FOREWORD

INTRODUCTION

BENZOYL PEROXIDE

CAS N°: 94-36-0
SIDnitial Assessment Report

For

SIAM 15

(Boston, USA, 22-25 October 2002)

1. Chemical Name: Benzoyl Peroxide
2. CAS Number: 94-36-0

3. Sponsor Country: Republic of Korea

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4. Shared Partnership with:

5. Roles/Responsibilities of the Partners:
   - Name of industry sponsor /consortium
   - Process used

6. Sponsorship History
   - How was the chemical or category brought into the OECD HPV Chemicals Programme?
     This substance is sponsored by Korea. The assessment process was started in 1999.

7. Review Process Prior to the SIAM:

8. Quality check process:
   - No testing ( )
   - Testing (x) :
     Algae Growth Inhibition Test (TG 201), Daphnia Acute Immobilization Test (TG 202), Acute Toxicity of Fish (TG 203), Acute Toxicity Test of Earthworm (TG 207), Acute Oral Toxicity (TG 401), Combined Repeated Dose Toxicity with the Reproduction/Developmental Toxicity Screening Test (TG 422), Bacterial Reverse Mutation Test (TG 471), Micronucleus test (TG 474)
9. Date of Submission:

10. Date of last Update:

11. Comments: Revised: 2002
### SIDS INITIAL ASSESSMENT PROFILE

<table>
<thead>
<tr>
<th>CAS No.</th>
<th>94-36-0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Name</td>
<td>Benzoyl peroxide</td>
</tr>
<tr>
<td>Structural Formula</td>
<td><img src="image" alt="Structural Formula" /></td>
</tr>
</tbody>
</table>

#### SUMMARY CONCLUSIONS OF THE SIAR

**Human Health**

The dry chemical becomes explosive above 105°C and when subjected to impact or friction.

The acute oral toxicity of benzoyl peroxide is very low: LD50 >2,000 mg/kg bw in mice, and 5,000 mg/kg bw in rats. No deaths occurred in male rats following inhalation of 24.3 mg/L. Visible effects included eye squint, dyspnea, salivation, lacrimation, erythema and changes of respiratory rates and motor activity.

Benzoyl peroxide was slightly irritating to skins in 24 hr-patch tests. Benzoyl peroxide was not irritating to the eyes of rabbits if washed out within 5 minutes after instillation, however, if the chemical was not washed out until 24 hours later, it proved to be irritating.

Positive results from sensitisation tests in guinea pigs and mice, and from a maximization test in human volunteers, indicate that benzoyl peroxide is a skin sensitizer.

In the combined repeated dose and reproduction/developmental toxicity study (OECD TG 422), benzoyl peroxide did not produce hematological or biochemical adverse effects. Repeated administration by oral gavage up to 1,000 mg/kg bw/day for 29 days resulted in decreased weights of testes and epididymis in male rats. The NOAEL for repeated dose toxicity was 500 mg/kg bw/day.

This substance did not cause gene mutation in bacteria (OECD TG 471 & 472) and *in vitro* chromosomal aberration in CHL (Chinese Hamster Lung) cells. An *in vivo* mammalian erythrocytes micronucleus test (OECD TG 474) produced negative result. The available evidence supports the conclusion that benzoyl peroxide is not a mutagen.

There is no evidence to suggest that benzoyl peroxide is a carcinogen. However, there is some evidence from non-guidelines studies that benzoyl peroxide is a skin tumour promoter.

In the combined repeated dose and reproduction/developmental toxicity study [OECD TG 422], no treatment-related changes in precoital time, rate of copulation, fertility and gestation were noted in any treated group. Adverse effects were shown at the highest dose of 1,000 mg/kg
bw/day in parental male rats with the reduction of reproductive organ weight and slight testes degeneration. In parental female rats, no adverse effects were observed during the test period. The NOAEL for reproduction toxicity in male rats was 500 mg/kg bw/day. In the offspring, the only effect seen was that body weight gain of pups at dose of 1,000 mg/kg bw/day was significantly decreased. The NOAEL for developmental toxicity was 500 mg/kg bw/day.

Environment

Benzoyl peroxide is commercially produced as a white granule with purities ranging from 22 to 95%. It has a melting point of 104-106 °C, vapor pressure of 0.00929 Pa, solubility of 9.1 mg/L in water at 25 °C, and log $P_{ow}$ of 3.43 at 25 °C. For indirect photolysis in the atmosphere, the half-life is estimated to be 3 days with the AOPWIN model. The substance is readily biodegradable (OECD TG 301C: 83% by BOD after 21 days) and hydrolyses rapidly in water [OECD TG 111] with a half-life of 11.87 hrs at pH 4.0 and 5.20 hr at pH 7.0 at 25 °C. The main hydrolysis product of benzoyl peroxide is benzoic acid (a SIDS assessment of benzoic acid is available: CAS No. 65-85-0). The estimated BCF of 92 with the BCFWIN model suggests that the chemical has a low potential for bioaccumulation.

The following studies for aquatic organisms are available:

- Green algae (*Selenastrum capricornutum*): 72 hr-E$_{bC_{50}}$ is 0.07 mg/L (biomass) and 0.44 mg/L (growth rate).
- Invertebrates (*Daphnia magna*): 48 hr-EC$_{50}$ is 0.07 mg/L.
- Fish (*Oryzias latipes*): 96 hr-LC$_{50}$ is 0.24 mg/L.
- Microorganism (activated sludge): 30 min.-EC$_{50}$ is 35 mg/L.

The toxicity observed is assumed to be due to benzoyl peroxide rather than benzoic acid, which shows much lower toxicity to aquatic organisms. One can assume that effects occur before hydrolysis takes place.

A generic fugacity model (Mackay level III) was used for environmental fate estimation. If the most realistic emission pattern to water is assumed then the substance will remain in the aquatic compartment.

Exposure

In Korea, the total production volume of benzoyl peroxide was 1,357 tonnes in 2001, and the chemical is produced in only one company. The amounts of import and export were estimated as 268 and 293 tonnes/year, respectively. 75% benzoyl peroxide is mainly used in the manufacture of expandable styrene polymer and other resins as initiators of polymerization. Benzoyl peroxide has also been used in the treatment of acne vulgaris and the medical product contains mainly 5-10 % benzoyl peroxide. A very small portion of benzoyl peroxide is used as flour bleaching agent.

The Danish, Norwegian and Swedish product register indicates that this substance is used in adhesives, cosmetics, dental products, process regulators, fillers, construction materials and paints. These products may contain 2-80 % of the substance depending upon the product.

The major routes of occupational exposure are inhalation and dermal. Limited data on exposure are available. At a production facility monitoring its workplace for the worker exposure annually, the concentration of airborne aerosols at personal sampling has been less than 1 mg/m³.
**RECOMMENDATION**

The chemical is a candidate for further work.

**RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED**

**Human Health:** The chemical possesses properties indicating hazards to human health (sensitisation, effect on testes weight, fetal body weight and skin tumour promotion activity) and is a candidate for further work, i.e. exposure assessment, and if considered necessary, risk assessment.

**Environment:** It is expected that the possibility of any environmental releases of benzoyl peroxide is low in the sponsor country. However, this substance is a candidate for further work, even if it hydrolyses rapidly and has a low bioaccumulation potential. The substance shows high acute toxicity to aquatic organisms and some information indicates wide-dispersive use of this substance. This could lead to local concern for the aquatic environment and therefore environmental exposure assessment is recommended.
SIDS Initial Assessment Report

1 IDENTIFY

1.1 Identification of the Substance

CAS Number: 94-36-0
IUPAC Name: Benzoyl peroxide
Molecular Formula: C_{14}H_{10}O_{4}
Structural Formula: \((\text{C}_6\text{H}_5\text{CO})_2\text{O}_2\)

Molecular Weight: 242.24
Synonyms: Benzoic acid, peroxide
Dibenzoyl peroxide
Benzoyl superoxide
Benzoperoxide
Benzoyl peroxide, remainder water
Lucidol

Benzoyl peroxide (CAS No. 94-36-0) is commercially produced as a white granule with purities ranging from 22 to 99 %. It has peroxo bond in the molecule. Its molecular weight is 242 g/mol. Physical-chemical properties and characteristics are as follow:

1.2 Purity/Impurities/Additives

> 97.3 % w/w

1.3 Physico-Chemical properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>104 - 106 °C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>explosive above 105 °C</td>
</tr>
<tr>
<td>Relative density</td>
<td>1.33 g/cm³ at 25 °C</td>
</tr>
<tr>
<td>Vapour pressure</td>
<td>0.00929 Pa at 25°C</td>
</tr>
<tr>
<td>Water solubility</td>
<td>9.1 mg/L at 25 °C</td>
</tr>
<tr>
<td>Partition coefficient n-octanol/water (log value)</td>
<td>3.43 at 25 °C</td>
</tr>
</tbody>
</table>

- Classification in member countries
At present, benzoyl peroxide is not classified as a toxic chemical in the Toxic Chemicals Control Act of the Republic of Korea, but it is in the process of being re-classified as a Toxic Chemical because of its high aquatic toxicity.
2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

In Korea, the total production volume of benzoyl peroxide was 1,357 tonnes in 2001 and the chemical is produced by only one company. The amounts of import and export were estimated to be 268 and 293 tonnes/year, respectively. Benzoyl peroxide is produced through the reaction of benzoyl chloride with hydrogen peroxide in alkaline solution. Benzoyl peroxide is commercialized as a solid (granules) with varying purities (22 %, 75 % or 95 %). The most often used industrial concentration is 75 %. The substance is mainly used as an initiator for polymerization in the manufacture of expandable styrene polymer and other resins. The world-wide production volume of this chemical is not known. The following table shows the general use pattern of benzoyl peroxide in Korea (Table 1).

