds ratio (OR) was 0.5 (95% CI: 0.2–1.5) for developing a malignant melanoma while using dibenzoyl peroxide and 1.1 (95% CI: 0.7–1.9) for developing a

melanoma after having acne in the past. Therefore, the use of dibenzoyl peroxide did not increase the risk of developing skin cancer with statistical significance (Cartwright et al. 1988). No information was given whether dibenzoyl peroxide had been used to treat acne and, if so, how often and in which concentrations. The study therefore cannot be used to evaluate the carcinogenic effects on the skin.

In the second case-control study, the skin cancer cases were identified from the files of the Saskatchewan Cancer Registry. The cases include about 90% of the cases of skin cancer that occurred in persons who may have used dibenzoyl peroxide between 1966 and 1988 and in persons who probably used dibenzoyl peroxide between 1975 and 1988 (prescribed use 1975–1988; non-prescribed use 1966–1988). The cases included patients with all forms of skin cancer and were not limited to melanomas. Mainly basal cell carcinomas (number not specified) were determined in the segments with prescribed and non-prescribed use, but also 41 squamous cell carcinomas and 25 malignant melanomas. In the part of the study that focused on the prescribed use of dibenzoyl peroxide (as from 1975), there were a total of 931 cases of skin cancer and 13 (1.4%) of these cases had used dibenzoyl peroxide. Of 7630 control persons without skin cancer, 66 (0.09%) had used dibenzoyl peroxide. The OR was 1.27 (95% CI: 0.69–2.35) for skin cancer in patients who had used dibenzoyl peroxide; this value is not statistically significant. In the second part of the study, data for acne and its treatment were collected by questionnaire from 964 persons with skin cancer and 3856 control persons who were matched by age and sex. The response rate was 90.9% for the cases and 79.9% for the controls. All participants were given a comprehensive list of acne medications that included products containing dibenzoyl peroxide that have been on the market since 1966. The respondents (cases and controls) were between 10 and 56 years old. Of the group of skin cancer patients who may have used dibenzoyl peroxide, which was marketed in Canada in 1966, 90% had skin cancer on the face. The cases and controls did not differ with statistical significance in terms of family history of acne, the severity of the acne, the number of different acne treatments that had been tried or how long the products containing dibenzoyl peroxide had been used. There were 146 respondents who reported having used dibenzoyl peroxide, 32 among the cases and 114 among the controls. The OR for skin cancer on the face and neck after having used dibenzoyl peroxide was 0.84 (95% CI: 0.51–1.38) and was therefore not increased with statistical significance. An OR of 0.80 (95% CI: 0.48–1.33) was obtained if the period of application was included in the calculation. The ORs for the other known risk factors for skin cancer, such as familial predisposition, sunburning easily or having light hair and skin, were increased with statistical significance (Hogan et al. 1991).

A study based on the Los Angeles County Cancer Surveillance Program in the United States interviewed male chemists with malignant melanomas and with other cancers (used as controls): 4 of the 7 chemists with a malignant melanoma, but none of the 9 controls, reported a history of exposure to dibenzoyl peroxide (among many other chemicals) (IARC 1999). However, these findings cannot be used for the evaluation due to the exposure to different substances and the lack of data for the duration and level of exposure.

4.7.3 Summary

The epidemiological studies that are available and suitable for evaluation did not find a statistically significant association between the use of dibenzoyl peroxide for acne treatment over several decades and the development of skin cancer.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

In an acute inhalation study from 1973, 10 male Spartan albino rats were exposed to 24 300 mg/m³ (78% dibenzoyl peroxide) in a sealed 59.1-litre glass chamber for 4 hours. All animals survived the exposure and for the observation period of 14 days. Clinical symptoms observed during the 4 hours of exposure were squinting, breathing difficulties, salivation, lacrimation, erythema, increased and reduced respiratory rates and increased and reduced motor activity. Several of the rats had eye irritation for 5 days after exposure (ECHA 2020; OECD 2002).

5.1.2 Oral administration

A limit test was carried out in 2001 with ICR mice according to OECD Test Guideline 401. Five male and 5 female mice were exposed to a dibenzoyl peroxide dose of 2000 mg/kg body weight. Mortality did not occur. No treatment-related findings were observed at necropsy. Piloerection was the only clinical symptom. The LD₅₀ value was therefore above 2000 mg/kg body weight (ECHA 2020; OECD 2002).

Another acute oral toxicity study in rats obtained similar results. Neither mortality, clinical symptoms, nor other toxic effects were reported after exposure to a single dose of 5000 mg/kg body weight. LD₅₀ values of 7710 or above 950 mg/kg body weight were determined in rats by other studies carried out in 1972 and 1973 (no other data; ECHA 2020; OECD 2002).

5.1.3 Dermal application

There are no data available.

5.1.4 Intraperitoneal injection

Studies from the 1950s to 1970s with intraperitoneal administration in mice reported LD₅₀ values of 168 to 250 mg/kg body weight (no other details; ECHA 2020; OECD 2002).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

5.2.2 Oral administration

Studies with repeated oral administration of dibenzoyl peroxide are shown in Table 3.

Tab. 3 Toxicity of dibenzoyl peroxide after repeated oral administration

Species, strain, number per group	Exposure	Findings ^{a)}	References
rat, Sprague Dawley, 10 ♂, 10 ♀	28 days (♂), 41–51 days (♀), 0, 250, 500, 1000 mg/kg body weight and day, gavage, 7 days/week, observation period 2 weeks, 71.8% DBPO, OECD TG 422	250 mg/kg body weight: ♀: aspartate aminotransferase ↓; 500 mg/kg body weight: NOAEL; ♀: haematology: total protein ↓; 1000 mg/kg body weight: NOAEL of the authors; ♂/♀: spleen: minimal focal pigmentation (2/10, sex not specified); ♂: feed consumption increased in weeks 1 and 4, absolute and relative testis weights ↓, relative epididymal weights ↓, erythrocytes and leukocytes increased at the end of the observation period, 2/10 haemorrhaging in the lungs (1/10 also in the positive controls with cyclophosphamide); slight testicular degeneration (1/10), minimal testicular degeneration (5/10), slight epididymal degeneration (3/10), severe epididymal degeneration with a decreased sperm count, deformed or immature sperm (1/10); ♀: body weight gains increased by 7% (in the observation group on day 29), slight increase in the absolute and relative kidney weights, haematocrit values decreased at the end of the observation period, thrombocytes ↑, uterus: slight epithelial vacuolization (1/10), minimal hyperplasia (1/10), inflammatory cell infiltration (1/10)	Song et al. 2003
rat, Han Wistar, 10 ♂, 10 ♀	90 days, 0, 100, 300, 1000 mg/kg body weight and day, 7 days/week, gavage, 75.6% DBPO, OECD TG 408	100 mg/kg body weight: NOAEL; 100 mg/kg body weight and above: ♂: glucose ↓ (unclear dose dependency), ♀: leukocytes ↓ (without statistical significance at 1000 mg/kg body weight), cholesterol levels (LDL and HDL) ↓ (except cholesterol at 300 mg/kg body weight); 300 mg/kg body weight: ♀: T3 and T4 ↑; 300 mg/kg body weight and above: ♂: leukocytes ↓, lymphocytes ↓, haemoglobin ↓, sodium and chloride levels ↑, sperm motility ↑, progressive sperm ↑; 1000 mg/kg body weight: NOAEL of the authors; ♂/♀: relative liver weights ↑ (♂ +7%, ♀ +19%), ♂: feed consumption ↑ (about 10%), spleen: extramedullary haematopoiesis ↑, severity of pigment deposition ↑, thrombocytes ↓, alanine aminotransferase ↑, aspartate aminotransferase ↑, serum protein ↓, albumin ↓, glucose ↓, T4 ↓, pH in urine 5.8 (controls 7.4), sperm count ↑, ♀: absolute liver weights ↑ (+13%), liver: periportal vacuolization ↑, haemoglobin ↓, triglycerides ↑	Charles River Laboratories 2023
mouse, Kunming, 8 ♂, 8 ♀	42 days, 0, 50, 100, 200 mg/kg body weight and day, 7 days/week, no data for purity	100 mg/kg body weight: NOAEL; 200 mg/kg body weight: SOD ↓ (not decreased with statistical significance at 100 mg/kg body weight and day), MDA ↑ (sign of lipid peroxidation), Mg ²⁺ -ATPase and Ca ²⁺ -ATPase activities ↓ (not decreased with statistical significance at 100 mg/kg body weight and day), no effects on body and liver weights, only antioxidant status of liver tested	Jia et al. 2011

^{a)} unless specified otherwise, the described changes are statistically significant

DBPO: dibenzoyl peroxide; MDA: malondialdehyde; NOAEL: no observed adverse effect level; SOD: superoxide dismutase; TG: test guideline

In a combined study carried out according to OECD Test Guideline 422 in Sprague Dawley rats to investigate reproductive toxicity (see Section 5.5.1 and 5.5.2) and toxicity after repeated oral exposure, groups of 10 males and 10 females were given dibenzoyl peroxide (71.8%) in gavage doses of 0, 250, 500 or 1000 mg/kg body weight and day for 29 days or for 41 to 51 days, respectively, during mating and gestation, beginning 14 days before mating and continuing up to lactation day 3. Additional animals were included in the high dose group to observe them for another 2 weeks after the end of exposure. No mortality occurred in the study. The body weight gains were not affected during the exposure period. The body weight gains were increased by about 7% in the females of the 1000 mg/kg observation group after 29 days. The average feed consumption was increased in the males with statistical significance at 1000 mg/kg body weight and day during weeks 1 and 4. The absolute and relative weight of the left testis and the relative weight of the left epididymis were decreased in the males with statistical significance. The same findings were described for the right testis and

epididymis, but the effects were not statistically significant. The effects were reversible during the observation period. The absolute and relative kidney weights were increased with statistical significance in the females in comparison with the values determined in the controls. The effects were reversible within the observation period. The erythrocyte and leukocyte counts were increased with statistical significance in the male animals at the end of the observation period (but not at the end of exposure), while the haematocrit values were decreased in the female animals with statistical significance at the end of the observation period (but not at the end of exposure) and the number of erythrocytes was increased. No substance-related findings were detected in any of the treated males as regards clinical chemistry. In the female animals, aspartate aminotransferase in the 250 mg/kg group and total protein in the 500 mg/kg group were reduced with statistical significance in comparison with the values determined in the controls; however, there was no dose–response relationship. Therefore, the findings cannot be attributed to the substance. The histopathological examination found haemorrhaging in the lungs in 2 male animals of the high dose group. A similar finding was determined in 1 of the positive controls with cyclophosphamide. One animal had severe testicular degeneration, 5 others had minimal, but statistically significant, testicular degeneration. Testicular degeneration was observed in only one other animal, an animal from the observation group, and the findings did not have any effects on fertility (see [Section 5.5.1](#)). Three of the 10 animals had slight, 1 animal severe degeneration of the epididymis. The sperm count was markedly reduced in this animal and the lumen contained deformed or immature sperm. Slight epithelial vacuolization or minimal hyperplasia of the uterus were observed in 1 of 10 females, respectively, of the high dose group. Likewise, inflammatory cell infiltration was found in the uterus of 1 animal. In 2 animals (sex not specified) of the high dose group, minimal, but irreversible, focal pigmentation of the spleen was observed. The authors derived a NOAEL (no observed adverse effect level) for male and female animals of 1000 mg/kg body weight and day (Song et al. 2003). The Commission considers 500 mg/kg body weight and day to be the NOAEL for both sexes based on the slight effects on the kidney weights observed in the females of the 1000 mg/kg group and the findings in the testes and epididymides of the male animals.

In a 90-day study carried out according to OECD Test Guideline 408, Wistar Han rats were given dibenzoyl peroxide (75.6%) in gavage doses of 0, 100, 300 or 1000 mg/kg body weight and day. Mortality did not occur and the substance did not have any effects on the body weights. The absolute liver weights of the females (+ 13%) and the relative liver weights of the males (+ 7%) and the females (+ 19%) were increased at 1000 mg/kg body weight and day. The male animals in the high dose group consumed about 10% more feed. In the high dose group, periportal vacuolization was increased in the livers of the females, and extramedullary haematopoiesis and pigment deposition were increased in the spleens of the males. The leukocyte, lymphocyte and haemoglobin values were decreased with statistical significance in the male animals at 300 mg/kg body weight and day and above and the number of thrombocytes was reduced with statistical significance only in the high dose group. In the females, the lymphocyte count was reduced at 100 mg/kg body weight and day and above, in the high dose group without statistical significance, and haemoglobin concentrations were reduced at 1000 mg/kg body weight and day. The values of several clinicochemical parameters were changed with statistical significance in the male animals of the high dose group: alanine aminotransferase and aspartate aminotransferase were increased, the serum protein, albumin and glucose levels were reduced. The glucose levels were reduced at doses of 100 mg/kg body weight and day and above, but without clear dose dependency. The sodium and chloride levels were increased with statistical significance at doses of 300 mg/kg body weight and day and above. In the females, the cholesterol levels (LDL and HDL) were reduced with statistical significance at 100 mg/kg body weight and day and above (with the exception of cholesterol at 300 mg/kg body weight and day) and the triglycerides were increased at 1000 mg/kg body weight and day. The T4 levels were decreased in the male rats at 1000 mg/kg body weight and day, while the T3 and T4 levels were increased in the females only at 300 mg/kg body weight and day. The urine of the males in the high dose group had a pH of 5.8 in comparison with the pH of 7.4 determined in the urine of the control animals. In addition, the males had increased sperm motility and progressive sperm at 300 mg/kg body weight and day and above. The sperm count was increased at 1000 mg/kg body weight and day. As the findings did not correlate with histopathological effects, the authors derived a NOAEL for this study of 1000 mg/kg body weight and day (Charles River Laboratories 2023). Even though the study that was carried out in Han Wistar rats (OECD Test Guideline 408) used a longer period of exposure, its findings did not include any of the effects in the testes, epididymides and kidneys observed in Sprague Dawley rats in the study described above (OECD Test Guideline 422). Furthermore, the findings of the study are inconsistent, such as the increased T3 and T4 levels determined in female animals at a dose of 300 mg/kg body weight

and day in comparison with the decreased T4 levels in male animals at 1000 mg/kg body weight and day. In both studies, the male animals consumed more feed at 1000 mg/kg body weight and day. In the study carried out according to OECD Test Guideline 408, a provisional NOAEL of 100 mg/kg body weight and day was derived based on the haematological findings observed in the male animals at 300 mg/kg body weight and day and above (in the females, these effects were observed at doses as low as 100 mg/kg body weight and day and above, but without clear dose dependency) in addition to the increased extramedullary haematopoiesis in male animals at 1000 mg/kg body weight and day. The NOAEL is provisional until the inconsistencies between the studies have been resolved.

In a study carried out in 2011, groups of 8 male and 8 female Kunming mice were given daily gavage doses of dibenzoyl peroxide of 0, 50, 100 or 200 mg/kg body weight for 42 days. Effects on the body and liver weights were not observed. The antioxidant status of the liver tissue was determined based on superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity and MDA levels. The SOD, Mg^{2+} -ATPase and Ca^{2+} -ATPase activities were not statistically significant at 100 mg/kg body weight and day, but were decreased with statistical significance at 200 mg/kg body weight and day, while the MDA levels were increased with statistical significance after exposure to 200 mg/kg body weight and day (1.93 nmol/mg protein compared with 1.57 nmol/mg in the controls) (Jia et al. 2011). Therefore, the NOAEL was 100 mg/kg body weight and day for effects on the antioxidant status of the liver in mice after gavage administration for 42 days. Other organs were not investigated. The increased MDA levels are a sign of lipid peroxidation in the liver.

A long-term study was carried out in 1964 (see also Section 5.7.2.1) with groups of 25 male and 25 female albino rats and mice (strains and ages not specified) that were fed a powder for 120 or 80 weeks, respectively, that contained 18% dibenzoyl peroxide (no data for the other ingredients) and was commercially used for the bleaching of flour. The groups were given 0 or 10, 100 or 1000 times the average daily intake of humans. The authors estimated dibenzoyl peroxide concentrations of 0, 28, 280 or 2800 mg/kg feed, which are equivalent to doses of about 1.9, 19 and 190 mg/kg body weight and day in the male rats and mice and 2.3, 23 and 230 mg/kg body weight and day in the female animals (applying the method used by the Commission, these are equivalent to doses of about 1.4, 14 and 140 mg/kg body weight and day for rats and 4.2, 42 and 420 mg/kg body weight and day for mice; conversion factors 0.05 or 0.15 (chronic exposure) for rats and mice, respectively, according to EFSA (2012)). The male and female rats that were fed dibenzoyl peroxide concentrations of 280 or 2800 mg/kg feed had reduced body weights. The authors assume that the weight loss of about 10% was caused by a minor nutritional deficiency. Infectious changes were a widespread effect, particularly in the lungs of rats of both sexes and in the uterus. In many cases, local vascular damage occurred together with infectious lesions. Degenerative changes were most often observed in the liver, kidneys, testes and epididymides of rats. Stomach ulcers were not found in the control rats, but occurred in 2 rats that received the high dibenzoyl peroxide dose. Testicular atrophy was observed at the high dose. The authors assume that the atrophy was caused by dibenzoyl peroxide, which probably led to a minimal decrease in the amount of vitamin E in the feed (Sharratt et al. 1964). The study has limitations with respect to its procedure and description. The NOAEL may be in the range of 2800 mg/kg feed (about 190–230 mg/kg body weight and day) (ECHA 2020; HCN 2012). This study is of only limited relevance to the evaluation because of deviations from the requirements of current test guidelines and the use of special feed (nutritional deficiencies caused by feeding the animals a powder that was used to bleach flour).

Summary: A NOAEL of 500 mg/kg body weight and day was derived from the combined study of repeated dose toxicity and reproductive and developmental toxicity that was carried out in 2001 with Sprague Dawley rats according to OECD Test Guideline 422 (exposure period: males 29 days, females 41–51 days) based on the effects in the testes and epididymides observed at 1000 mg/kg body weight and day and the slight effects on the kidney weights in the females. These effects were not supported by the findings of a 90-day study carried out in Wistar Han rats according to OECD Test Guideline 408, even though the study used a longer period of exposure. The inconsistencies cannot be explained at present. A provisional NOAEL of 100 mg/kg body weight and day was derived from the study carried out according to OECD Test Guideline 408 based on the haematological findings observed in the males at 300 mg/kg body weight and day and above (in the females, these effects were observed at doses as low as 100 mg/kg body weight and day and above, but without clear dose dependency) and the increased incidence of extramedullary haematopoiesis in the males at 1000 mg/kg body weight and day. The NOAEL is provisional until the inconsistencies between the studies have been resolved.

A NOAEL of 100 mg/kg body weight and day was determined for the effects on the antioxidant status of the liver in mice after gavage administration for 42 days. Other organs were not investigated.

This NOAEL is not contradicted by the findings of the chronic study published in 1964, which are of only limited relevance for the evaluation because of deviations from the requirements of current guidelines and the use of a special feed (nutritional deficiencies caused by feeding the animals a powder that was used to bleach flour).

5.2.3 Dermal application

In a 13-week study in F344 rats and B6C3F1 mice from 1997, which is available only as an abstract and was carried out as a preliminary study for a carcinogenicity study, the skin of the animals was treated daily with different doses of dibenzoyl peroxide in Carbopol® gel (a water-soluble polymer that is used as an emulsifying agent, stabilizing agent, suspending agent and thickener and as a gelling agent in hand disinfectants and other products (Silverman Machines 2023)). The rats were given 15, 45, 75 or 150 mg/animal, the mice 5, 15, 25 or 50 mg/animal. The incidence and severity of acanthosis, hyperkeratosis and subacute inflammation of the skin were increased in B6C3F1 mice in a dose-dependent manner. The liver and gall bladder weights were increased. In F344 rats, the incidence and severity of acanthosis, hyperkeratosis and skin inflammation were likewise increased in a dose-dependent manner. Severe hyperkeratosis was more frequently observed in female rats and tended to occur in animals that had an accumulation of test substance. The kidney weights were increased in rats. The application of dibenzoyl peroxide increased cell proliferation in the skin of mice and rats with statistical significance and in a dose-dependent manner; this was determined by proliferating cell nuclear antigen immunostaining (PCNA) (no other details). Acanthosis is caused by chronic inflammation. The doses chosen for the chronic study below were based on this study.

Section 5.7.2.2 describes a 104-week study in CDF®(F-344)CR1BR rats that was carried out according to GLP guidelines. In this study, the application of dibenzoyl peroxide in Carbopol® gel in concentrations of up to 15% (about 100 mg/kg body weight and day for the male animals and about 150 mg/kg body weight and day for the female animals) to the shaved dorsal skin (probably non-occlusive) did not lead to systemic toxicity. Skin irritation was observed at concentrations as low as 1.67% (0.3 mg/cm²/day) (ECHA 2020).

Systemic toxicity was not observed in B6C3F1/CR1BR mice exposed under the same experimental conditions to concentrations up to 25% (about 833 mg/kg body weight and day for the males and about 1000 mg/kg body weight and day for the females). The NOAEC (no observed adverse effect concentration) for skin irritation was 1% (0.17 mg/cm²/day) (ECHA 2020).

Summary: There was no evidence of systemic toxicity after daily topical application of dibenzoyl peroxide gels to rats and mice in doses of 100 and 833 mg/kg body weight and day, respectively, for 104 weeks. Skin irritation was observed in rats at concentrations as low as 1.67% dibenzoyl peroxide and above; in mice, the NOAEC for skin irritation was 1% (ECHA 2020).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In a study published in 1973, 500 mg of 78% granular dibenzoyl peroxide was applied to the abraded or intact dorsal skin of 3 male and 3 female New Zealand White rabbits and the site was covered semi-occlusively for 4 hours. After 4 hours, the exposed areas were rinsed with lukewarm water. The skin was examined for injury or irritation after 4, 24 and 72 hours and scored using the Draize scale. The irritation scores for erythema and oedema were 0 on a scale with a maximum of 4. Dibenzoyl peroxide granules did not cause irritation of the skin in this study (ECHA 2020; OECD 2002).