Table 1. Use pattern of benzoyl peroxide in Korea

<table>
<thead>
<tr>
<th>Use</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production of expandable styrene (styropon) in the polymer industry</td>
<td>87.9</td>
</tr>
<tr>
<td>Production of sizing agent for the textile industry</td>
<td>5.8</td>
</tr>
<tr>
<td>Manufacture of acrylic resin for paint products</td>
<td>5.5</td>
</tr>
<tr>
<td>Flour bleaching agent in food processing</td>
<td>0.1</td>
</tr>
<tr>
<td>Other uses (adhesive, other resins, etc.)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Benzoyl peroxide has also been used in the treatment of acne vulgaris. All of the medicines containing benzoyl peroxide are imported into Korea with various concentrations as 2.5, 4, 5 and 10 %. Most available acne treatment products contain 5 - 10 % benzoyl peroxide in gel or lotion type.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Benzoyl peroxide hydrolyses to more than 90 % in water after 5 days at 50 °C. Its half-life at 25 °C is 11.9 hr at pH 4 and 5.2 hr at pH 7 (OECD TG 111, NIER, Korea, 2001a). Hydrolysis may be an important environmental fate process of benzoyl peroxide. Benzoyl peroxide is expected to react with hydroxyl radicals in the atmosphere. The estimated half-life is about 3 days (NIER, Korea, 2002a). The substance is readily biodegradable (OECD TG 301C : 83 % by BOD after 21 days). This substance easily passed a ready biodegradation test due to rapid hydrolysis of the parent substance, followed by rapid biodegradation of benzoic acid, which is the hydrolysis product. ABCF of 92, estimated with the BCFWIN model based on a logPow of 3.43, suggests that the chemical has a low potential for bioaccumulation. (Chem. Inspect Test Inst, Japan, 1992 ; Lyman, W.J., et al, 1990 ; OECD, 2000). If it is released into the soil, benzoyl peroxide is expected to have a low mobility in soil based on an estimated Koc value of 1,800 (TOXNET, 2002 ; Lyman, W.J., et al., 1990). Benzoyl peroxide is expected to volatilize from moist soil surfaces based on an estimated Henry's Law constant of 3.5 x 10-6 atm-cu m/mole (Meylan, W.M., 1991). A generic fugacity...
model (Mackay level III) is used for the environmental fate estimation. The result is presented in table 2. Benzoyl peroxide is mainly distributed to soil (99.9 %).

Releases to air, water and sediment are negligible. If the substance is emitted to air, it will mainly partition to soil (98.9 %) and if it is released to water, it will mainly remain in water (85.0 %). If it is released to soil, it will mainly remain in soil (99.9 %). (NIER, Korea, 2002a)

Table 2. Environmental Distribution of Benzoyl peroxide using the Fugacity Model (Mackay level III)

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Release 100 % to air</th>
<th>Release 100 % to water</th>
<th>Release 100 % to soil</th>
<th>All three (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>1.08</td>
<td>0.068</td>
<td>0.007</td>
<td>0.04</td>
</tr>
<tr>
<td>Water</td>
<td>0.01</td>
<td>85.0</td>
<td>0.0068</td>
<td>0.02</td>
</tr>
<tr>
<td>Soil</td>
<td>98.9</td>
<td>6.24</td>
<td>99.999</td>
<td>99.9</td>
</tr>
<tr>
<td>Sediment</td>
<td>0.001</td>
<td>8.65</td>
<td>0.0007</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Based on the chemical structure, the main hydrolysis product of benzoyl peroxide is benzoic acid. Benzoic acid is mainly distributed to soil (64.2 %) and water (34.8 %) according to a fugacity level III model. No hydrolysis is expected at a pH range of 4 - 11. The substance is readily biodegradable (> 90 % after 28 days) and has a low potential for bioaccumulation (see corresponding initial assessment for benzoic acid, CAS No 65-85-0).

2.3 Human Exposure

2.3.1 Occupational Exposure

Benzoyl peroxide is produced by chemical reaction in a closed reactor. Potential exposure to benzoyl peroxide is limited to the packing process at the production facility. This chemical is used mainly as an initiator for polymerization in which the exposure to this chemical is very limited. The major routes of occupational exposure are inhalation and dermal. The occupational exposure limit of this chemical is set at 5 mg/m³ TWA in Korea. Limited data on exposure are available. Annual monitoring of the concentration of benzoyl peroxide at the workplace of the production facility has shown concentrations in airborne aerosols (personal sampling) of less than 1 mg/m³ (Hansol Chem. Co., 2002).

2.3.2 Consumer Exposure

A very small portion of benzoyl peroxide is used as a flour bleaching agent. The purity of benzoyl peroxide used in the food product is usually less than 22 %. There is no information on actual benzoyl peroxide content in food products. Furthermore, it is well known that benzoyl peroxide is used in the treatment of acne vulgaris and most medical products contain 5 - 10 % benzoyl peroxide.
3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1. Toxicokinetics, Metabolism and Distribution

*Studies in Animals and Humans*

*In vitro and In vivo Studies*

Benzoyl peroxide is rapidly converted to benzoic acid in the skin of both animals and humans. Absorption of the benzoic acid occurs as benzoate through the blood vessels in the dermis. This metabolite enters the blood circulation and is rapidly cleared through the kidney (Nacht, S. *et al*, 1981; Yeung, D., *et al*, 1983; Morsches, B. and Holzmann, H., 1982; Wepierre, J., *et al*, 1986). Topically applied benzoyl peroxide penetrates unchanged through the stratum corneum or follicular openings of excised human skin and is converted metabolically to benzoic acid within the skin (Nacht, S. *et al*, 1981). A study in rhesus monkeys *in vivo* showed that this benzoic acid is systemically absorbed as benzoate and rapidly excreted in the urine in an unchanged form, without being conjugated to hippuric acid, as would be predicted to occur following oral administration.

*In vitro* and *in vivo* assessments of percutaneous penetration and metabolite analysis of benzoyl peroxide were performed using human skin and in 5 patient with leg ulcers, respectively (Morsches, B., *et al*, 1982). The *in vitro* study showed that benzoyl peroxide absorbed by the skin was converted to benzoic acid in the dermis. The metabolite penetrating through the skin was benzoic acid only. Also in patients treated with benzoyl peroxide, no benzoyl peroxide could be detected in the serum. The authors suggested that benzoyl peroxide was absorbed by the skin, but was systemically absorbed only after transformation to benzoic acid. Therefore, a systemic-toxic effect in local therapy with benzoyl peroxide can be excluded. The rhesus monkey study supports the human study indicating no evidence of parental benzoyl peroxide in the systemic circulation.

3.1.2 Acute Toxicity

*Inhalation*

In an acute inhalation study, a single group of 10 male rats were placed in a sealed 59.1 liter glass chamber and exposed to a dynamic atmosphere containing the dust of benzoyl peroxide for 4 hrs. All the rats exposed to 24.3 mg/l of 78 % benzoyl peroxide, survived during the 14 days observation period. Observable signs during the 4 hr exposure period were eye squint, dyspnea, salivation, lacrimation, erythema, increased and decreased respiratory rates, and increased and decreased motor activity. A few of the rats showed ocular irritation at 5 days after exposure (Wazeter, F.X., *et al*¹, 1973). Other acute toxicity studies were reported for rats and mice as shown in table 3.
Table 3. Acute toxicity for rats and mice

<table>
<thead>
<tr>
<th>Route</th>
<th>Species</th>
<th>Type</th>
<th>Values</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Mouse</td>
<td>LD₅₀</td>
<td>&gt; 2000 mg/kg</td>
<td>NIER, Korea (2001)</td>
</tr>
<tr>
<td>Oral</td>
<td>Mouse</td>
<td>LD₅₀</td>
<td>5700 mg/kg</td>
<td>Sanitariya, G.I. (1936)</td>
</tr>
<tr>
<td>Oral</td>
<td>Rat</td>
<td>LD₅₀</td>
<td>&gt; 5000 mg/kg</td>
<td>Wazeter, F.X. et al (1973)</td>
</tr>
<tr>
<td>Oral</td>
<td>Rat</td>
<td>LD₅₀</td>
<td>&gt; 950 mg/kg</td>
<td>Eastman Kodak Co. (1964)</td>
</tr>
<tr>
<td>Oral</td>
<td>Rat</td>
<td>LD₅₀</td>
<td>7710 mg/kg</td>
<td>Marhold, J.V. (1972)</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Rat</td>
<td>LCₐ₀₋₄₄0</td>
<td>24.3 mg/l</td>
<td>Wazeter, F.X. et al (1973)</td>
</tr>
<tr>
<td>i.p.</td>
<td>Mouse</td>
<td>LD₅₀</td>
<td>213 mg/kg</td>
<td>Horgan, V.J. et al (1957)</td>
</tr>
<tr>
<td>i.p.</td>
<td>Mouse</td>
<td>LD₅₀</td>
<td>168 mg/kg</td>
<td>Philpot, J. et al (1959)</td>
</tr>
<tr>
<td>i.p.</td>
<td>Mouse</td>
<td>LD₅₀</td>
<td>250 mg/kg</td>
<td>Takahashi, A. (1976)</td>
</tr>
</tbody>
</table>

**Oral**

The acute oral toxicity of benzoyl peroxide is likely to be low. In an acute oral toxicity test with ICR mice, a limit test at dose level of 2,000 mg/kg benzoyl peroxide was carried out in a group of 5 males and 5 females using OECD TG 401 (NER[c], Korea, 2001). There were no deaths in treated animals. No significant findings were observed at necropsy. The only clinical symptom observed in the highest dose group was piloerrection. The study concluded that the LD₅₀ value was greater than 2,000 mg/kg for males and females. Similar results were obtained in another acute oral study in rats. No mortality, toxic symptoms or signs were reported at the single dose of 5,000 mg/kg (Wazeter, F.X., et al(c), 1973).

**Conclusion**

The acute oral toxicity of benzoyl peroxide is very low: LD₅₀ in mice > 2,000 mg/kg, and in rats 5,000 mg/kg. No deaths occurred in male rats following inhalation of 24.3 mg/l.

### 3.1.3 Irritation

#### Skin Irritation

In a rabbit study in which 78 % granular benzoyl peroxide was applied to the back of 3 males and 3 females, the substance was held in place for 4 hours with a gauze bandage. After 4 hours, the bandages were removed and the exposed areas washed with lukewarm water. The skin was examined for any injury or irritation according to Draize scale at 4, 24 and 72 hours. No signs of skin irritation were observed at 1, 3 days after 4 hr exposure (Wazeter, F.X., et al(c), 1973). But 24 hrs-patch tests of different cases indicated that benzoyl peroxide has an irritant potential. Pure benzoyl peroxide and 10 % solution of benzoyl peroxide in propylene glycol led to slight erythema in guinea pigs under patches for 24 hrs (Eastman Kodak Co., 1964). In another 24 hrs-patch test, different concentrations of benzoyl peroxide in yellow soft paraffin were applied to shaved areas on the back of rabbits under occlusion for 24 hrs to determine which causes an erythematous reaction after single epicutaneous application in 50% of the treated animals. The lowest benzoyl peroxide irritant concentration was 1 % for one animal. All rabbits reacted with 10 %, 15% and 30% concentrations without exception. The ID₅₀ of benzoyl peroxide was 2.52 %. This result suggests that benzoyl peroxide is a skin irritant (Haustein, U.F., et al., 1985). In a cumulative skin irritation study, when 100 µl of 10 % Benzoyl peroxide was applied to the entire dorsum of mice for 6 months, keratinocytes showed marked variations in size and shape (atypia). Some were degenerating and separating each other.
A focal serous crust lay over the epidermis (Kligman, A.M., et al, 1998). Another 21-day cumulative test to determine the skin irritation profiles of benzoyl peroxide when entrapped in the polystyrene system and dispersed in oil-in-water vehicles was conducted. The cumulative 21-day irritancy score in six rabbits per group showed reduced skin irritation with the entrapped/controlled-release system (Wester RC et al, 1991).

Eye Irritation

In a study on eye irritation in rabbits, 70 % granular benzoyl peroxide was not irritating to the eye of 3 rabbits when immediately washed after instillation, whereas one rabbit in which benzoyl peroxide was not washed out immediately showed eye irritation until 72 48 hrs after application of 100 mg benzoyl peroxide. Corrosiveness was not observed in all animals (NIER, Korea, 2002(f)). In another eye irritation test, 8 male and female rabbits were divided into 2 groups. The 5 rabbits in group 1 were exposed to 111.4 mg benzoyl peroxide for 5 minutes. The rabbits in group 2 were exposed to 120.7 mg of the substance for 24 hrs. The study concluded that benzoyl peroxide was not irritating to the eyes of albino rabbits if it was washed out within 5 minutes after being placed in the conjunctival sac, however, if 78 % benzoyl peroxide was not washed out until 24 hr later, it proved to be a strongly irritating (Wazeter, F.X., et al(d), 1973).

Conclusion

Benzoyl peroxide was slightly irritating to skins in 24 hr-patch tests. Benzoyl peroxide was not irritating to the eyes of rabbits if washed out within 5 minutes after instillation, however, if the chemical was not washed out until 24 hours later, it proved to be irritating.

3.1.4 Sensitisation

Studies in Animals

Several skin sensitization tests have been performed with benzoyl peroxide according to standard protocols, with a good concordance (table 4). In a study with mouse, benzoyl peroxide was evaluated in each of five independent laboratories using either the standard murine local lymph node assay (LLNA) protocol (Kimber, I., et al, 1998 & Basketter, D.A, et al, 1996) or minor modifications of it. Stimulation indices (SI) of 3 (EC3 values) or greater was considered to have skin sensitizing activity. Benzoyl peroxide elicited strong LLNA response in all trials by 5 laboratories. Even at the lowest concentration tested (0.5 %), benzoyl peroxide induced stimulation indices of considerably greater than 3, and for this reason it proved to be impossible to derive EC3 values mathematically (Kimber, I., et al, 1998).

<table>
<thead>
<tr>
<th>Methods</th>
<th>Species</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLNA</td>
<td>Mouse</td>
<td>Positive</td>
<td>Kimber, I., et al., 1998</td>
</tr>
<tr>
<td>TINA test</td>
<td>Guinea pig</td>
<td>Positive</td>
<td>Haustein, U.F., et al., 1985</td>
</tr>
<tr>
<td>Maximization test</td>
<td>Human</td>
<td>Positive</td>
<td>Leyden, J.J., et al., 1977</td>
</tr>
</tbody>
</table>
**Studies in Humans**

Allergic contact dermatitis from benzoyl peroxide in a therapeutic as well as an occupational context is well documented. Several positive results were obtained in the patch tests performed on human patients with leg ulcers or acne (Eaglstein, W.H., 1968; Von Bahmer, F.A., et al., 1984; Morillas, I.M., et al., 1987; Agathos, M., et al., 1984; Rietschel, R.L. et al., 1982). Loosening of a hip prosthesis was reported from allergy to benzoyl peroxide used as an activator of acrylic bone cement (Jäger, M., et al., 1979; Mosby Year Book, 1992). A few cases of allergic reaction were reported in dentists, bakers or other workers who might be exposed to benzoyl peroxide in their working environment (Bonnekoh, B., et al., 1984; Santiago, Q., et al., 1993; Gebhardt, M., et al., 1996).

In a human maximization test, 4 formulations containing benzoyl peroxide, two 5% and two 10% gel preparations for acne, were assayed for contact sensitizing capability (Leyden, J.J., et al., 1977). 38 of 50 subjects became sensitized and the sensitized subjects reacted to all four formulations. The authors, meanwhile, referred that the actual rate of sensitization in clinical usage is dependent on many variables such as rapid loss and dilution by facial sweat, instability of benzoyl peroxide, which all minimize the likelihood of sensitization.

### 3.1.5 Repeated Dose Toxicity

A study conducted by NIER was identified as the key study because it was well conducted under the GLP using OECD test guideline 422 (NIER(d), Korea, 2001). In this study, the rats were exposed to benzoyl peroxide at levels of 0, 250, 500 and 1,000 mg/kg/day for 29 days for males and for 41-51 days for females. No deaths were found in any animals including control groups during exposure period. Hematemesis was observed in one male receiving 500 mg/kg but this is not related to benzoyl peroxide exposure. No hematological effect attributable to benzoyl peroxide was observed in any treated groups. A significant dose-related decrease in the weight of testes and epididymis was observed in males treated with 1,000 mg/kg. In the males, receiving 1,000 mg/kg, testis degenerations were observed microscopically (5 animals of 10). In females at 1,000 mg/kg, slight effects in uterus such as epithelial vacuolation or hyperplasia were observed (control 0/10; 250 mg/kg 0/10, 500 mg/kg 2/10; 1000 mg/kg 3/10). There were no significant dose-related changes in any other pathological findings. Since reproductive organ weights were significantly changed in treated animals this study suggested the NOAEL as to 500 mg/kg for male rats.

In a long term feeding study (Sharratt, M., et al., 1964), groups of rats and mice were fed on diets of wholemeal flour and breadcrumbs made with treated flour containing benzoyl peroxide. The flour contained 2800 ppm, 280 ppm, 28 ppm and 2.8 ppm of benzoyl peroxide. The experiment was terminated after 80 and 120 weeks treatment in mice and rats, respectively. All animals that were killed at these times, or that died were autopsied. No effect on weight gain was found during the first 12 months in rats eating bread prepared from flour treated with benzoyl peroxide. The reduced rate of weight gain was seen in the rats whose diets contained flour treated with 2,800 ppm and 280 ppm benzoyl peroxide. The study indicated that the flour treated with 28 ppm benzoyl peroxide had no significant effect on the rate of weight gain of rats. There was no significant difference between treated and control groups in the mortality of the animals (rat and mice) except the group receiving 280 ppm benzoyl peroxide, in which there were a large number of accidental deaths. There were statistically significant incidence of atrophy of the testicles in the rats given the diet based on flour treated with benzoyl peroxide at 2800 ppm and in the rats receiving bread treated with flour containing benzoyl peroxide at 28 ppm and 2.8 ppm. Accurate amount of dose cannot be determined because actual consumption amount of the diet was not described in the study.
**Conclusion**
Repeated administration by oral gavage to 1,000 mg/kg/day for 29 days resulted in decreased weights of testes and epididymis in male rats. The NOAEL for repeated dose toxicity is 500 mg/kg/day.

### 3.1.6 Mutagenicity

**In vitro Studies**

Several in vitro studies show that benzoyl peroxide is non-mutagenic to test strains *Salmonella typhimurium* TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, and *Escherichia coli* WP2 uvrA in the presence and absence of a metabolic activation system (NIER(6), Korea, 2001; Fujita, H., et al., 1987; Dillon, D., et al., 1998; Zeiger, E., et al., 1988). Also one mammalian chromosomal aberration test in vitro with Chinese Hamster Lung (CHL) cells yields a negative result without metabolic activation at 0.2 mg/ml, the upper limit concentration to allow the cell proliferation (Ishidate, M.J., et al., 1980).

**In vivo Studies**

An in vivo study, a mammalian erythrocytes micronucleus test, was conducted in accordance with OECD TG 474 and GLP. Benzoyl peroxide was administered once by intraperitoneal injection to male and female ICR mice at doses up to 200 mg/kg b.w. Benzoyl peroxide did not influence the incidence of micronuclei formation up to a maximum concentration of 200 mg/kg (NIER(6), Korea, 2001). Similarly, a dominant lethal assay with the ICR mouse strain was also negative at 54 and 62 mg/kg (Epstein, J., et al., 1972).

**Conclusion**
Benzoyl peroxide does not cause gene mutations in bacteria nor in vitro chromosomal aberrations in Chinese Hamster Lung (CHL) cells. In a mammalian erythrocytes micronucleus test performed in vivo, negative results were obtained. It can be concluded that benzoyl peroxide is not genotoxic.

### 3.1.7 Carcinogenicity

**In vivo Studies in Animals**

**Dermal**

A two-year dermal carcinogenicity study conducted according to GLP found no evidence of oncongenicity resulting from daily topical application of a benzoyl peroxide gel in mice at doses that meet the maximum tolerance dose (CHPA, 2001). In this study benzoyl peroxide was applied at doses of 1, 5 and 25 mg per mouse once daily for 104 weeks to a 2 x 3 cm area on the dorsal skin of animal. Discontinuous-treatment groups were applied the high dose of benzoyl peroxide, 25 mg per mouse, for 52 weeks and the vehicle for the rest of the study period. The animals were sacrificed at 52 weeks (interim sacrifice) or 104 weeks, and complete necropsies were performed. Benzoyl peroxide had no effect on survival, weights, food consumption, or gross pathology, except for treatment-site ulceration in the high-dose group, and produced no evidence of systemic toxicity. Microscopic evaluation revealed treatment-related findings confined to the site of application. The study concluded that there were no treatment related adverse effects in any of the neoplastic lesions analyzed in either sex.
Benzoyl peroxide was first reported to have the possible activity of promoter of cutaneous papilloma and squamous cell carcinomas in female SENCAR mice initiated with DMBA (Slaga, T.J., et al., 1981) at the concentrations of 1, 10, 20 and 40 mg of benzoyl peroxide for 52 weeks. In another study, tumor-promoting activity was found in 30 SENCAR mice initiated with 10 nmols of DMBA with 0.1, 0.3, 0.6, 2.0 and 20 mg of benzoyl peroxide given twice a week for 100 weeks. From this study, the lowest tumor promoting dose was 0.6 mg, and no tumors were induced in initiated mice treated with either 0.1 or 0.3 mg of benzoyl peroxide (Gimenez-Conti, I.B., et al., 1993). Including these in vivo mice skin tumor studies, relatively consistent positive results have been found in skin tumor promotion experiments in which SENCAR mice, one of the most sensitive types, were treated with experimental initiation agents such as 7,12-dimethyl benz[a]anthracene (DMBA) or N-methyl-N’-nitrosoguanidine (MNNG) (Slaga, T.J., et al., 1981; Gimenez-Conti, I.B., et al., 1993; Sharratt, M., et al., 1964; O’Connell, J.F., et al., 1986; Kurokawa, Y., et al., 1984). These in vivo mice studies suggest that benzoyl peroxide may not be a complete carcinogen and/or initiator, but it seems to be a tumor promoter in skin of mice.