In another test, concentrations of 0.1% to 30% dibenzoyl peroxide in yellow soft paraffin were applied occlusively to shaved areas on the backs of rabbits for 24 hours. In 1 animal, the lowest concentration that caused irritation was 1% dibenzoyl peroxide. All rabbits reacted to concentrations of 10% and above. The ID₅₀ value for dibenzoyl peroxide

(irritation observed in 50% of the animals) was 2.52% (1.36%–4.04%). This value suggests that dibenzoyl peroxide in soft paraffin causes irritation of the skin. The application of the test substance was repeated once a day for a maximum period of 10 days and was stopped when erythematous reactions occurred. After exposure to 0.1%, 1% and 5% dibenzoyl peroxide, irritation was observed in 50% of the animals (IT_{50}) after 8.35 (7.06 to 10.40), 4.34 (3.44 to 5.16) and 2.31 (1.75 to 2.80) days, respectively (ECHA 2020; OECD 2002).

In a study published in 1964, dibenzoyl peroxide was tested in guinea pigs in the form of a solid and as a 10% dibenzoyl peroxide solution in propylene glycol. Slight erythema was observed after 24 hours under occlusive conditions (ECHA 2020; OECD 2002).

In a cumulative skin irritation study, 100 µl of 10% dibenzoyl peroxide was applied daily to the entire dorsum of mice for 6 months. The keratinocytes showed marked variations in size and shape (atypia) (ECHA 2020; OECD 2002).

Dibenzoyl peroxide is not classified as a skin irritant according to the Global Harmonized System (ECHA 2020).

Summary: After 24-hour occlusive application, granular dibenzoyl peroxide does not cause irritation, but causes irritation of the skin in rabbits in soft paraffin or in propylene glycol.

5.3.2 Eyes

A study carried out in New Zealand White rabbits according to OECD Test Guideline 405 investigated eye irritation after instillation of 100 mg of 70% granular dibenzoyl peroxide. Dibenzoyl peroxide did not cause irritation in 3 rabbits if the eyes were rinsed directly after instillation. However, severe eye irritation was observed in 1 rabbit after the dibenzoyl peroxide was not immediately rinsed out of the eyes. At the readings taken at 24, 48 and 72 hours, the scores for irritation were 0.63 on a scale of 4 for corneal opacity, 0.63 of 2 for the iris, 1.3 of 3 for the conjunctivae and 1.0 of 4 for chemosis. All findings were reversible within 72 hours. Corrosive effects were not observed (ECHA 2020; OECD 2002).

In a study carried out in New Zealand White rabbits in 1973, 0.1 cm³ of 78% granular dibenzoyl peroxide did not cause irritation of the eyes in 5 animals if the eyes were rinsed 5 minutes after instillation. Slight redness was observed in the eye of 1 animal and swelling in the eyes of 2 of the 5 animals. The eyes of 3 rabbits were not immediately rinsed after instillation of the test substance, resulting in irritation of the eyes up to 72 hours later. At the readings taken at 24, 48 and 72 hours, the irritation score determined in this treatment group (unrinsed) was 0.3 on a scale of 4 for corneal opacity (effects observed in all 3 animals); the findings were reversible after 48 hours. The scores were 0 on a scale of 2 for irritation of the iris, 1 of 3 for the conjunctivae (effects observed in 2 animals) and 1.22 of 4 for chemosis. The latter 2 effects were reversible within the observation period of 7 days (ECHA 2020; OECD 2002).

Dibenzoyl peroxide is classified in Category 2 (eye irritation) according to the Globally Harmonized System (ECHA 2020).

Summary: Granular dibenzoyl peroxide causes marked, reversible irritation of the eyes in rabbits.

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

5.4.1.1 Animal experiments

The last documentation (Greim 1999) described positive results that were obtained in a maximization test, a TINA test and a Buehler test. The results of a mouse ear swelling test (MEST) were contradictory. A local lymph node assay (LLNA) carried out by 5 laboratories yielded positive results. These tests have now been re-evaluated and the results continue to be relevant by today's standards. Current reviews have published EC₃ values as mean or median values that place the substance in the range of a strong allergen (Basketter and Kimber 2006; Hoffmann et al. 2018; Kleinstreuer et al. 2018; Urbisch et al. 2015).

5.4.1.2 Studies with New Approach Methods (NAMs)

The skin sensitizing properties of a substance are determined by combining the results of test methods that investigate the key events of the Adverse Outcome Pathway (AOP) as described by OECD Guideline 497. The results of different test methods are taken into consideration to derive the sensitizing potential of a substance because it is assumed that a single test method cannot fully cover the complex series of steps involved in the development of sensitization.

The experimental test methods that were validated by the OECD are based on the AOP for skin sensitization (OECD 2012). The first key event (key event 1 (KE1) and molecular initiating event) is evaluated using methods that analyse the ability to bind to skin proteins (electrophile–nucleophile interactions). The second key event (KE2) is evaluated using methods that analyse the activation of keratinocytes by the substance. The third key event (KE3) is evaluated by analysing the maturation of dendritic cells induced by the substance. A validated test method for the fourth key event (KE4), T-cell proliferation, is not available at the present time. In addition to the results of experimental test methods used to analyse the key events, which are based on in-chemico approaches (KE1) and in vitro methods (KE2–KE3), the evaluation may also include data obtained from models (in silico) as well as data for the mechanism of action.

Comprehensive results are available for dibenzoyl peroxide; these are shown in [Table 4](#).

5.4.1.2.1 Key event 1 of the AOP for skin sensitization: testing the substance for peptide reactivity

At present, there are a number of different methods available for testing a substance for peptide reactivity that have been validated by the OECD (Test Guideline 442C). Three methods were used to investigate dibenzoyl peroxide (the standard direct peptide reactivity assay (DPRA), the amino acid derivative reactivity assay (ADRA) and the kinetic DPRA (kDPRA)). Positive results were obtained with dibenzoyl peroxide in all tests with a cysteine peptide (DPRA (Natsch et al. 2013; Takenouchi et al. 2015), ADRA (Fujita et al. 2019) and kDPRA (OECD 2020)). However, the test results may have been due to the oxidative properties of the substance. Tests that are not affected by this property yielded 2+ results for lysine reactivity (DPRA and ADRA (Fujita et al. 2019; Natsch et al. 2013)); another test that is not affected produced negative results (Takenouchi et al. 2015).

5.4.1.2.2 Key event 2 of the AOP for skin sensitization: evaluation of the substance for substance-induced activation of keratinocytes

The second key event is evaluated by analysing the activation of keratinocytes by the substance. Different methods are available that have been validated by the OECD (Test Guideline 442D) in addition to scientifically approved methods.

Overall, 6 different methods were used to investigate dibenzoyl peroxide. The molecule yielded negative results in the KeratinoSensTM (Natsch et al. 2013) and borderline positive results in the LuSens (secondary citation in Urbisch et al. (2015), unpublished data, evaluation according to Kolle et al. (2021)). Dibenzoyl peroxide was initially classified as a moderate allergen based on the results of the SENS-IS[®] (Cottrez et al. 2016) and then later as a strong allergen (Na et al. 2022). In the RHE IL-18 EpiDermTM and RHE IL-18 epiCSTM, negative results were initially obtained with dibenzoyl peroxide under standard conditions. However, unblinded retesting with the RHE IL-18 EpiDermTM using lower concentrations yielded positive results (Mehling et al. 2019). The negative results in the RHE IL-18 epiCSTM are uncertain because of the high concentration of the parent solution close to the solubility limit.

5.4.1.2.3 Key event 3 of the AOP for skin sensitization: evaluation of the substance-induced maturation of dendritic cells

The results of 7 tests are available for the third key event (the human cell line activation test (h-CLAT), the U-SensTM (U937 cell line activation test, formerly MUSST), the interleukin-8 reporter gene assay (IL-8 Luc)). The h-CLAT yielded negative results (Ashikaga et al. 2010; Nukada et al. 2012; Takenouchi et al. 2015), while positive results were obtained with the substance in the U-SensTM (EURL ECVAM 2016; Natsch et al. 2013; Piroird et al. 2015). Dibenzoyl peroxide yielded positive results in the IL-8 Luc assay (Kimura et al. 2015).

5.4.1.2.4 Integration of the results

The following examples show how the available results can be combined using integrated approaches described in OECD Guideline 497. The “2 of 3” approach was used to integrate the data from the standard DPRA, the KeratinoSens™ and the h-CLAT, yielding negative results for dibenzoyl peroxide. However, if the principle were extended and the positive results obtained with the U-Sens™ were considered instead of the negative results from the h-CLAT, the overall results would be positive.

Other integrated testing strategies (according to OECD Guideline 497) are based on the evaluation of KE1 and KE3. The integrated testing strategy version 1 (ITSv1) additionally uses the data from computer-assisted methods (statistical quantitative structure–activity relationship (QSAR) models). The integrated testing strategy version 2 (ITSv2) includes the data from Derek Nexus, a mechanistic prediction model.

Positive results were obtained by applying ITSv1 and ITSv2 to integrate the individual results for dibenzoyl peroxide (QSAR: Li et al. 2007; Liu et al. 2008; Urbisch et al. 2015; Derek Nexus: Takenouchi et al. 2015).

The ITSv1 or ITSv2 can furthermore be used to classify a substance by potency. The individual results are first quantified by points (Table 4), which are then added together. Taking into consideration the results of the DPRA, h-CLAT and additional data from the QSAR (ITSv1) or Derek Nexus (ITSv2), which were each assigned 1/1 point, dibenzoyl peroxide is assigned a total number of points of 4 of 7 for both strategies. This is equivalent to classification in Category 1B according to the CLP Regulation (2–5 of 7 points). At present, it is not possible to take the U-Sens™ into account and quantify the results of the assay in points. Overall, NAMs can be used to derive the skin sensitizing potential and to categorize (1B) dibenzoyl peroxide.

Tab. 4 Results obtained by applying new approach methods (NAMs) relating to the key events of the AOP for skin sensitization according to OECD Test Guideline 168 (OECD 2012) for dibenzoyl peroxide ($\log K_{OW} = 3.43$ (calculated), solubility: 9.1 mg/l water, MW: 242.22 g/mol). The table provides data for the test systems including the procedures and results, in addition to the evaluation of the data according to the OECD using the “2 of 3” approach (1: positive/0: negative) and integrated testing strategies (ITS) (quantification of the results as scores)

KE of the AOP (OECD 2012)	Test system	Procedure	Results	References	Evaluation according to OECD using the “2 of 3” approach ^{a)}	Evaluation according to OECD using ITS
1	DPRA	equivalent to OECD Test Guideline 442C	depletion Cys: 100%, Lys: 81.3%	Natsch et al. 2013	1	score 3/3
		according to OECD Test Guideline 442C	Cys: 100%, Lys: 5.6%	Takenouchi et al. 2015	1 or 0 (only Lys)	score 3/3
	kDPRA	comparable with OECD-Test Guideline 442C (kinetic DPRA validation study report)	$\log K_{max} = 0.74$	OECD 2020	(1)	not included in the ITS
	ADRA	according to OECD Test Guideline 442C	Cys: 100%, Lys: 50.6%	Fujita et al. 2019	(1)	not included in the ITS

Tab. 4 (continued)

KE of the AOP (OECD 2012)	Test system	Procedure	Results	References	Evaluation according to OECD using the “2 of 3” approach ^{a)}	Evaluation according to OECD using ITS
2	KeratinoSens TM	equivalent to OECD Test Guideline 442D	negative	Natsch et al. 2013; Urbisch et al. 2015	0	not included in the ITS
	LuSens	according to OECD Test Guideline 442D tested: 20–50 µM	negative / borderline	secondary citation in Urbisch et al. (2015, unpublished data; evaluated according to Kolle et al. (2021))	(0)	not included in the ITS
	SENS-IS [®]	according to Cottrez et al. 2016, method at the peer review stage	positive	Cottrez et al. 2016	(1)	not included in the ITS
	RHE IL-18 epiCS TM	Corsini et al. 2013; Gibbs et al. 2013	positive	Mehling et al. 2019	(1)	not included in the ITS
	RHE IL-18 EpiDerm TM	Corsini et al. 2009; Gibbs et al. 2013	negative results under standard conditions; individual, unblinded retesting produced positive results	Mehling et al. 2019	(1)	not included in the ITS
3	h-CLAT	equivalent to OECD Test Guideline 442E, CV75 = 41 µg/ml	RFI CD86 negative MIT: not calculated RFI CD54 negative	Ashikaga et al. 2010; Nukada et al. 2012	0	score 0/3
		CV75 = 34.9 µg/ml	RFI CD86 negative MIT: not calculated RFI CD54 negative	Takenouchi et al. 2015	0	score 0/3
	U-Sens TM	equivalent to OECD Test Guideline 442E	EC ₁₅₀ (MIT) = 15.7 µM (no other data)	Natsch et al. 2013	(1)	not included in the ITS
		equivalent to OECD Test Guideline 442E in DMSO, CV70 = 64 µg/ml	EC ₁₅₀ (MIT) = 28 µg/ml (no other data)	Piroird et al. 2015	(1)	not included in the ITS
		equivalent to OECD Test Guideline 442E in DMSO, CV70 = 33 µg/ml	EC ₁₅₀ (MIT) = 27 µg/ml (no other data)	EURL ECVAM 2016	(1)	not included in the ITS
	IL-8 Luc	equivalent to OECD Test Guideline 442 E	positive (no other data)	Kimura et al. 2015	(1)	not included in the ITS

ADRA: amino acid derivative reactivity assay; CD54/CD86: cell surface proteins; CV70: 70% cell viability; Cys: cysteine peptide; DMSO: dimethyl sulfoxide; DPRA: standard direct peptide reactivity assay; h-CLAT: human cell line activation test; IL-8 Luc: interleukin-8 reporter gene assay; ITS: integrated testing strategy; kDPRA: kinetic DPRA; Lys: lysine peptide; MIT: minimum induction threshold; MW: molecular weight; RFI: relative fluorescence intensity; RHE IL-18 epiCSTM/RHE IL-18 EpiDermTM: IL-18 assays with reconstructed human epidermis; U-SensTM: U937 cell line activation assay

^{a)} Data in parentheses: methods that have not been included in the guidelines officially, but are scientifically comparable

Dibenzoyl peroxide was furthermore evaluated using other defined approaches that have been validated scientifically, but have not been included in the OECD test guidelines (Kleinstreuer et al. 2018). Positive results were obtained with dibenzoyl peroxide using methods that focus on qualitative aspects for assessment (sensitizing/not sensitizing) (Asturiol et al. 2016; Natsch et al. 2015) and those carried out with the objective of classifying potency in up to 5 subgroups (Hirota et al. 2015; Jaworska et al. 2015; Otsubo et al. 2020; Strickland et al. 2016).

Another scientifically validated 3D epidermis model SensCeeTox[®], which tests KE1 and KE2, is used to analyse more extensive gene expression profiles (omics) in human epidermal skin samples. An algorithm integrates the individual results of the analysed key events to calculate an overall result (McKim et al. 2012). A positive overall result was calculated for dibenzoyl peroxide using this method (Mehling et al. 2019). This confirms the positive results obtained by the evaluation according to OECD Guideline 497.

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

The combined study of the toxic effects induced by repeated oral doses and a screening test for reproductive and developmental toxicity that was described above in [Section 5.2.2](#) was carried out in Sprague Dawley rats according to OECD Test Guideline 422. Dibenzoyl peroxide (71.8%) in corn oil was given to groups of 10 male animals for 29 days and groups of 10 female animals for 41 to 51 days in gavage doses of 0, 250, 500 or 1000 mg/kg body weight and day, beginning 14 days prior to mating and continuing during the mating and gestation periods up to postnatal day 3. The results for developmental toxicity are described in [Section 5.5.2](#). The NOAEL of 500 mg/kg body weight and day for the male parent animals was derived based on testicular and epididymal degeneration and the decrease in the number of sperm in the high dose group. The findings in the uterus in the females were not attributed to treatment. As a result, the NOAEL for effects on the female reproductive organs was 1000 mg/kg body weight and day. The precoital period (the number of days prior to mating) was not affected by exposure in any of the groups and the copulation and gestation indices likewise remained unchanged. The fertility index in the male and female animals of the high dose group was 90% of the value of the controls (not statistically significant), which is above the average rate of conception of 88.6% for Sprague Dawley rats and therefore not regarded as induced by the substance (Song et al. 2003). As the fertility of the male animals was not impaired despite the testicular and epididymal degeneration, the NOAEL for fertility in both sexes was 1000 mg/kg body weight and day.

The limited study of Sharratt et al. (1964) that was described in [Section 5.7.2.1](#) likewise found that oral exposure to dibenzoyl peroxide leads to testicular atrophy in rats (OECD 2002).

5.5.2 Developmental toxicity

In a preliminary study with dibenzoyl peroxide (74.8%) that was carried out in preparation for the developmental toxicity study below, groups of 8 female Sprague Dawley rats were given dibenzoyl peroxide in gavage doses of 0, 100, 300 or 1000 mg/kg body weight and day from gestation days 6 to 20. No mortality and no clinical symptoms were observed up to the high dose. At 1000 mg/kg body weight and day, the body weight gains were 31% lower than the values in the control animals from gestation days 6 to 9. This was observed concurrently with a 12% reduction in feed consumption. No unusual findings were observed at necropsy. The body weights of the foetuses were reduced by 10% in the high dose group. No unusual external findings were observed (CiToxLab 2014 a).

In a developmental toxicity study carried out in Sprague Dawley rats (CrI CD[®] (SD) IGS BR) according to OECD Test Guideline 414, groups of 24 female animals per dose group were given dibenzoyl peroxide (vehicle: 0.5% methyl cellulose) in gavage doses of 0, 100, 300 or 1000 mg/kg body weight and day from gestation days 6 to 20. Two dams of the high dose group were sacrificed prematurely on gestation day 21 after their offspring were stillborn. As the dams had not shown any symptoms previously, the stillbirths were evaluated as coincidental. At the end of the study, 22, 20, 22 and 19 females exposed to doses of 0, 100, 300 and 1000 mg/kg body weight and day, respectively, had living foetuses. The small number of litters in the high dose group did not negatively affect the evaluation and interpretation of the study because a sufficient number of foetuses was available for examination in each group. The only clinical sign was a reddish

vaginal discharge on gestation days 13 or 15 in 1, 0, 1 and 3 of 24 dams at 0, 100, 300 and 1000 mg/kg body weight and day, respectively. This effect was not associated with the increased incidence of late post-implantation losses or late resorptions. In the dams of the group exposed to 1000 mg/kg body weight and day, the mean body weight gains from gestation days 6 to 21 minus the gravid uterus weights were lower than the values determined in the control animals (–17%). This difference can be attributed to the lower body weight gains (–33%, $p < 0.05$) from gestation days 18 to 21, in comparison with the weight gains observed in the control animals, and correlated with a statistically significant decrease in feed consumption (–15%; $p < 0.001$) during this period. The mean gravid uterus weights determined in the dams at 1000 mg/kg body weight and day were lower (–10%) than the values determined in the controls. The NOAEL for maternal toxicity was therefore 300 mg/kg body weight and day.

The increased incidences of post-implantation losses at 300 and 1000 mg/kg body weight and day were regarded as physiological variants (0, 100, 300, 1000 mg/kg body weight and day: $2.6\% \pm 4.7\%$, $5.0\% \pm 5.9\%$, $6.7\% \pm 12.5\%$, $6.3\% \pm 7.2\%$) because a mean value of 6.5% (range: 2.0%–8.7%) was calculated from the historical control data (February 2008 to March 2012, 7 studies, 162 dams). At 1000 mg/kg body weight and day, delays in growth were observed in the foetuses, such as reduced mean body weights (–16%), and the incidence of incomplete ossification of the skull, vertebrae, sternum and limbs was increased with statistical significance. At 300 mg/kg body weight and day, the incidence of incomplete ossification of the caudal vertebral arches was increased with statistical significance on a foetal basis, but not on a litter basis (controls, 100, 300, 1000 mg/kg body weight and day; litter basis: 0, 10.0%, 18.2%, 42.1%; foetal basis: 0, 1.4%, 4.1%, 9.4%). Teratogenicity was not observed up to 1000 mg/kg body weight and day. The authors derived a NOAEL of 300 mg/kg body weight and day for developmental toxicity (CiToxLab 2014 b). The Commission considers the NOAEL for developmental toxicity to be 100 mg/kg body weight and day because the effects had already begun at the dose of 300 mg/kg body weight and day. The incidence of incomplete ossification was increased at this dose, but without statistical significance.

The combined repeated dose toxicity study and screening test for reproductive and developmental toxicity that was carried out in Sprague Dawley rats according to OECD Test Guideline 422 (see Section 5.2.2 and 5.5.1 for the exposure conditions, the findings in the parent animals and for reproductive toxicity) derived a NOAEL of 500 mg/kg body weight and day in the parent animals. The body weights were reduced with statistical significance ($p < 0.01$) in the offspring on postnatal day 3 at the high dose of 1000 mg/kg body weight and day (males –9%, females –12.9% of the weights of the controls). A case of spina bifida was observed in the 250 mg/kg group, but was interpreted as a coincidental finding. Slight developmental delays (no further details) were observed in 14.2%, 12.4%, 11.5% and 41.4% of the offspring at doses of 0, 250, 500 and 1000 mg/kg body weight and day, respectively, and in 100% of the positive controls (Song et al. 2003). The NOAEL for perinatal developmental toxicity was therefore 500 mg/kg body weight and day. As the post-implantation losses were not found to be increased, the interpretation of the post-implantation losses as a physiological variant by the study carried out according to OECD Test Guideline 414 (CiToxLab 2014 b) is considered valid.

5.6 Genotoxicity

5.6.1 In vitro

Dibenzoyl peroxide did not form bonds with the DNA in studies investigating the mechanism of action (see Section 2.1).

In vitro studies of genotoxicity are shown in Table 5.