However, Kurokawa et al. observed significant increases in the incidence of skin tumors when benzoyl peroxide alone was applied at 20 mg for 51 weeks. The first skin tumor was observed in week 24 in a mouse treated with benzoyl peroxide. At the end of study, 8 out of 20 mice developed skin tumors related to the substance, of which 5 had squamous cell carcinomas. They concluded that the chemical has possible complete carcinogenic properties as well as a definite promoter activity (Kurokawa, Y., et al., 1984). On the other hand, the published studies of potential interactions between benzoyl peroxide in gel and lotion vehicles, typical types of medications for acne, and UV radiation in mouse skin provide no evidence that benzoyl peroxide promoted or enhanced UV radiation-induced skin carcinogenesis (Iversen, O.H., et al., 1988; Epstein, J., et al., 1988).

Oral

Two oral carcinogenicity studies were also conducted by Sharratt et al., (1964). In these studies, benzoyl peroxide was added to the diet in the form of commercial flour bleach at levels of 28, 280, or 2,800 mg/kg diet for 120 weeks (albino rats) or 80 weeks (albino mice) and there was no evidence of compound–related tumor induction. In the same in vivo study, single subcutaneous injection of benzoyl peroxide suspended in starch solution did not induce exposure-related tumors. These other exposure experiments also elicited the negative findings of carcinogenicity (Sharratt, M., et al., 1964).

Studies in Humans

In the case of in vitro studies, benzoyl peroxide has been observed to induce DNA single strand breaks, which is an indication that treatments lead to events reducing the average size of single-strand DNA fragments in treated cells. For example, in normal human bronchial epithelial cells, the induction of DNA single strand breaks was observed at the concentration shown to inhibit growth (Saladino, A.J., et al., 1985). One pilot case-control epidemiological study with 159 cases and 213 age- and sex-matched controls showed no significant association between the prescribed use of benzoyl peroxide to treat acne and malignant melanoma, or between the occurrence of acne and malignant melanoma (Cartwright, R.A., et al., 1988). In a much larger case-control study, no statistically significant association was found between all prescription and nonprescription use of benzoyl peroxide-containing acne medications and skin cancer involving 964 skin cancer cases and 3856 controls (Hogan, D.J., et al., 1991).
Conclusion

There is no evidence to suggest that benzoyl peroxide is a carcinogen. However, there is some evidence from non-guidelines studies that benzoyl peroxide is a skin tumour promoter.

3.1.8 Toxicity for Reproduction

A combined repeated dose and reproduction/developmental toxicity screening test (OECD TG 422) was conducted using Sprague-Dawley rats (NIER (d), Korea, 2001). Benzoyl peroxide was administered to rats by gavage at doses of 0, 250, 500 and 1,000 mg/kg/day. Males were dosed for 29 days and females were dosed for 41 – 51 days from 14 days before mating to day 3 of lactation throughout the mating and pregnancy period. No treatment-related changes in precoital time and rate of copulation, fertility and gestation were noted in any benzoyl peroxide treated groups. Minimal symptoms such as vacuolation or hyperplasia, were seen in 1000 mg/kg group, but this is not considered to have been related to benzoyl peroxide treatment. Adverse effects on reproduction were shown at the highest dose of 1,000 mg/kg/day in male rats with the reduction of reproductive organ’s weight and slight testes degenerations. The Sharratt et al study referred in section 3.1.3, indicating testicular atrophy in rates treated with benzoyl peroxide support the result of this study. In female rats, no adverse effects were observed during the test period. The NOAEL for reproduction toxicity in male rats was 500 mg/kg/day. No variants were found. High birthrate of runt was seen and body weight gain of pups was significantly decreased (male 9 % ; female 12.9 % of control wt) at dose of 1,000 mg/kg/day. The study concluded that Benzoyl peroxide has adverse effects on development of pups with high birthrate of runt at 1000 mg/kg dose level. The NOAEL for developmental toxicity was determined as 500 mg/kg/day.

Conclusion

The NOAEL for reproduction toxicity in male rats is 500 mg/kg based on reduced weight of testes and epididymis at 1,000 mg/kg. NOAEL for developmental toxicity is also 500 mg/kg based on significant decreased weight gain of pups with high birthrate of runt at 1,000 mg/kg.

3.2 Initial Assessment for Human Health

In Korea, total production volume of benzoyl peroxide was 1,357 tonnes in 2001, and the chemical is produced by only one company. The amounts of import and export were estimated as 268 and 293 tonnes/year, respectively. 75 % of benzoyl peroxide is mainly used as an initiator of polymerization in the manufacture of expandable styrene polymer and other resins. Benzoyl peroxide is used in the treatment of acne vulgaris and the medical products contain mainly 5 - 10 % benzoyl peroxide. A very small portion of benzoyl peroxide is used as a flour bleaching agent.

The acute oral toxicity of benzoyl peroxide is likely to be low since the LD₅₀ is higher than 2,000 mg/kg in mice and 5,000 mg/kg in rats. Inhalation LC₉₀ is 24.3 mg/l in male rats with observable signs of eye squint, dyspnea, salivation, lacrimation, erythema and changes of respiratory rates and motor activity.

Benzoyl peroxide was slightly irritating to skin of test animals in 24 hour-patch tests. Benzoyl peroxide was not irritating to the eyes of rabbits if it was washed out within 5 minutes after instillation, however, if the chemical was not washed out until 24 hr later, it proved to be irritating.

Benzoyl peroxide was skin sensitizing in mice and guinea pigs when tested using the LLNA (Local Lymph Node Assay) and Buehler test or in human volunteers using the maximization test.
In the combined repeated dose and reproduction/developmental toxicity study (OECD TG 422), benzoyl peroxide did not lead to hematological- and biochemical-related adverse effects. Repeated administration by oral gavage to 1,000 mg/kg/day for 29 days resulted in decreased weights of testes and epididymis in male rats. The NOAEL for repeated dose toxicity was 500 mg/kg/day.

This substance did not cause gene mutation in bacteria (OECD TG 471 & 472) and in vitro chromosomal aberration in CHL (Chinese Hamster Lung) cells. An in vivo mammalian erythrocytes micronucleus test (OECD TG 474) showed negative results. This means that benzoyl peroxide is not genotoxic.

Benzoyl peroxide is not likely to be a complete carcinogen and/or initiator, but it seems to be a tumor promoter in mouse skin in an experimental two-stage model of carcinogenesis.

In the above combined repeated dose and reproduction/developmental toxicity study, no treatment-related changes in precoital time, rate of copulation, fertility and gestation were noted in any treated group. The adverse effects on reproduction were shown at the highest dose of 1,000 mg/kg/day in male rats with the reduction of reproductive organ’s weight and slight testes degenerations. In female rats, no adverse effects were observed during the test period. The NOAEL for reproduction toxicity in male rats was 500 mg/kg/day. There was no evidence of teratogenic effects of benzoyl peroxide, but the body weight gain of pups at a dose of 1,000 mg/kg/day was significantly decreased. The NOAEL for developmental toxicity was 500 mg/kg/day.

The major routes of occupational exposure are inhalation and dermal. Limited data on exposure are available. Annual monitoring of the concentration of benzoyl peroxide at the workplace of the production facility has shown concentrations in airborne aerosols (personal sampling) of less than 1 mg/m³.
4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

The acute toxicity data of benzoyl peroxide to fish, daphnia, algae and microorganisms were investigated for the aquatic effects. Only a few studies with the substance were available. Results of aquatic effects are summarized in Table 5.

Two acute Algae growth inhibition tests (OECD TG 201) showed comparable results. The 72 hr-EbC\textsubscript{50} (biomass) of Selenastrum capricornutum was 0.07 mg/L and the 72 hr-ErC\textsubscript{50} (growth rate) was 0.44 mg/L in a static system based on nominal concentrations (NIER, Korea, 2001f). This test was well documented and performed according to OECD test guidelines and GLP. It can be considered to be valid without restrictions. In another study using Pseudokirchneriella subcapitata, a 72 hr-EbC\textsubscript{50} of 0.44 mg/L and a 72 hr-ErC\textsubscript{50} of 0.83 mg/L had been derived in static test (Akzo Nobel, the Netherlands).

Table 5. Effects of Benzoyl peroxide on Aquatic Organisms

<table>
<thead>
<tr>
<th>Organism</th>
<th>Species</th>
<th>Test Duration</th>
<th>Result (mg/L)</th>
<th>Remarks</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algae</td>
<td>Selenastrum capricornutum</td>
<td>72 hr</td>
<td>EbC\textsubscript{50} = 0.07, ErC\textsubscript{50} = 0.44</td>
<td>OECD TG 201 (static, nominal concentration)</td>
<td>NIER, Korea, 2001f</td>
</tr>
<tr>
<td></td>
<td>Pseudokirchneriella subcapitata</td>
<td>72 hr</td>
<td>EbC\textsubscript{50} = 0.44, ErC\textsubscript{50} = 0.83</td>
<td>OECD TG 201 (static, nominal concentration)</td>
<td>Akzo Nobel, The Netherlands</td>
</tr>
<tr>
<td>Invertebrates</td>
<td>Daphnia Magna</td>
<td>48 hr</td>
<td>EC\textsubscript{50} = 0.07</td>
<td>OECD TG 202 (static, nominal concentration)</td>
<td>NIER, Korea, 2001g</td>
</tr>
<tr>
<td></td>
<td>Daphnia Magna</td>
<td>48 hr</td>
<td>EC\textsubscript{50} = 2.91</td>
<td>OECD TG 202 and EEC Directives (static, nominal concentration)</td>
<td>Wijk, R.J. van et al, 1999</td>
</tr>
<tr>
<td>Fish</td>
<td>Oryzias latipes</td>
<td>96 hr</td>
<td>LC\textsubscript{50} = 0.24</td>
<td>OECD TG 203 (flow-through, mean measured concentration)</td>
<td>NIER, Korea, 2002c</td>
</tr>
<tr>
<td></td>
<td>Poecilia reticulata</td>
<td>96 hr</td>
<td>LC\textsubscript{50} = 2.0</td>
<td>OECD TG 203 and EEC method, part C (semi-static, nominal concentration)</td>
<td>Mark, U et al, 1989</td>
</tr>
<tr>
<td>Microorganisms</td>
<td>activated sludge</td>
<td>30 min.</td>
<td>EC\textsubscript{50} = 35</td>
<td>OECD TG 209</td>
<td>Ginkel, C.G. van et al, 1990</td>
</tr>
</tbody>
</table>

The 48 hr-EC\textsubscript{50} of Daphnia magna in an immobilization test (OECD TG 202) was calculated to be 0.07 mg/L. The test was performed in a static system based on nominal concentrations (NIER,
Korea, 2001g). A 48 hr-EC$_{50}$ of 2.91 mg/L has been derived for *Daphnia magna* in another test with a static system (Wijk, R.J. van *et al.*, 1999).

A 96 hr-LC$_{50}$ of 2.0 mg/L has been derived for guppies (*Poecilia reticulata*) in a semi-static test based on nominal concentration of 0.7, 1.3, 2.4 and 4.2 mg/L (Mark, U *et al.*, 1989). In a study with *Oryzias latipes*, the 96 hr-LC$_{50}$ was calculated to be 0.24 mg/L. The nominal concentrations were 0.25, 0.5, 1.0, 2.0 and 4.0 mg/L but the mean measured concentrations of benzoyl peroxide in the test solution of the flow-through system were 0.23, 0.47, 0.69, 1.54, and 2.17 mg/L, respectively (NIER, Korea, 2002c). In another study, a 96 hr-LC$_{50}$ of 3.9 mg/L was reported using a static system based on nominal concentration (MOE, Korea, 1996). These results indicated that different test results could be obtained according to the test protocols because benzoyl peroxide is very unstable in water (half-life : 5.20 hr at pH 7.0).

From the chemical structure, benzoyl peroxide is expected to be hydrolyzed to benzoic acid. The toxicity of benzoic acid to aquatic organisms is as follows (see corresponding SIAR for benzoic acid, CAS No. 65-85-0):

Acute toxicity to fish: LC$_{50}$ (96 hr) for *Lepomis macrochirus* is 44.6 mg/L and for *Salmo gairdneri* is 47.3 mg/L in static conditions.

Acute toxicity to aquatic invertebrates: EC$_{50}$ (48 hr) for *Daphnia magna* is 100 mg/L in static conditions.

Acute toxicity to aquatic plants: EC$_{50}$ (3 h) for *Scenedesmus quadricauda* is 75 mg/L (inhibition of photosynthesis).

**Conclusion**

Benzoyl peroxide is toxic to aquatic organisms. On the acute toxicity basis, the most sensitive aquatic organism is algae with an EC$_{50}$ in the range of 0.07 - 0.44 mg/L.

### 4.2 Terrestrial Effects

Toxicity to terrestrial organisms was tested in a limited number of species. An earthworm acute toxicity test (OECD TG 207) was performed with *Eisenia foetida* on artificial soil. The 14d-LC$_{50}$ for *Eisenia foetida* was more than 1,000 mg/kg because the limit test of 1,000 mg/kg showed no mortality (NIER, Korea, 2002d). This toxicity value suggests that toxicity of benzoyl peroxide to soil dwelling organisms would be low.

Toxicity to non-mammalian terrestrial species (Chicken embryo) was investigated. For the toxic effect upon embryos, benzoyl peroxide was injected into the shell membrane of 3-day chicken eggs in the air chamber for 14 days. The 2d-LD$_{50}$ for chicken embryos was 0.99 µmoles/egg and the 14d-LD$_{50}$ was 0.82 µmoles/egg (Korhonen, A, *et al.*, 1984).

Information on effects of benzoyl peroxide on birds, mammals, plants, invertebrates and other terrestrial organisms are not available.

### 4.3 Other Environmental Effects

No data available
4.4 Initial Assessment for the Environment

Benzoyl peroxide is commercially produced as a white granule with purities ranging from 22 to 99%. It has a melting point of 104 - 106 °C, vapour pressure of 0.00929 Pa, solubility of 9.1 mg/L in water at 25 °C, and log $P_{ow}$ of 3.43 at 25 °C. In indirect photolysis, half-life is estimated to be 3 days by the AOPWIN model. The substance is readily biodegradable (OECD TG 301C: 83% as BOD after 21 days) and hydrolyses rapidly in water [OECD TG 111] with a half-life of 11.87 hrs at pH 4.0 and 5.20 hrs at pH 7.0 at 25 °C. The main hydrolysis product of benzoyl peroxide is benzoic acid (a SIDS assessment of benzoic acid is available, CAS No 65-85-0). An estimated BCF of 92 with the BCFWIN model suggests that this chemical has a low potential for bioaccumulation. A generic fugacity model (Mackay level III) was used for environmental fate estimation. If the most realistic emission pattern to water is assumed then the substance will remain in the aquatic compartment.

Benzoyl peroxide has toxic effects on the aquatic organisms. The range of 72 hr-$E_bC_{50}$ (biomass) and 72 hr-$ErC_{50}$ (growth rate) values for algae is 0.07 - 0.44 mg/L and 0.44 - 0.88 mg/L. The 48 hr-$EC_{50}$ for daphnia is 0.07 - 2.91 mg/L and the $LC_{50}$ for acute toxicity to fish is 0.24 - 2.0 mg/L. Although benzoyl peroxide is highly toxic to aquatic organisms, the substance is not bioaccumulated because of the rapid removal by hydrolysis (half-life = 5.2 hr at pH 7 at 25 °C) and biodegradation. The toxicity observed is assumed to be due to benzoyl peroxide rather than benzoic acid, which shows much lower toxicity to aquatic organisms. One can assume that effects occur before hydrolysis takes place. The toxicity for terrestrial organisms (earthworms) is low (14d-$LC_{50}$ > 1,000 mg/kg for Eisenia fetida).
5 RECOMMENDATIONS

Human Health: The chemical possesses properties indicating hazards to human health (sensitisation, effect on testes weight, fetal body weight and skin tumour promotion activity) and is a candidate for further work, i.e. exposure assessment, and if considered necessary, risk assessment.

Environment: It is expected that the possibility of any environmental releases of benzoyl peroxide is low in the sponsor country. However, this substance is a candidate for further work, even if it hydrolyses rapidly and has a low bioaccumulation potential. The substance shows high acute toxicity to aquatic organisms and some information indicates wide-dispersive use of this substance. This could lead to local concern for the aquatic environment and therefore environmental exposure assessment is recommended.
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SIDS DOSSIER

Benzoyl peroxide

CAS No. : 94-36-0

Sponsor Country : Republic of Korea

Date of submission to OECD : August 2002
1.01 SUBSTANCE INFORMATION

*A. CAS number : 94-36-0  
B. Name (Primary name) : Benzoyl peroxide  
*C. Name (OECD name) : Benzoyl peroxide  
†D. CAS Descriptor :  
E. EINECS-Number : 202-327-6  
F. Molecular Formula : C\textsubscript{14}H\textsubscript{10}O\textsubscript{4}  
*G. Structural Formula : 

\[
\text{Smiles Code} : O=C(OOC(=O)c(cccc1)c1)c(cccc2)c2
\]

H. Substance Group :  
I. Substance Remark (Indicate the substance remark as prescribed in the EINECS Inventory, if possible)  
J. Molecular Weight : 242.24

1.02 OECD INFORMATION

A. Sponsor Country : Republic of Korea  
B. Lead Organisation : Environmental Risk Assessment Division, National Institute of Environmental Research  
Contact person : Dr. Hyun-Mi Kim  
Address : Environmental Research Complex  
Street : Gyeongseo-dong, Seo-gu  
Postal code : 404-170  
Town : Incheon  
Country : Republic of Korea  
Tel : +82-32-560-7124  
Fax : +82-32-568-2037  
E-mail : hmikim@me.go.kr  

C. Name of responder (Information on a responder should be provided when companies respond to Lead Organisation or SIDS Contact Points.)  
Name : same as above  
Address : same as above
1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance: organic

B. Physical State (at 20 °C and 1.013 hPa): solid

C. Purity: 95 % (remainder water)
75 % (remainder water)
22 - 27 % (Mixture of 79 % benzoyl peroxide and some chemical additives for bleaching agent use)

Source: Hansol chemical company (2001)

1.2 SYNONYMS:
- Benzoic acid, peroxide
- Dibenzoyl peroxide
- Benzoperoxide
- Benzoyl Superoxide
- Benzoyl peroxide, remainder water
- Lucidol

1.3 IMPURITIES:
No data

1.4 ADDITIVES

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<td>Additive in 22 % benzoyl peroxide used in bleaching agent.</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CAS No.</th>
<th>EINECS No.</th>
<th>Name</th>
<th>Value</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Starch</td>
<td>&lt; 78 %</td>
<td>Additive in 22 % benzoyl peroxide used in bleaching agent.</td>
</tr>
</tbody>
</table>
1.5 QUANTITY

Estimated production:
- Production in Korea: 1,375 tonnes/year

Remarks:
- Imported into Korea: 268 tonnes/year
- Exported to EU: 293 tonnes/year

References:
- National Institute of Environmental Research (NIER), Korea, survey on circulation volume and use pattern of benzoyl peroxide in Korea, 2001

1.6 LABELLING AND CLASSIFICATION

The following classifications have been established:

- EEC Classification, Packaging, and Labeling of Dangerous Substances

EC No.: 202-327-6
Index No.: 617-008-00-0
Classification: E, R2; Xi, R 36; R 43
Danger Symbol: E, Xi

R-phrases: R: 2-36-43
S-phrases: S: (2-) 3/7-14-36/37/39

Remarks: Benzoyl peroxide is presently not classified as a toxic chemical under the Toxic Chemical Control Act in Republic of Korea. It is in the process of being reclassified to toxic chemical because of its high aquatic toxicity.