Tab. 5 Genotoxicity of dibenzoyl peroxide in vitro

End point	Test system	Concentration [µg/plate] ^{a)}	Effective concentration ^{a)}	Cytotoxicity ^{a)}	Results		References
					–m. A.	+m. A.	
SOS chromotest gene mutations	Escherichia coli PQ37	no data	no data	no data	+	n. t.	ECHA 2020
	Escherichia coli PM21	no data	no data	no data	–	n. t.	
	Escherichia coli GC4798	no data	no data	no data	–	n. t.	
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	+m. A.: 0, 0.8–100; –m. A.: 0, 0.8–500 (75%)	–	100–500	–	–	
	Salmonella typhimurium TA98, TA100, TA1535, TA1537 (OECD TG 471)	0, 0.247–60 (71.8%)	–	> 60	–	–	
	Escherichia coli WP2 uvr A (OECD TG 472)	0, 1–60 (71.8%)	–	> 60	–	–	
	Salmonella typhimurium TA97, TA98, TA100, TA102, TA104, TA1535	tested up to cytotoxicity, no other details, +m. A.: rat 10% and 30% S9 mix, hamster 10% S9 mix	–	tested up to cytotoxicity, no other data	–	–	
	Salmonella typhimurium TA97a, TA100, TA102, TA104	0, 1–100 (purity not specified)	–	100	–	–	
	Salmonella typhimurium TA97, TA98, TA100, TA1535	0, 0.03–200 (purity not specified), +m. A.: rat 10% and 30% S9 mix	–	–m. A.: tested up to cytotoxicity +m. A.: no data	–	–	
	Salmonella typhimurium TA92, TA94, TA98, TA100, TA1535, TA1537	0 to 2500 (purity not specified)	–	no data	–	–	
	Salmonella typhimurium TA1535, TA1537, TA1538	0, 0.1875% (78%); m. A.: tissue homogenates from the liver, lungs, testes; S9 mix from mice, rats and monkeys	–	no data	–	–	
	Salmonella typhimurium TA97, TA102	0, 0.001–0.1 (purity not specified)	–	–m. A.: slight cytotoxicity at 0.05 and above +m. A.: > 0.1	–	–	
	Salmonella typhimurium TA97, TA98, TA100, TA102, TA1535, TA1537, TA1538	no data	–	no data	–	–	De Flora et al. 1984
	Salmonella typhimurium TA98, TA100	300	–	no data	–	–	Yamaguchi and Yamashita 1980
SCE	human peripheral lymphocytes	0, 25–100 µg/ml, (purity not specified), 24 and 48 hours	100	100 µg/ml	+/-	n. t.	Yavuz et al. 2010
	CHO cells	no data (abstract)	no data	tested up to cytotoxicity	–	+	ECHA 2020
DNA strand breaks (alkaline elution)	primary epidermal cells from newborn BALB/c mice	0, 0.1 mM (purity not specified), 3 or 24 hours	no data	no data	+	n. t.	
	10 cell lines from chemically induced mouse skin papillomas	0, 0.1 mM (purity not specified), 3 or 24 hours	no data	no data	1 × + 3 × +/- 6 × –	n. t.	

Tab. 5 (continued)

End point	Test system	Concentration [µg/plate] ^{a)}	Effective concentration ^{a)}	Cytotoxicity ^{a)}	Results		References
					–m. A.	+m. A.	
DNA single strand breaks (method not specified)	primary human bronchial epithelial cells	no data	no data	no data	+	n. t.	HCN 2012
	2 human lung carcinoma cell lines	no data	no data	no data	–	n. t.	
	JB6 epidermal mouse cells	50 µM	50 µM	> 50 µM	+	n. t.	
	human leukocytes	20–80 µM	no data	no data	+	n. t.	
	mouse keratinocyte cell line 308	30–300 µM	no data	no data	+	n. t.	
	mouse keratinocytes	100 nM	no data	no data	+	n. t.	
	primary human bronchial epithelial cells	100 µM	100 µM	50% inhibition of growth	+	n. t.	
DNA–protein crosslinks	primary human bronchial epithelial cells	100 µM	no data	50% inhibition of growth	+	n. t.	ECHA 2020
oxidative DNA damage (8-OxodG)	keratinocyte cell line 308	0, 1–50 µM (purity not specified), 6, 12 or 24 hours	no data	30 µM and above	+	n. t.	
	human leukaemia HL-60 cells	0, 0.05–0.2 µM (purity not specified), 2.5 hours	dependent on concentration	no data	+	n. t.	
	H ₂ O ₂ -resistant human leukaemia HL-100 cells (catalase activity 18 × higher than in HL-60 cells)	0, 0.05–0.2 µM (purity not specified), 2.5 hours	dependent on concentration	no data	+	n. t.	
	CHL cells	0 to 200 µg/ml (purity not specified), 48 hours	–	200 µg/ml	–	n. t.	
chromosomal aberrations	human peripheral lymphocytes	0, 25–100 µg/ml (purity not specified), 24 and 48 hours	75 µg/ml	100 µg/ml	+/-	n. t.	Yavuz et al. 2010
micronuclei	human peripheral lymphocytes	0, 25–100 µg/ml (purity not specified), 24 and 48 hours	100 µg/ml	100 µg/ml	+/-	n. t.	
TK ^{+/–} mutation test	L5178Y mouse lymphoma cells (OECD TG 476)	+m. A., 3 hours Test 1: 0, 0.78–100; Test 2: 0, 3.13–100 –m. A., 3 hours: 0, 0.39–50; 24 hours 0, 1.56–50 (74.6%)	–	–m. A.: > 12.5 +m. A.: 25 and 50, respectively	–	–	ECHA 2020

^{a)} unless specified otherwise, data given in µg/plate

8-OxodG: 8-oxo-2'-deoxyguanosine; m. A.: metabolic activation; n. t.: not tested; TG: test guideline; +/-: results not clear

Numerous studies have shown that dibenzoyl peroxide is not mutagenic in the *Salmonella typhimurium* strains TA97, TA97a, TA98, TA100, TA102, TA104, TA1535 and TA1537, in *Escherichia coli* WP2 uvrA or in *Saccharomyces cerevisiae* either in the presence or in the absence of a metabolic activation system (ECHA 2020; HCN 2012; IARC 1999; Kraus et al. 1995; OECD 2002).

Dibenzoyl peroxide induced a slight increase in sister chromatid exchange (SCE) in human peripheral lymphocytes at cytotoxic concentrations in the absence of a metabolic activation system. Positive results obtained in another SCE test using V79 cells were described in an abstract. However, no data were provided for test concentrations and cytotoxicity (ECHA 2020).

Dibenzoyl peroxide induced DNA strand breaks in epidermal mouse keratinocytes. Cell lines from chemically induced mouse skin papillomas, by contrast, were relatively resistant to dibenzoyl peroxide (ECHA 2020). An abstract described similar findings of strand breaks in cultured human bronchial epithelial cells, but not in 2 lung carcinoma cell lines, after treatment with dibenzoyl peroxide (HCN 2012). Many other studies found that dibenzoyl peroxide induces DNA strand breaks; however, most tested only 1 concentration (see Table 5).

At a concentration of 100 µM, dibenzoyl peroxide induced DNA–protein crosslinks in primary human bronchial epithelial cells with 50% growth inhibition (Saladino et al. 1985) and increased 8-oxodG levels in the DNA of cultured mouse keratinocytes and human leukaemia cells (HL 60) (ECHA 2020).

Dibenzoyl peroxide induced a slight increase in chromosomal aberrations in human peripheral lymphocytes at cytotoxic concentrations in the absence of a metabolic activation system. Another chromosomal aberration test obtained negative results after incubating CHL cells (lung fibroblasts from Chinese hamsters) at a dibenzoyl peroxide concentration of 200 µg/ml, the highest non-cytotoxic concentration, for 24 and 48 hours without the addition of a metabolic activation system. Dibenzoyl peroxide induced a slight increase in micronuclei in human peripheral lymphocytes at cytotoxic concentrations in the absence of a metabolic activation system (ECHA 2020).

In a TK^{+/-} mutation test with L5178Y mouse lymphoma cells that was carried out in 2010 according to OECD Test Guideline 476, dibenzoyl peroxide (74.6%) was not found to be genotoxic either in the presence or in the absence of a metabolic activation system (ECHA 2020).

5.6.2 In vivo

In a micronucleus test that was carried out in 2001 according to OECD Test Guideline 474, dibenzoyl peroxide (71.8%) was given to groups of 6 male ICR mice by intraperitoneal injection in doses of 0, 50, 100 or 200 mg/kg body weight and day on 2 days. The animals in the high dose group exhibited reduced activity and had reduced body weights. The PCE/(PCE + NCE) ratio was slightly reduced at this dose. Dibenzoyl peroxide did not increase the micronuclei frequency in the bone marrow (ECHA 2020; OECD 2002).

After dibenzoyl peroxide (75%) was applied to the skin of 10 female Sencar mice per dose group, the treated areas of skin were examined for 8-oxodG formation, epidermal hyperplasia and mutations at codons 12, 13 and 61 of c-Ha-ras. The test substance was applied to the skin in doses of 0, 6.25, 62.5 or 125 µmol/mouse twice a week for 4 weeks and the animals were subsequently observed for 2 additional days. Neither clinical symptoms nor effects on body weights, body weight gains or feed consumption were observed. In comparison with the incidence determined in the controls, a slight, but not statistically significant, increase in epidermal hyperplasia was observed at all doses. An assessment of dermal cellularity did not show that treatment with dibenzoyl peroxide causes inflammation. In comparison with the values determined in the control animals, dibenzoyl peroxide did not induce c-Ha-ras mutations in this test system, and increased 8-oxodG levels with statistical significance by a factor of 2.4 only in the high dose group (ECHA 2020).

Germ cells

A dominant lethal assay found that the incidence of dominant lethal mutations in CR/Ha Swiss mice given dibenzoyl peroxide doses of 0, 54 or 62 mg/kg body weight by intraperitoneal injection was not increased in comparison with the incidence found in the control animals. Seven to 9 male animals per dose group and 10 control animals were tested. Each male animal was mated with 3 untreated female animals per week, for a total of 8 weeks. The foetuses were examined 10 days later. No treatment-induced effects, early foetal mortality or pre-implantation losses were observed. The positive control verified the correct functioning of the test system (ECHA 2020).

5.6.3 Summary

Exposure to dibenzoyl peroxide increased 8-oxodG levels in vitro and in vivo, and increased the frequency of DNA strand breaks in vitro.

Dibenzoyl peroxide did not induce mutagenic effects in bacteria. A TK^{+/-} mutation assay in L5178Y mouse lymphoma cells yielded negative results. SCE was observed at cytotoxic concentrations. Standard tests for clastogenic effects in vitro yielded negative results overall. The assays included 2 chromosomal aberration tests and a micronucleus test; the 2 tests with human lymphocytes detected a slight increase in aberrations and micronuclei, respectively, only at cytotoxic concentrations. The negative results were verified by in vivo studies. A micronucleus test in mice that was carried out

according to an OECD test guideline and an earlier dominant lethal assay in mice yielded negative results. The induction of Ha-ras mutations was not increased in the skin of Sencar mice.

In summary, dibenzoyl peroxide has at most a weak genotoxic potential at high concentrations.

5.7 Carcinogenicity

5.7.1 Short-term studies

5.7.1.1 Dermal application

Dibenzoyl peroxide (purity not specified) doses of 0, 1, 10, 20 or 40 mg/animal in 0.2 ml acetone were applied to the skin of groups of 30 female Sencar mice, aged 7 to 9 weeks, twice a week for 52 weeks. Mortality was not increased and no carcinomas were detected on the skin. The incidence of skin papillomas found in the exposed animals and in the control animals did not differ with statistical significance (Slaga et al. 1981).