1.7 USE PATTERN

A. General

Type of Use: Category
- non-dispersive use
- wide dispersive use

(a) main industrial use:
- Plastic and polymer industry
- Initiator of polymerization

(b) main industrial use:
- Fabric industry
- Manufacture of sizing agents

(c) main industrial use:
- Paints producing industry
- Manufacture of acrylic resin

(d) main industrial use:
- Food industry
- Bleaching agents in flour

(e) main industrial use:
- pharmaceutical industry
1. GENERAL INFORMATION

ID 94-36-0
DATE: AUGUST 2002

acne vulgaris treatment

Remarks : 
References : National Institute of Environmental Research (NIER), Korea, survey on circulation volume and use pattern of benzoyl peroxide in Korea, 2001

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

<table>
<thead>
<tr>
<th>Exposure limit value</th>
<th>Type</th>
<th>Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TLV (Korea)</td>
<td>5 mg/m³ (8 hours TWA)</td>
<td>Industrial safety and health act in Korea, 1998</td>
</tr>
<tr>
<td></td>
<td>TLV (US)</td>
<td>5 mg/m³ (8 hours TWA)</td>
<td>ACGIH TLVs and Biological Exposure Indices for 1999</td>
</tr>
<tr>
<td></td>
<td>PEL</td>
<td>5 mg/m³</td>
<td>OSHA Permissible Exposure Levels, CFR v.29 Section 1910.1000, 1996</td>
</tr>
</tbody>
</table>

1.9 SOURCES OF EXPOSURE

<table>
<thead>
<tr>
<th>Source</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacture</td>
<td>Process : reaction (NaOH + H₂O₂ + 2C₆HCOCl) – Washing – Dewatering – Drying</td>
</tr>
<tr>
<td></td>
<td>Possible release source : washing process (into wastewater treatment facility)</td>
</tr>
<tr>
<td></td>
<td>Number of site : 1</td>
</tr>
<tr>
<td></td>
<td>Workplace exposure level : &lt; 1 mg/m³ (as aerosol)</td>
</tr>
</tbody>
</table>

References : Hansol Chemical Company in Korea

1.10 ADDITIONAL REMARKS

None
2.1 MELTING POINT

(a) Preferred Result
Value : = 104 - 106 °C
Remarks : Purity = 97 %
Reliability : (2) Reliable with restrictions
References : Aldrich, Catalog handbook of fine chemicals, Milwaukee, WI, Aldrich chem. Co., 164, 2000 ~ 2001

(b) Value : = 103 - 105 °C
Reliability : (2) Reliable with restrictions

(c) Value : = 106 °C
Reliability : (2) Reliable with restrictions

(d) Value : = 105 °C
Reliability : (2) Reliable with restrictions

(e) Value : = 103 - 106 °C
Reliability : (2) Reliable with restrictions

(f) Value : = 103 - 105 °C
Reliability : (2) Reliable with restrictions

(g) Value : = 106 - 108 °C
Reliability : (2) Reliable with restrictions
### 2. PHYSICO-CHEMICAL DATA

**ID 94-36-0**  
**DATE: AUGUST 2002**

#### 2.1 Boiling Point

<table>
<thead>
<tr>
<th>(h)</th>
<th>Value</th>
<th>= 103 - 105 °C</th>
<th>Reliability</th>
<th>(2) Reliable with restrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
<td>Value</td>
<td>= 103 °C</td>
<td>Decomposition</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reliability</td>
<td>(2) Reliable with restrictions</td>
</tr>
</tbody>
</table>

#### 2.2 BOILING POINT

##### (a) Preferred Result

<table>
<thead>
<tr>
<th>Value</th>
<th>Decomposes explosively above 105 °C</th>
<th>Reliability</th>
<th>(2) Reliable with restrictions</th>
</tr>
</thead>
</table>

##### (b)

<table>
<thead>
<tr>
<th>Value</th>
<th>Decomposes explosively</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(2) Reliable with restrictions</td>
</tr>
</tbody>
</table>

#### 2.3 DENSITY (RELATIVE DENSITY)

##### (a)

<table>
<thead>
<tr>
<th>Type</th>
<th>Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>1.33 g/cm³</td>
</tr>
<tr>
<td>Temperature</td>
<td>25 °C</td>
</tr>
<tr>
<td>Reliability</td>
<td>(2) Reliable with restrictions</td>
</tr>
</tbody>
</table>

##### (b)

<table>
<thead>
<tr>
<th>Type</th>
<th>Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>1.33 g/cm³</td>
</tr>
<tr>
<td>Temperature</td>
<td>25 °C</td>
</tr>
<tr>
<td>Reliability</td>
<td>(2) Reliable with restrictions</td>
</tr>
</tbody>
</table>


2.4 VAPOUR PRESSURE

(a) Preferred Result

Value : 0.00929 Pa
Temperature : 25 °C
Method : Estimated by MPBPWIN model
Remarks : Input data (melting point = 105 °C)
Reliability : (2) Reliable with restrictions
References : National Institute of Environmental Research (NIER), Korea, Estimation of Physical Chemical Properties and Environmental Fate of SIDS Chemicals (II)-on Benzoyl peroxide, 2002

(b)

Value : Much less than 1 mmHg
Temperature : 20 °C
Reliability : (2) Reliable with restrictions

2.5 PARTITION COEFFICIENT Log_{10} P_{ow}

(a) Preferred Result

Log P_{ow} : 3.43
Temperature : 25 °C
Method : Estimated by KOWWIN model
Remarks : Input data (experimental Log P_{ow} = 3.46)
Reliability : (2) Reliable with restrictions
References : National Institute of Environmental Research (NIER), Korea, Estimation of Physical Chemical Properties and Environmental Fate of SIDS Chemicals (II)-on Benzoyl peroxide, 2002

(b)

Log P_{ow} : 3.46
Temperature : 25 °C
Method : other (measured) : no data
Reliability : (2) Reliable with restrictions
References : Online Toxicology Data Network (TOXNET), Hazardous
2.6 WATER SOLUBILITY

(a) Preferred Result
Value: 9.1 mg/l
Temperature: 25 °C
Reliability: (2) Reliable with restrictions
References:
1. Online Toxicology Data Network (TOXNET), Hazardous Substances Data Bank (HSDB), 2002
2. Chem. Inspect Test Inst; Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan, Published by Japan Chemical Industry Ecology-Toxicology & Information Center, ISBN 4-89074-101-1, 1992

(b)
Value: Slightly soluble in water
Reliability: (2) Reliable with restrictions
References:

(c)
Value: Insoluble in water
Reliability: (2) Reliable with restrictions
References:

(d)
Value: Sparingly soluble in water
Reliability: (2) Reliable with restrictions
References:

(e)
Value: Very sparingly soluble in water
Reliability: (2) Reliable with restrictions
References:

(f)
Value: Insoluble in water
Reliability: (2) Reliable with restrictions
References:
2.7 FLASH POINT

(a)
Value: 40 °C
Reliability: (2) Reliable with restrictions
References: Baker, J., Material Safety Data Sheet (MSDS) Number, B1831 Effective Date, 11/02/01 by Mallinckrodt chemicals

(b)
Value: 41 °C
Reliability: (2) Reliable with restrictions
References: Hazardous Chemical Database, hardy Research Group the University of AKRON, Department of Chemistry, 2001

2.8 AUTO FLAMMABILITY

(a)
Value: 80 °C
Remarks: 176 F
Reliability: (2) Reliable with restrictions

(b)
Value: 80 °C
Remarks: 176 F
Reliability: (2) Reliable with restrictions

(c)
Value: 69 °C
Remarks: Calculated value
Reliability: (2) Reliable with restrictions

2.9 FLAMMABILITY

(a)
Result: Flammable
Remarks: The decomposition product
Reliability: (2) Reliable with restrictions
2. PHYSICO-CHEMICAL DATA

(b) Results: Highly Flammable
Reliability: (2) Reliable with restrictions

(c) Results: Highly Flammable
Remarks: In the dry state
Reliability: (2) Reliable with restrictions

(d) Results: Highly Flammable
Remarks: In the dry state
Reliability: (2) Reliable with restrictions

2.10 EXPLOSIVE PROPERTIES

(a) Results: May explode spontaneously when dry (< 1 % of water)
Reliability: (2) Reliable with restrictions

(b) Results: May explode spontaneously when heated to above melting point, or when overheated under confinement. It is moderately sensitive to heat, shock, friction, or contact with combustible materials. Explosive decomposition above the mp forms flammable products.
Reliability: (2) Reliable with restrictions

(c) Results: May explode when heated.
Reliability: (2) Reliable with restrictions
References: Budavari, S.ed. The Merck Index - An Encyclopedia of Chemicals,
Results: Explodes when heated oxidizer
Reliability: (2) Reliable with restrictions
References: Aldrich, Catalog handbook of fine chemicals, Milwaukee, WI, Aldrich chem. Co., 64, 2000 ~ 2001

(e)
Results: When heated above melting point (103 - 105 °C), instantaneous and explosive decomposition occurs without flame, but the decomposition products are flammable. If under confinement, decomposition may be violently explosive.
Reliability: (2) Reliable with restrictions

(f)
Results: May decompose explosively if subjected to excessive heat, friction or sudden shock.
Reliability: (2) Reliable with restrictions

(g)
Results: Liable to explode when heated above melting point or when subjected to friction or shock when dry.
Reliability: (2) Reliable with restrictions

(h)
Results: At elevated temperatures became unstable spontaneously explosive and extremely explosion-sensitive to shock (impact, blows), heat and friction.
Reliability: (2) Reliable with restrictions

(i)
Results: Benzoyl peroxide decomposes when heated above 75 °C (167 F) and will explode when subjected to shock and friction. At elevated temperatures it can be unstable and is spontaneously explosive.
Reliability: (2) Reliable with restrictions
References: U.S. Department of Health and Human Services and U.S.
2.11 OXIDIZING PROPERTIES

(a) Results: Active oxygen, approximately 6.5 %
Reliability: (2) Reliable with restrictions

(b) Results: A powerful oxidizer
Reliability: (2) Reliable with restrictions

(c) Results: Oxidizer irritant, purity = 75 %
Reliability: (2) Reliable with restrictions
References: Aldrich, Catalog handbook of fine chemicals, Milwaukee, WI, Aldrich chem. Co., 164, 2000 ~ 2001

(d) Results: An oxidizing agent and strong supporter of combustion
Reliability: (2) Reliable with restrictions

2.12 OXIDATION: REDUCTION POTENTIAL

No data

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

(a) Value: \( K_{oc} = 1,800 \)
Method: Determined from an experimental log\(K_{ow}\) of 3.46 and a recommended regression-derived equation
Reliability: (2) Reliable with restrictions
References: 1. Online Toxicology Data Network (TOXNET), Hazardous Substances Data Bank (HSDB), 2002
B. Henry’s Law Constant

(a)
Value : 0.36 Pa m^3/mole
Method : Estimated by HENRYWIN model
Reliability : (2) Reliable with restrictions
References : National Institute of Environmental Research (NIER), Korea, Estimation of Physical Chemical Properties and Environmental Fate of SIDS Chemicals (II)-on Benzoyl peroxide, 2002

C. Volatilization from Soil/Water

(a)
Result : Volatilization from moist soil surfaces may be important (1)
Remarks : (1) Given by estimated Henry’s law constant of \(3.54 \times 10^{-6}\) atm m^3/mole
Remarks : (2) Based on estimated vapor pressure of \(7.1 \times 10^5\) mmHg
Reliability : (2) Reliable with restrictions
References : 1. Online Toxicology Data Network (TOXNET), Hazardous Substances Data Bank (HSDB), 2002

(b)
Result : Volatilization from water surfaces
Remarks : Given by estimated Henry’s law constant of \(3.54 \times 10^{-6}\) atm m^3/mole
Reliability : (2) Reliable with restrictions
References : 1. Online Toxicology Data Network (TOXNET) : Hazardous Substances Data Bank (HSDB), 2002
3.1 Stability