The NTP (National Toxicology Program) tested the carcinogenic potential of dibenzoyl peroxide in B6C3F1, Swiss (CD-1) and Sencar mice. Dibenzoyl peroxide (20 mg per animal, dissolved in acetone) was applied to the skin of groups of 30 animals per sex and strain once a week for 52 weeks. The control animals were treated with 0.1 ml acetone. Necropsy was performed after 52 weeks. Skin tumours were not induced by dibenzoyl peroxide in any of the test strains (NTP 1996).

A group of 20 four-week-old female Sencar mice was treated dermally with 0.2 ml of a 100 mg/ml dibenzoyl peroxide solution in acetone twice a week for 51 weeks. The skin was initially shaved 48 hours before treatment and then once a week. A control group of 15 mice was treated with 0.2 ml of acetone. No skin tumours were detected in the control mice. In the group of mice treated with dibenzoyl peroxide, 8 animals had skin tumours ($p < 0.05$); 5 of the tumours were squamous cell carcinomas. The first tumour was observed in week 24. Six of the 20 mice had epidermal hyperplasia (Kurokawa et al. 1984). This study differs from the studies carried out by other authors because it used a different kind of bedding and the mice were shaved weekly at the application site. In the other studies, the animals were shaved only at the beginning of the study. Furthermore, different criteria were used by the study pathologists to evaluate the tumours. This may have contributed to the large number of tumours that were found. Moreover, in comparison with the results obtained by other authors, this laboratory observed an unusually high incidence of papillomas and carcinomas while following the standard initiation/promotion protocol (see below). The Sencar mice used for this study may have had an unusually high background of initiated cells (ECHA 2020; Kraus et al. 1995).

Dibenzoyl peroxide doses of 0, 1, 5 or 10 mg/animal in 0.2 ml of acetone were applied twice a week for 20 weeks to the shaved dorsal skin of groups of 5 male heterozygous TG:AC mice (unstable v-Ha-ras gene) that were derived from the wild-type FVB/N strain. Groups of 5 male wild-type FVB/N mice were treated in the same way. In the TG:AC mice, the incidence of papillomas was increased in both high dose groups (0/5, 0/5, 3/5 and 3/4 at 0, 1, 5 and 10 mg dibenzoyl peroxide, respectively). One papilloma-bearing mouse in the 10 mg group died before the end of the study. No papillomas formed in the wild-type mice (Spalding et al. 1993). Dibenzoyl peroxide quite probably induced skin tumours in the susceptible TG:AC mice due to its promoting properties.

5.7.1.2 Subcutaneous injection

Groups of 25 male and 25 female albino mice (age and strain not specified) were given a single subcutaneous injection of 50 mg or 120 mg dibenzoyl peroxide (purity not specified) in the form of a 20% suspension in a starch solution and were then observed for 80 weeks. Based on the given body weights, the doses were equivalent to about 250 and 600 mg/kg body weight, respectively, in the male mice and 500 and 1200 mg/kg body weight, respectively, in the female mice. For each dose group, the same number of control animals were given an injection of only the starch solution. In the groups exposed to 50 mg dibenzoyl peroxide, 9 of the exposed male animals and 7 of the exposed female animals survived, but none of the male controls and 6 of the female controls. In the groups exposed to the high dose, 10 of the exposed male

animals and 9 of the exposed female animals survived, as well as 16 male controls and 17 female controls. Tumours were not observed at the injection site or at other sites (Sharratt et al. 1964). The study cannot be included in the evaluation because the duration of the study was too short, mortality was very high, particularly in the low dose group, and the exposure levels were very low.

In another study carried out in the 1960s, groups of 20 male Charles River CD rats (age not specified) were given 2.9 mg dibenzoyl peroxide (purity not specified) in 0.2 ml trioctanoin (tricaprylin) or only trioctanoin (control group) by subcutaneous injection in the right rear limb twice a week for 12 weeks. The animals were then observed for 14 months for the formation of tumours. None of the animals died prematurely and carcinomas were not observed at the injection site or in the internal organs (Poirier et al. 1967). The exposure period was too short for the evaluation of carcinogenicity.

In another study from the 1960s, a gelatine capsule containing 50 mg dibenzoyl peroxide (purity not specified) was implanted subcutaneously in the nape of the neck of groups of 20 male and 15 female Bethesda Black rats (NIH black rats). The animals were then observed for 24 months. The mortality was 9/35 (sex not specified) in week 52 and 22/35 in week 78. None of the animals developed a tumour at the implantation site (Hueper 1964).

5.7.1.3 Cell transformation tests

In a cell transformation assay with SHE (Syrian hamster embryo) cells, exposure to 5 to 150 µM dibenzoyl peroxide did not increase the number of transformed colonies. The cells were treated for 7 days and then cultured for 2 additional days without dibenzoyl peroxide before being fixated and counted (Rivedal et al. 2000).

5.7.1.4 Initiation studies

Dibenzoyl peroxide (purity not specified) was studied in groups of 30 Sencar mice aged 7 to 9 weeks for its ability to initiate skin tumours. For this purpose, 0.2 ml of acetone alone or 1, 10, 20 or 40 mg of dibenzoyl peroxide in acetone was applied to the skin once a day. After 1 week, 2 µg of 12-O-tetradecanoylphorbol-13-acetate (TPA) in acetone was applied to the site twice a week for 52 weeks. The incidences of papillomas and carcinomas were not increased in comparison with the values determined in the control animals. After 30 weeks, 24 to 29 mice survived in all groups (Slaga et al. 1981).

In an earlier study, 0.5% dibenzoyl peroxide (purity not specified) in acetone was applied to the skin of a group of 21 female Swiss mice (age not specified) twice a week for 80 weeks. No skin tumours were observed. Another group of 20 female animals was treated with 0.5% dibenzoyl peroxide in acetone twice a week for 3 weeks and subsequently with 5% croton oil in mineral oil twice a week for 80 weeks. Skin tumours were not observed in this study (Saffiotti and Shubik 1963). There are no data for the survival of the animals.

5.7.1.5 Promotion studies

5.7.1.5.1 Mouse

The NTP (National Toxicology Program) carried out a comparison study with B6C3F1, CD-1 and SEN mice. Groups of 30 male and 30 female mice of each strain were treated on the shaved skin as follows (Table 6):

Tab. 6 Exposure groups of the promotion study in mice (NTP 1996)

Group	Treatment
A	0.1 ml acetone as the control (0.1 ml) once a week
B	2.5 µg 7,12-dimethylbenz[a]anthracene (DMBA) once, promotion after 1 week: 0.1 ml acetone once a week, 51 weeks
C	like B, but promotion with 25 µg DMBA
D	20 mg dibenzoyl peroxide once, promotion: 20 mg dibenzoyl peroxide in 0.2 ml acetone once a week, 51 weeks
E	like B, but promotion: 20 mg dibenzoyl peroxide in 0.2 ml acetone once a week, 51 weeks
F	like C, but promotion: 20 mg dibenzoyl peroxide in 0.2 ml acetone once a week, 51 weeks
G	100 µg <i>N</i> -methyl- <i>N'</i> -nitro- <i>N</i> -nitrosoguanidine (MNNG), promotion: 0.1 ml acetone once a week, 51 weeks

Tab. 6 (continued)

Group	Treatment
H	like G, but 500 µg MNNG
I	like D, but 1000 µg MNNG
J	like G, but promotion: 20 mg dibenzoyl peroxide in 0.2 ml acetone once a week, 51 weeks
K	like H, but promotion: 20 mg dibenzoyl peroxide in 0.2 ml acetone once a week, 51 weeks

The number of surviving animals was decreased with statistical significance ($p < 0.01$) in the male CD-1 and SEN mice of Group H. The body weight gains were reduced with statistical significance ($p < 0.01$) in the female B6C3F1 mice of Group K. Dibenzoyl peroxide did not act as a complete skin carcinogen in any of the strains (Group D), but was a tumour promotor in both sexes of SEN mice after initiation with 7,12-dimethylbenz[a]anthracene (DMBA) or *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) at both doses, respectively. The CD-1 strain and particularly the B6C3F1 strain were much less sensitive than the SEN strain (NTP 1996).

In another study, dibenzoyl peroxide exhibited tumour-promoting activity in the skin of Car-S mice. Eleven (± 1.3) papillomas per mouse were detected in the animals, which were first treated with DMBA and then twice a week with 7.5 mg dibenzoyl peroxide/mouse. The tumour incidence was 86%; no papillomas were found in the control animals that received only DMBA (Mancuso et al. 2004).

Dibenzoyl peroxide (purity not specified) was investigated for promoting activity in the skin using groups of 30 Sencar mice aged 7 to 9 weeks. A single application of 10 nmol DMBA in 0.2 ml acetone to the skin of the mice was followed 1 week later by applications of 1, 10, 20 or 40 mg dibenzoyl peroxide in 0.2 ml acetone twice a week for 52 weeks. A control group was treated with acetone alone. After 30 weeks, the incidence of papilloma-bearing mice in each group was 1/28 (control), 9/29 (1 mg), 20/28 (10 mg), 21/27 (20 mg) and 20/24 (40 mg). After 52 weeks, the incidence of carcinoma-bearing mice in each group was 0/28, 1/29, 6/28, 12/27 and 10/24, respectively. After 30 weeks, 24 to 29 mice had survived in all groups (Slaga et al. 1981). Even though the study did not include a control group that was treated with only DMBA, it is evident that dibenzoyl peroxide induces marked tumour-promoting activity in the mouse skin after pre-treatment of the skin with DMBA.

Groups of 30 to 40 female Sencar mice, aged 7 to 8 weeks, received a single application of 10 nmol DMBA in 0.2 ml acetone on the skin and, 1 week later, were treated twice weekly either with 2 µg TPA in 0.2 ml acetone or with 20 mg of dibenzoyl peroxide (purity not specified) in 0.2 ml acetone for 48 weeks. The incidence of skin papillomas was 100% after 20 weeks in the TPA group and about 80% after 48 weeks in the dibenzoyl peroxide group. The incidence of squamous cell carcinomas was 0% in the TPA group and about 50% in the dibenzoyl peroxide group. Additional groups of 30 to 40 female C57BL/6 mice received a single application of 400 or 800 nmol DMBA or 1600 or 3200 nmol benzo[a]pyrene (BP) in 0.2 ml acetone and, 1 week later, were treated twice a week with 4 µg TPA in 0.2 ml acetone or 20 mg dibenzoyl peroxide in 0.2 ml acetone for 48 weeks. The incidence of squamous cell carcinomas was about 60% in the animals treated with DMBA and dibenzoyl peroxide, less than 50% in those treated with DMBA and TPA, more than 50% in the group treated with BP and dibenzoyl peroxide and less than 50% in the group treated with BP and TPA (Reiners et al. 1984). The values were taken from graphs as no actual numbers were given. Even though there are no data for survival or for the controls with DMBA or BP, it is evident that dibenzoyl peroxide has marked tumour-promoting activity in the mouse skin after dermal pre-treatment with DMBA or BP.

The tumour-promoting activity of dibenzoyl peroxide in the skin was investigated in groups of 20 female SEN mice administered 20 nmol DMBA in a single topical application followed by either 0.2 ml of a dibenzoyl peroxide solution (100 mg/ml in acetone) or acetone alone twice weekly for 51 weeks. The application site of the mice was shaved every week. At the end of the study, no skin tumours were detected among the 15 control mice. Skin tumours were observed in all mice that were treated with dibenzoyl peroxide ($p < 0.01$); 18 of these tumours were squamous cell carcinomas. The first tumour developed in week 8. All 20 treated mice had epidermal hyperplasia (Kurokawa et al. 1984). The incidence of papillomas and carcinomas found by this laboratory using the standard DMBA initiation-TPA promotion protocol was unusually high in comparison with the findings of other authors using this protocol. This study differs from the

studies carried out by other authors in the type of bedding that was used and the weekly shaving of the application site as opposed to the shaving of the site only at the beginning of the study as was usual in the other studies. Another explanation may be possible differences in the criteria that were used by the study pathologists to assess the tumours. Furthermore, the animals of this study were suspected of having an unusually high background of initiated cells. It is not possible to identify the cause of the strong response observed in the group treated with DMBA and TPA because the study does not include a control group that was treated only with the skin tumour promoter TPA. Therefore, the findings cannot be interpreted because there was no TPA-only control group and because of the disparity with the findings of other publications that also used the standard DMBA–TPA protocol (ECHA 2020; Kraus et al. 1995).

Groups of female SEN mice, aged 5 to 7 weeks, were treated with a single topical application of 10 nmol DMBA to the shaved dorsal skin. After 2 weeks, 1 µg TPA was applied twice a week for 20 weeks. Beginning in week 21, one group of 21 papilloma-bearing mice continued to receive 1 µg TPA, while another group of 20 papilloma-bearing mice was treated twice a week with 20 mg dibenzoyl peroxide. All solutions were applied in 0.2 ml acetone and treatment was ended after week 40. In weeks 21 to 40, no new tumours were observed in the animals treated with dibenzoyl peroxide. At the end of the experiment, 70% of the mice in the group treated with dibenzoyl peroxide had skin carcinomas, compared with 38% in the group treated with TPA. The cumulative number of carcinomas in the group treated with dibenzoyl peroxide was higher by a factor of 3.25. All skin tumours that were present at the end of the study were examined histologically. While no keratoacanthomas were identified in the group treated with TPA, 17 keratoacanthomas were found in the group treated with dibenzoyl peroxide. The authors concluded that dibenzoyl peroxide enhances the progression from benign to malignant tumours (O’Connell et al. 1986).

However, in a similarly designed and executed study, it was found that dibenzoyl peroxide did not enhance the progression of papillomas to squamous cell carcinomas in SEN mice. In this study, a “three stage” treatment protocol was used to test the ability of dibenzoyl peroxide to induce the progression of pre-existing papillomas to squamous cell carcinomas. In stage I, the mice were initiated with 0.5 µg DMBA. In stage II, promotion was carried out by applying 1 or 2 µg TPA twice a week for 15 weeks. In stage III, the mice were treated with acetone, TPA (1 or 2 µg) or dibenzoyl peroxide (20 mg) for another 45 weeks. The mean number of papillomas per mouse was very similar in all groups, as was the incidence of carcinomas and the mean number of carcinomas per mouse. Therefore, dibenzoyl peroxide did not enhance the progression of papillomas to squamous cell carcinomas under these experimental conditions (Battalora et al. 1996).

In a study from the 1980s, 3 groups of 16 male and 16 female hr/hr Oslo mice were administered a single topical application of 51.2 µg DMBA in 100 µl acetone. One group was then treated with PanOxyl, a gel containing 5% dibenzoyl peroxide that is rubbed into the skin (quantity not specified) for the treatment of acne, twice a week for up to 60 or 61 weeks. A second group was similarly treated, but with a gel that did not contain dibenzoyl peroxide, a third group was given only DMBA and a fourth group only PanOxyl. The total number of skin tumours found in each group of mice was: DMBA alone 22/32 (18 papillomas, 4 squamous cell carcinomas), PanOxyl gel alone 2/32 (2 squamous cell carcinomas), DMBA and PanOxyl gel 51/30 (48 papillomas, 3 squamous cell carcinomas), DMBA and gel that did not contain dibenzoyl peroxide 31/32 (31 papillomas). In both cases, the gel increased the incidence of papillomas induced by DMBA, irrespective of whether it contained dibenzoyl peroxide (Iversen 1986).

5.7.1.5.2 Hamster

In a study from the 1980s, male Syrian hamsters (age not specified) were divided into 5 groups of 20 animals and treated as follows (Table 7):

Tab. 7 Exposure groups of the promotion study in hamsters (Schweizer et al. 1987)

Group	Treatment
1	1 ml acetone, 3 times a week on the shaved dorsal skin
2	10 mg DMBA/kg body weight, once by gavage in sesame oil
3	160 mg dibenzoyl peroxide in 1 ml acetone, 3 times a week on the shaved dorsal skin

Tab. 7 (continued)

Group	Treatment
4	like Group 2, after 1 week 80 mg dibenzoyl peroxide in 1 ml acetone, 3 times a week on the shaved dorsal skin
5	like Group 2, but 160 mg dibenzoyl peroxide

All surviving hamsters were sacrificed after 16 months. Survival was reduced to 25% of the animals in Group 1 after 442 days, in Group 2 after 376 days, in Group 3 after 427 days, in Group 4 after 342 days and in Group 5 after 407 days. The number of melanotic foci detected per hamster (arithmetic mean and 95% CI) was: Group 2: 6.3 (3.6–9.0); Group 4: 17.4 (13.2–21.6); Group 5: 26.9 (22.5–31.2). The corresponding number of melanotic tumours per hamster was: Group 2: 0.6 (0.2–1.0); Group 4: 2.2 (1.3–3.1); Group 5: 2.9 (2.0–3.7). Dibenzoyl peroxide was thus found to have dose-dependent tumour-promoting activity in Syrian hamsters after oral pre-treatment with DMBA, leading to melanotic skin tumours (Schweizer et al. 1987).

In a study carried out in the 1980s, 0.1% DMBA in oil was instilled into the buccal pouch of hamsters 3 times a week for 10 weeks. DMBA did not induce carcinomas in the pouch up to 25 weeks after the experiment began. However, if the application of DMBA and a treatment-free period of 6 weeks were followed by another 6 weeks of treatment of the buccal pouch with 40% dibenzoyl peroxide, carcinomas rapidly developed, which indicates that dibenzoyl peroxide has tumour-promoting activity. Dibenzoyl peroxide alone and the solvent acetone were not carcinogenic (Odukoya and Shklar 1984).

5.7.1.6 Summary

Numerous short-term studies that investigated dermal and subcutaneous exposure to dibenzoyl peroxide did not report findings of carcinogenic effects. The only positive results, which were obtained in a study of Kurokawa et al. (1984), are regarded as questionable.

In a cell transformation test with SHE cells, the number of transformed colonies did not increase after treatment with dibenzoyl peroxide.

Dibenzoyl peroxide did not have initiating effects in 2 mouse studies with dermal application, but induced tumour-promoting activities in a number of different dermal mouse and hamster models.

5.7.2 Long-term studies

5.7.2.1 Oral

In a study carried out in 1964, rats and mice (strain not specified) were given a powder with the feed for 120 or 80 weeks, respectively. The powder contained 18% dibenzoyl peroxide (no data for the other ingredients) and was used commercially for the bleaching of flour. The dose groups were made up of 25 animals of each sex. The groups were given 0, 10, 100 or 1000 times the average daily uptake for humans, which Kraus et al. (1995) calculated to be equivalent to dibenzoyl peroxide concentrations of 0, 28, 280 and 2800 mg/kg feed. These values are equivalent to doses of about 1.4, 14 and 140 mg/kg body weight and day for rats and 4.2, 42 and 420 mg/kg body weight and day for mice (conversion factors 0.05 and 0.15 (chronic exposure) for rats and mice, respectively, according to EFSA (2012)) when converted using the standard procedure adopted by the Commission. The body weights were reduced in the male and female animals given dibenzoyl peroxide concentrations of 280 or 2800 mg/kg feed. According to the authors, the addition of the test substance reduced the nutrients in the feed in the high dose groups. The mortality in the rats (dose group not specified) was increased with statistical significance in comparison with the mortality observed in the controls. The tumour incidences were not increased in any of the groups (Sharratt et al. 1964). The study has limitations with respect to its procedure and description. The findings are of only limited relevance for the evaluation because of deviations from the requirements of current test guidelines and the use of special feed (nutritional deficiencies caused by feeding a powder that was used to bleach flour).

5.7.2.2 Dermal

A study that was carried out according to GLP guidelines investigated the carcinogenic potential of dibenzoyl peroxide gel after daily topical application to the shaved dorsal skin of rats for 104 weeks. Dibenzoyl peroxide in Carbopol® gel was applied once a day to groups of 10 male and 10 female CDF® (F-344) CR1BR rats in concentrations of 1.67%, 5.0% or 15% (5, 15 and 45 mg/rat/day, respectively) on a surface area of skin that was about $3.5 \times 5 \text{ cm}^2$ in size. The control animals were treated with 0.3 ml of Carbopol® gel. The treatment did not have any influence on survival, body weights, feed consumption, clinical observations, findings at the application site, gross-pathological findings and organ weight changes at interim necropsy and on the gross-pathological findings at the end of the study. The histopathological examination found treatment-related effects at interim and final necropsy and at the application site. All animals treated with dibenzoyl peroxide had hyperkeratosis, acanthosis, sebaceous hyperplasia and chronic subepidermal inflammation; the findings were mostly of minimal to slight severity. The effects increased only slightly between weeks 52 and 104. The incidence of hyperkeratosis was about twice as high in the observation group (15% dibenzoyl peroxide for 52 weeks, followed by the vehicle for 52 weeks) compared with the incidence found in the vehicle control group or the untreated control group, but less than half the incidence found in the animals treated with dibenzoyl peroxide for 104 weeks. The incidence of acanthosis was not noticeably increased in the observation group when compared with the incidence in the control group and sebaceous hyperplasia was only a questionable finding. There was no evidence that dibenzoyl peroxide causes carcinogenic effects under these study conditions (CHPA 2001). The acanthosis was a reaction to the chronic inflammation.

The same GLP-compliant protocol was used in a second study to investigate male and female B6C3F1/CR1BR mice. Dibenzoyl peroxide in 0.1 ml Carbopol® gel was topically applied to the shaved dorsal skin of the mice for 104 weeks. The test concentrations were 1%, 5% and 25%/15% dibenzoyl peroxide (1, 5 and 25/15 mg/animal and day). In the group exposed to 25% dibenzoyl peroxide, the concentration was reduced to 15% at the beginning of week 57 after ulcers formed at the application site. As there was no noticeable improvement, the animals in this group were treated only with the vehicle (gel) during the last 13 weeks. Except for ulceration at the application site, dibenzoyl peroxide had no effects on survival, body weights and feed consumption and no clinical observations were reported. Hyperkeratosis (1%, 5% and 25% dibenzoyl peroxide), subacute subepidermal inflammation (5% and 25%) and sebaceous hyperplasia (male animals at 5% and 25%, female animals at 1% and above) were observed at the application site at interim necropsy (week 53). The incidence and severity of these effects were dependent on the concentration. Similar findings were observed at the end of the study after 105 to 106 weeks, but there are no data for the high exposure group. Dibenzoyl peroxide was not found to induce carcinogenic effects under these study conditions (CHPA 2001).

About 100 mg of dibenzoyl peroxide (purity not specified) dissolved in 5% benzene was applied to the shaved dorsal skin of a group of 30 male, 8-week-old ICR/Ha mice 3 times a week over their entire lifetime. The mean survival was 292 days. One mouse developed a skin papilloma. A total of 150 mice (from 4 different control groups) were treated with benzene alone. These mice had a mean survival of 262 to 412 days. Eleven skin tumours including one carcinoma were observed (van Duuren et al. 1963).

In 2 earlier studies in Swiss mice, dermal application of 0.5% dibenzoyl peroxide (no data for purity) in acetone or about 50 mg of a 50% dibenzoyl peroxide suspension (no data for purity) in a flour paste twice a week for 80 weeks did not induce skin tumours (Saffiotti and Shubik 1963; Sharratt et al. 1964). Neither of the studies provide data for the survival of the animals.

5.7.2.3 Summary

A 120-week and an 80-week study in rats and mice, respectively, that were carried out in 1964 with dibenzoyl peroxide concentrations of up to about 2800 mg/kg feed, did not find an increased incidence of tumours (Sharratt et al. 1964). The study has limitations with respect to its procedure and description. It is of only limited relevance for the evaluation because of deviations from the requirements of current test guidelines and the use of a special feed (nutritional deficiencies after feeding a powder used to bleach flour).

No evidence that dibenzoyl peroxide has carcinogenic potential was found by 2 dermal carcinogenicity studies carried out in rats and mice according to GLP regulations or by other earlier, insufficiently reported dermal carcinogenicity studies in mice (CHPA 2001).

6 Manifesto (MAK value/classification)

The critical effect is irritation of the eyes. Dibenzoyl peroxide had tumour-promoting effects on the skin of mice and hamsters.

MAK value. Dibenzoyl peroxide did not cause irritation of the skin of rabbits after 4-hour exposure, but slight irritation after 24-hour exposure. Marked irritation was observed in the eyes of rabbits.

Studies that investigated repeated inhalation exposure are not available. In a study carried out in Wistar Han rats according to OECD Test Guideline 408 (90-day study), haematological and clinicochemical effects were observed at doses of 300 mg/kg body weight and day and above. A NOAEL of 100 mg/kg body weight and day was derived from these findings.

A NOAEL of 100 mg/kg body weight and day was established for mice based on effects on the antioxidant status of the liver after gavage administration for 42 days. No other organs were investigated in this study.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 100 and 100 mg/kg body weight and day for rats and mice, respectively, to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days a week exposure at the workplace (7:5), the corresponding species-specific correction values for the rat and mouse (1:4; 1:7), the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m³) of the person and the assumed 100% absorption by inhalation. The concentrations calculated from these values are 245 and 140 mg/m³, respectively. Using a concentration of 140 mg/m³ as the basis for calculation and after extrapolating the data from animal studies to humans (1:2) and taking into consideration a possible intensification of the effects after chronic exposure (1:4, because the study duration lies between subacute and subchronic), a concentration of 17.5 mg/m³ I is calculated for protection against systemic effects.

However, dibenzoyl peroxide causes marked irritation of the eyes, which means that an inhalation study is required for the derivation of a MAK value. As no such study is available, the data for benzoic acid, the hydrolysis product of dibenzoyl peroxide, are used.

One molecule of dibenzoyl peroxide undergoes hydrolysis to form 2 molecules of benzoic acid. However, benzoic acid is a much stronger irritant than dibenzoyl peroxide (see Section 5.3.2), causing irreversible corneal damage in the eyes of rabbits (BUA 1995; ECHA 2011; Hartwig and MAK Commission 2018; Monsanto Company 1992 a, b). In addition, the half-life of hydrolysis for dibenzoyl peroxide is 5.2 hours at a pH of 7 (OECD 2002). Dermal studies (Wepierre et al. 1986; see Section 3.2) show that dibenzoyl peroxide is converted to benzoic acid only slowly. In the following, the calculation takes the weaker irritant effect produced by dibenzoyl peroxide into account by assuming that only half of the dibenzoyl peroxide undergoes hydrolysis to form benzoic acid.

MAK value for the I (inhalable) fraction

Therefore, in analogy to the MAK value of 2 mg/m³ I that was established for benzoic acid (Hartwig and MAK Commission 2025), a MAK value of 4 mg/m³ I has been derived for dibenzoyl peroxide.

MAK value for the R (respirable) fraction

The target organ of benzoic acid are the lungs. As a result, a MAK value is likewise derived for the R fraction of dibenzoyl peroxide. On the basis of the assumptions above, the MAK value for the R fraction of benzoic acid of 0.5 mg/m³ R (Hartwig and MAK Commission 2018) is used to calculate a MAK value of 1 mg/m³ R for the R fraction of dibenzoyl peroxide.

Peak limitation.**I fraction**

The I fraction has been classified in Peak Limitation Category I because of the immediate irritation of the eyes and upper respiratory tract. An excursion factor of 2 has been established for peak limitation in analogy to that derived for benzoic acid (Hartwig and MAK Commission 2025).

R fraction

Peak limitation has been established in analogy to the classification derived for benzoic acid (Hartwig and MAK Commission 2018) with assignment to Peak Limitation Category II and an excursion factor of 4.

Prenatal toxicity. In a prenatal developmental toxicity study that was carried out according to OECD Test Guideline 414 with gavage administration of dibenzoyl peroxide in Sprague Dawley rats, delays in foetal growth in the form of reduced body weights and incomplete ossification were observed at the high dose of 1000 mg/kg body weight and day. Teratogenicity did not occur. At this dose, the dams had lower body weight gains and reduced feed consumption. The NOAEL for maternal toxicity was 300 mg/kg body weight and day and the NOAEL for developmental toxicity was 100 mg/kg body weight and day (CiToxLab 2014 a) because incomplete ossification occurred at doses of 300 mg/kg body weight and day and above. In the study that was carried out according to OECD Test Guideline 422 with a screening test for reproductive and developmental toxicity, gavage doses given to Sprague Dawley rats led to a decrease in the foetal body weights on postnatal day 3 at the high dose of 1000 mg/kg body weight and day with concurrent maternal toxicity (increased kidney weights, slight histological effects in the uterus). The NOAEL for perinatal developmental toxicity and maternal toxicity was 500 mg/kg body weight and day (Song et al. 2003).

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAELs for prenatal and perinatal developmental toxicity of 100 mg/kg body weight and day and 500 mg/kg body weight and day, respectively, to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days a week exposure at the workplace (7:5) (in the study carried out according to OECD Test Guideline 422), the corresponding species-specific correction value for the rat (1:4), the assumed oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. The concentrations calculated from this are 175 and 1225 mg/m³, respectively. These values are 44 to 306 times the MAK value of 4 mg/m³ I. As the margins to the MAK value are sufficiently large, no teratogenicity was observed and the effects induced agree well with those induced by the metabolite benzoic acid both qualitatively and quantitatively (see Hartwig and MAK Commission 2018), dibenzoyl peroxide has been classified in Pregnancy Risk Group C.

Carcinogenicity. Dibenzoyl peroxide has tumour-promoting effects on the skin of mice and hamsters. No signs of carcinogenic effects were found in rats and mice after oral and dermal exposure. Furthermore, in spite of the widespread clinical use of dibenzoyl peroxide for the dermal treatment of acne, no case of substance-related skin cancer in humans has been reported.

Substances that induce tumour-promoting activity at high concentrations or through non-specific effects are not classified by the Commission in any of the carcinogen categories (Schwarz et al. 2015). Dibenzoyl peroxide was not classified; this decision is supported by the negative findings obtained in rats and mice in dermal carcinogenicity studies and the lack of an association between the use of dibenzoyl peroxide for the treatment of acne over several decades and the development of skin cancer in humans.

Germ cell mutagenicity. Dibenzoyl peroxide increased 8-oxodG levels in vivo and in vitro and increased the incidence of DNA strand breaks in vitro. SCE is observed at cytotoxic concentrations.

However, numerous bacterial assays carried out with dibenzoyl peroxide did not find evidence of mutagenic effects. A TK^{+/-} mutation test with L5178Y mouse lymphoma cells yielded negative results. The overall results of 2 chromosomal aberration tests and a micronucleus test are considered negative because the slight increase in aberrations and micronuclei detected in the 2 tests in human lymphocytes was observed only at cytotoxic concentrations. The negative

results in vitro were confirmed by in vivo studies. A micronucleus test carried out in mice according to OECD test guideline and a dominant lethal test in mice yielded negative results. The induction of Ha-ras mutations was not increased in the skin of Sencar mice. As a result, dibenzoyl peroxide has not been classified in a category for germ cell mutagens.

Absorption through the skin. A 2-year study in rats and mice did not find any evidence of systemic toxic effects after daily dermal application of dibenzoyl peroxide gels in doses of 100 or 833 mg/kg body weight and day, respectively.

Data for the absorption of dibenzoyl peroxide through the skin are available from in vitro and in vivo studies. According to these data, as the compound passes from the surface of the skin into systemic circulation, it undergoes quantitative conversion to benzoic acid, which is then excreted via the kidneys in unconjugated form after absorption through the skin. The flux calculated from the experiments with dibenzoyl peroxide was considerably lower than that obtained for benzoic acid (which is designated with an “H”) after direct application to the skin (for example, human skin in vitro: benzoic acid 13 to 166 µg/cm² and hour, dibenzoyl peroxide 5 µg/cm² and hour; rhesus monkey in vivo: dibenzoyl peroxide 0.075 µg/cm² and hour, see also Hartwig and MAK Commission 2018). Based on a flux of 5 µg/cm² and hour, it is calculated that 10 mg of dibenzoyl peroxide is taken up under standard conditions (2000 cm², 1 hour of exposure). Assuming a respiratory volume of 10 m³ in 8 hours and 100% absorption by inhalation, a systemically tolerable amount of 175 mg is calculated based on the NAEC (no adverse effect concentration) of 17.5 mg/m³ that was derived above for systemic toxicity. On the basis of these data, dibenzoyl peroxide is expected to make only a negligible contribution to systemic toxicity after absorption through the skin. The substance has therefore not been designated with an “H” (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. Experimental studies in animals and NAMs show that dibenzoyl peroxide has sensitizing potential. In humans, however, allergic reactions to dibenzoyl peroxide occur mainly after high levels of exposure for therapeutic purposes. Contact allergic reactions developed only in isolated cases even after the daily application of high doses to the skin for several months for the treatment of acne. The literature describes numerous positive reactions that were obtained in patch tests; however, these findings are generally not accompanied by any information relating to their relevance and genesis. Furthermore, most were attributed to irritation caused by dibenzoyl peroxide. There is no well-documented evidence of an increased risk due to possible occupational exposure; for this reason, dibenzoyl peroxide has not been designated with “Sh” (for substances which cause sensitization of the skin). As there are no data for sensitizing effects on the airways, dibenzoyl peroxide has not been designated with “Sa” (for substances which cause sensitization of the airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

The views expressed in these publications are those of the individual authors acting in their personal capacity as experts and do not represent the positions of their respective institutions or employers.

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