3.1.1 Photodegradation

(a) Preferred Result

Type: Air
Indirect Photolysis
Type of sensitizer: OH radical
Concentration of sensitizer: Based on intensity of sunlight
Rate constant (radical): $3.55 \times 10^{-12}$ cm$^3$/molecule-sec
Degradation: ca. 50% after 3 days (36.1 hours)
Method: Estimated by APOWIN model
Reliability: (2) Reliable with restrictions
References: National Institute of Environmental Research (NIER), Korea, Estimation of Physical Chemical Properties and Environmental Fate of SIDS Chemicals (II)-on Benzoyl peroxide, 2002

(b)
Light spectrum: < 300 nm
Remarks: Can decompose on photolysis
Reliability: (2) Reliable with restrictions

(c)
Light spectrum: > 290 nm
Remarks: May directly photolyze
Reliability: (2) Reliable with restrictions
References: Online Toxicology Data Network (TOXNET), Hazardous Substances Data Bank (HSDB), 2002

3.1.2 Stability in Water

(a) Preferred Result

Type: Abiotic (hydrolysis)
Half-life at 25 °C:
- $t_{1/2}$ at pH 4 = 11.9 hours (Rate Constant, $k_{obs} = 1.62$ l/s × 10$^5$)
- $t_{1/2}$ at pH 7 = 5.2 hours (Rate Constant, $k_{obs} = 3.72$ l/s × 10$^5$)
- $t_{1/2}$ at pH 9 = Not detected (Rate Constant, $k_{obs} = $ Not detected)
Degradation %: The preliminary test at 50 °C for 5 days = 93.5% at pH 4.0
94.1% at pH 7.0
94.2% at pH 9.0
Method: OECD TG 111, “Hydrolysis as a Function of pH”
Year: 2001
GLP: No
Test substance: Benzoyl peroxide, Source – sigma (Lot No. 21K0966), purity = 70%
Remarks: Concentration of test substance was 4 mg/l. The preliminary test was performed at 50 °C for 5 days at pH 4.0, 7.0 and 9.0. To test for first - order behavior, test substance was analysed at 25 °C at pH 4.0, 7.0 and 9.0. Analysis of these tests was determined by HPLC.

Reliabilities: (2) Reliable with restrictions
References: National Institute of Environmental Research (NIER), Korea, The Test of Benzoyl peroxide Hydrolysis as a Function of pH (tested by LGCI), 2001

3.1.3 STABILITY IN SOIL

No data

3.2 MONITORING DATA (ENVIRONMENT)

No data

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 TRANSPORT

(a)
Type: Volatility
Media: Water-Soil
Method: Estimated volatilization of half-lives
Results: A model river: 17 days, A model lake: 123 days
Remarks: (2) Reliable with restrictions
References: 1. Online Toxicology Data Network (TOXNET), Hazardous Substances Data Bank (HSDB), 2002
3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

(a) Preferred Result

Media: Air-biota-sediment-soil
Method: Fugacity level III
Results: Benzoyl peroxide would be distributed into environmental compartment; Air (0.04 %), Water (0.02 %), Soil (99.9 %) and Sediment (0.002 %).

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Release 100 % to air</th>
<th>Release 100 % to water</th>
<th>Release 100 % to soil</th>
<th>All three</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>1.08</td>
<td>0.068</td>
<td>0.007</td>
<td>0.04</td>
</tr>
<tr>
<td>Water</td>
<td>0.01</td>
<td>85.0</td>
<td>0.0068</td>
<td>0.02</td>
</tr>
<tr>
<td>Soil</td>
<td>98.9</td>
<td>6.24</td>
<td>99.999</td>
<td>99.9</td>
</tr>
<tr>
<td>Sediment</td>
<td>0.001</td>
<td>8.65</td>
<td>0.0007</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Input parameters

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Type</td>
<td>1</td>
</tr>
<tr>
<td>Molecular Weight (g/mol)</td>
<td>242.23</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>25</td>
</tr>
<tr>
<td>Water Solubility (g/m³)</td>
<td>9.1</td>
</tr>
<tr>
<td>Vapor Pressure (Pa)</td>
<td>0.00929</td>
</tr>
<tr>
<td>Log P&lt;sub&gt;ow&lt;/sub&gt;</td>
<td>3.43</td>
</tr>
<tr>
<td>Melting Point (°C)</td>
<td>105</td>
</tr>
<tr>
<td>Half-life (hour(s))</td>
<td>Air 36 (estimated by AOPWIN)</td>
</tr>
<tr>
<td></td>
<td>Water 5 (derived from hydrolysis in water)</td>
</tr>
<tr>
<td></td>
<td>Soil 1E + 11 (default value)</td>
</tr>
<tr>
<td></td>
<td>Sediment 1E + 11 (default value)</td>
</tr>
</tbody>
</table>

Remarks: The EQC model was used for calculation.
Reliabilities: (2) Reliable with restrictions
References: National Institute of Environmental Research (NIER), Korea, Estimation of Physical Chemical Properties and Environmental Fate of SIDS Chemicals (II)-on Benzoyl peroxide, 2002

(b)

Media: Air-biota-sediment-soil
Method: Fugacity level I
3. ENVIRONMENTAL FATE AND PATHWAYS

OECD SIDS

ID 94-36-0
DATE: AUGUST 2002

Results:

- In air: 1.43%
- In water: 28.7%
- In soil: 68.3%
- In sediment: 1.52%

Remarks:
The EQC model was used for calculation.

Reliabilities:
(2) Reliable with restrictions

References:
National Institute of Environmental Research (NIER), Korea, Estimation of Physical Chemical Properties and Environmental Fate of SIDS Chemicals (II)-on Benzoyl peroxide, 2002

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

No data

3.5 BIODEGRADATION

(a) Preferred Result

Type: Aerobic
Inoculum: Activated sludge, 30 mg/L as suspended solid
Concentration: 100 mg/L related to test substance without pre-acclimation
Contact time: 21 days
Medium: Water
Degradation: 83% after 21 days (based on BOD)
Results: Readily biodegradable
Kinetic:
- 47% after 7 days (based on BOD)
- 83% after 14 days (based on BOD)
- 83% after 21 days (based on BOD)
- 88% after 21 days (based on TOC)
- 100% after 21 days (based on HPLC analysis)

Method:
OECD TG 301 C, “Ready Biodegradability; Modified MITI Test (I)”

Year: 1981

GLP: No

Test substance: Benzoyl peroxide

Remarks:
Temperature of incubation: 25 ± 1°C
300 ml of test solution was made up of 100 mg/L test substance in mineral medium with 30 mg/L activated sludge. Activity control (aniline in mineral medium at 100 mg/L with 30 mg/L activated sludge) and inoculum blank (mineral medium with 30 mg/L activated sludge) were used. Automatic electrolytic biochemical oxygen demand meter for BOD, total organic carbon analyzer for TOC and HPLC were used. BOD was analyzed continuously, TOC and HPLC were measured once after inoculation.

Reliabilities:
(2) Reliable with restrictions

References:
Ministry of International Trade and Industry, Japan, Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL, 1992
(b)
Type: Aerobic
Inoculum: Adapted; Secondary activated sludge, domestic
Concentration: mg/L related to DOC
Contact time: 28 days
Medium: Water
Degradation: 56 % after 28 days (based on the ratio of BOD to ThOD)
Results: Readily biodegradable
Method: OECD TG 301D and EEC Part C.6 Degradation-biotic degradation: Closed bottle Test
Year: 1990
GLP: Yes
Test substance: Lucidol (Benzoyl peroxide), Source - Akzo Chemicals BV (Lot No. 589076897), purity = 74.4 %
Remarks: Since test substance is poorly soluble in water, it was first dissolved in dichloromethane.
Reliabilities: (2) Reliable with restrictions

3.6 BOD5, COD OR RATIO BOD5/COD

No data

3.7 BIOACCUMULATION

(a) Preferred Result
BCF: 92
Method: Estimated by BCFWIN model
Reliability: (2) Reliable with restrictions
References: National Institute of Environmental Research (NIER), Korea, Estimation of Physical Chemical Properties and Environmental Fate of SIDS Chemicals (II) -on Benzoyl peroxide, 2002

(b)
BCF: 250
Method: Calculated from experimental logP_{ow} of 3.46 and a recommended regression-derived equation
Reliability: (2) Reliable with restrictions
References: 1. Online Toxicology Data Network (TOXNET) : Hazardous Substances Data Bank (HSDB), 2002
3.8 ADDITIONAL REMARKS

Remarks: From the chemical structure, benzoyl peroxide is expected that it is hydrolyzed to benzoic acid. Benzoic acid is mainly distributed to soil (64.2 %) and water (34.8 %) by Fugacity Level III. No hydrolysis is expected at pH range 4 ~ 11. The substance is readily biodegradable (> 90 % after 28 days) and has a low potential for bioaccumulation.

References: The OECD HPV program, SIDS Initial Assessment Report for 13th SIAM - Benzoates category
4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a) Preferred Result

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Flow-through</td>
</tr>
<tr>
<td>Species</td>
<td><em>Oryzias latipes</em></td>
</tr>
<tr>
<td>Exposure period</td>
<td>96 hours</td>
</tr>
<tr>
<td>Unit</td>
<td>mg/L</td>
</tr>
<tr>
<td>Analytical monitoring</td>
<td>HPLC monitoring was performed at 0, 48 and 96 hours.</td>
</tr>
<tr>
<td>LC₅₀</td>
<td>0.24</td>
</tr>
<tr>
<td>Method</td>
<td>OECD TG 203, “Fish, Acute Toxicity Test”</td>
</tr>
<tr>
<td>Year</td>
<td>2002</td>
</tr>
<tr>
<td>GLP</td>
<td>Yes</td>
</tr>
<tr>
<td>Test substance</td>
<td>PEROX-B95 (Benzoyl peroxide), Source – Hansol chemience Co. Ltd. (Lot No. 020502), purity = 97.3 %</td>
</tr>
<tr>
<td>Remarks</td>
<td>Test fish ; Age = 9 months / Length = 3.5 ± 0.1 cm / Weight = 0.34 ± 0.04 g</td>
</tr>
<tr>
<td></td>
<td>Test conditions ; Exposure vessel type = 8.7 liter glass aquarium/ Light = 284 ~309 Lux/ Light periocity = 16/8 hr (light/dark)/DO = 8.0 ~ 8.6 mg/L/pH = 7.27 ~ 7.55/Temperature range = 24.4 ~ 25.0 °C</td>
</tr>
<tr>
<td></td>
<td>Fish were fed brine shrimp in the morning and tetramin flake in the afternoon.</td>
</tr>
<tr>
<td></td>
<td>Fish were acclimated for 7 days before testing. Dilution water source was tap water which was passed through activated carbon and membrane filter (1 μm). The water had a hardness of 53.5 mg/L as CaCO₃ and an alkalinity of 30.5 mg/l as CaCO₃. Test substance was made up to stock solution of 343, 685, 1370, 5193 and 10277 mg/L. 0.15 ml/min of stock solution and 200 ml/min of dilution water were supplied to mixing chamber in continuous flow-through test system. Flow rate was 167 ml/min. Dilution water control and acetone control (750 mg/L) were used 10 fish per vessel were exposed to each of five test concentrations. Moving-Average Angle was used for statistical method to determine 95 % confidence limits. Nominal concentrations = 0.25, 0.5, 1.0, 2.0 and 4.0 mg/L Measured concentrations = 0.23, 0.47, 0.69, 1.54 and 2.17 mg/L (mean measured concentration)</td>
</tr>
</tbody>
</table>
Table showing cumulative mortality:

<table>
<thead>
<tr>
<th>Nominal concentrations (mg/L)</th>
<th>Mean measured concentration (mg/L)</th>
<th>Cumulative mortality (percent mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>24 hr</td>
</tr>
<tr>
<td>Control</td>
<td>Control</td>
<td>0(0)</td>
</tr>
<tr>
<td>Solvent control</td>
<td>Solvent control</td>
<td>0(0)</td>
</tr>
<tr>
<td>0.25</td>
<td>0.23</td>
<td>0(0)</td>
</tr>
<tr>
<td>0.5</td>
<td>0.47</td>
<td>2(20)</td>
</tr>
<tr>
<td>1.0</td>
<td>0.69</td>
<td>4(40)</td>
</tr>
<tr>
<td>2.0</td>
<td>1.54</td>
<td>10(100)</td>
</tr>
<tr>
<td>4.0</td>
<td>2.17</td>
<td>10(100)</td>
</tr>
</tbody>
</table>

Lowest test substance concentration causing 100% mortality was 0.47 mg/L and mortality of controls was none. Loss of equilibrium was observed in 24 and 48 hours at 0.47 mg/L and in 24 hr at 0.69 mg/L. Precipitation of test substance and test substance at the surface were observed at 0.47 - 2.17 mg/L.

Reliabilities: (1) Reliable without restrictions

References: National Institute of Environmental Research (NIER), Korea, The Acute Toxicity of Benzoyl peroxide to Fish (Report No. EG01077, tested by KRICT), 2002

(b)
Type: Semistatic
Species: Poecilia reticulata (guppy, local aquarium)
Exposure period: 96 hours
Unit: mg/L
LC50: 2.0
Analytical monitoring: No
Method: OECD TG 203 and EEC method, part C
GLP: Yes
Test substance: Lucidol (Benzoyl peroxide), Source- Akzo Chemicals BV (Lot No. 5589076897), purity = 74.4%
Remarks: The range of test concentration (nominal) was 0.7, 1.3, 2.4 and 4.2 mg/L and 10 fish (per test concentration and control) were used. The diluting water was DSW (Dutch Standard Water) and acetone (0.1 ml/L) was used as dispersant. Acetone control and fish water control were also included. A slight precipitate on the surface of the test medium at all test concentrations was observed.
Reliabilities: (2) Reliable with restrictions

(c)
Type: Static
Species: Oryzias latipes
Exposure period: 96 hours
Unit: mg/L
4. ECOTOXICITY

[57x780]UNEP PUBLICATIONS

Analytical monitoring : No data
LC50 : 3.9
Method : OECD TG 203, “Fish, Acute Toxicity Test”
Year : 1996
GLP : No
Test substance : No data
Remarks : Dimethylsulfoxide (DMSO) was used as a dispersant.
Reliabilities : (2) Reliable with restrictions
References : Ministry of Environment (MOE), Korea, Establishment of Advanced Testing Methods for Hazardous Chemicals, tested by KRICT, 1996

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

(a) Preferred Result
Type : Static
Species : Daphnia Magna
Exposure period : 48 hours
Unit : mg/L
EC50 : 0.07
Analytical monitoring : Yes, analytical monitoring was performed by HPLC at 0, 1, 3 and 5 hours.
Method : OECD TG 202, part 1, “Daphnia sp., Acute Immobilisation Test”
Year : 2001
GLP : Yes
Test substance: Benzoyl peroxide, Source-Lancaster Synthesis Ltd (Lot No. 13174), purity = 79.4%

Remarks: Test organisms were supplied from GSF Institute of Ecological Chemistry, Germany and juveniles within 24 hours old. Control group and solvent control (Acetone 1000 mg/l) were used. Stock solutions preparations: 14 mg test substance was dissolved in 10ml acetone then diluted with diluting water.

Test conditions; Test temperature range = 21.0 - 21.1 °C / Exposure vessel type = 100 ml test solution in a 150 ml crystallizing dish / Dilution water source = Elendt M4 (OECD TG 211 Annex 2)/Dilution water chemistry; hardness = 226.5 mg/l as CaCO3, alkalinity = 39.0 mg/l as CaCO3 ; pH = 8.0/ Lighting = 1427 - 1457 Lux/Light periocity = 16/8 hr (light/dark)/Water chemistry in test and in the control ; DO = 7.5 - 8.6 mg/l, pH = 7.7 - 8

Analytical monitoring was performed by HPLC at 0, 1, 3 and 5 hours to identify the stability of benzoyl peroxide. In the result of the test, contents of benzoyl peroxide decreased below 80% for 1 hr. Due to rapid hydrolysis of benzoyl peroxide, nominal concentrations were used for calculating EC50 value in static system.30 daphnids (3 replicates : 10 organisms per replicate) were exposed to concentration of 0.03, 0.06, 0.13, 0.25 and 0.50 mg/l (nominal concentrations).

Moving-Average Angle was used for statistical method to determine 95 % confidence limits.

Cumulative immobilization:

<table>
<thead>
<tr>
<th>Nominal Concentration (mg/L)</th>
<th>Cumulative number of organisms immobilized (percent immobilized)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24hr</td>
</tr>
<tr>
<td>Control</td>
<td>0(0)</td>
</tr>
<tr>
<td>Solvent control</td>
<td>0(0)</td>
</tr>
<tr>
<td>0.03</td>
<td>0(0)</td>
</tr>
<tr>
<td>0.06</td>
<td>0(0)</td>
</tr>
<tr>
<td>0.13</td>
<td>30(100)</td>
</tr>
<tr>
<td>0.25</td>
<td>30(100)</td>
</tr>
<tr>
<td>0.50</td>
<td>30(100)</td>
</tr>
</tbody>
</table>

30 Daphnids were immobilized in 0.13, 0.25, 0.50 mg/L at 24 hours and 3 Daphnids in 0.06 mg/L at 48 hours. Added acetone concentration was exceeded 100 mg/L but daphnia response in solvent control was normal.
4. ECOTOXICITY

4.1 BENZOYL PEROXIDE

Reliabilities: (1) Reliable without restrictions
References: National Institute of Environmental Research (NIER), Korea, The acute toxicity of Benzoil peroxide to Aquatic Invertebrate (Daphnia) (Report No. EG01006, tested by KRICT), 2001

(b)

Type: Static
Species: Daphnia Magna
Exposure period: 48 hours
Unit: mg/L
EC$_{50}$: 2.91
Analytical monitoring: Yes, measured by NPOC (non-purgeable organic carbon) at 0 hr and 48 hrs.
Method: OECD TG 202 and EEC Directives
Year: 1999
GLP: Yes
Test substance: Lucidol (Benzoil peroxide), Source - Akzo Chemicals BV, Purity = 74.4%
Remarks: 20 Daphnids divided into 4 batches of 5 animals were used per test concentration and control. The test was carried out as a WAF (Water Accommodated Fraction) with several dilutions. The DSW (Dutch Standard Water) was used as the test medium. The test concentrations were determined by NPOC analysis that was “indicative” or “representative” of test concentrations but not actually measured. These were performed on the undiluted fraction and control.

Reliabilities: (2) Reliable with restrictions
References: Wijk, R.J.van and Groenenboom Ir.C.J., Akzo Nobel, The Netherlands, Acute Toxicity of Lucidol to Daphnia magna, 1999

4.3 TOXICITY TO AQUATIC PLANTS

Algae

(a) Preferred Result
Species: Selenastrum capricornutum (Strain No. ATCC 22662)
Endpoint: Biomass, Growth rate
Exposure period: 72 hours
Unit: mg/L
EC$_{50}$: 0.07
E$_{C50}$: 0.44
Analytical monitoring: Yes, HPLC monitoring was done at 0 and 24 hours because test substance was not detected after 24 hours.
Method: OECD TG 201, “Algae, Growth Inhibition Test”
Year: 2001
GLP: Yes
Test substance: Benzoyl peroxide, Source - Lancaster Synthesis Ltd., (Lot No.13174), purity = 79.4 %

Remarks: Laboratory culture of algae was OECD medium and was shook at 100 rpm.

Test Conditions: Test temperature range = 22 - 24 °C/Dilution water source: acetone/Exposure vessel type: 100 ml medium in an Erlenmeyer flask/Water chemistry in test (pH) = pH 7.45 - 7.78 at start (0 hr) and pH 7.45 - 8.01 at end of the test (72 hours), hardness = 226.5 mg/L as CaCO3, alkalinity = 39.0 mg/L as CaCO3/Stock solutions preparation: 17 mg test substance was dissolved in 25 ml acetone and diluted with acetone. Light levels and quality during exposure: 8772 - 9106 Lux, Continuously control and solvent control (acetone 1,700 mg/L) were used. Initial cell number of algae was 1 × 10^4 cells/ml and three replicate vessels were maintained for each treatment and control group. Comprehensive Toxicity Data Analysis and Database Software (Version 5.0) and Dunnett’s test (p < 0.05) were used for determination of EC50, LOEC and NOEC value.

Nominal concentrations: 0.05, 0.1, 0.2, 0.4 and 0.8 mg/L Cell density at each flask at each measuring point:

### Percent biomass/growth rate inhibition per concentration

<table>
<thead>
<tr>
<th>Nominal Concentration (mg/L)</th>
<th>Cell density (×10^4 cells/ml)</th>
<th>0 hour</th>
<th>24 hours</th>
<th>48 hours</th>
<th>72 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>1.4</td>
<td>3.1</td>
<td>32</td>
<td>130</td>
</tr>
<tr>
<td>Solvent control</td>
<td></td>
<td>1.2</td>
<td>2.4</td>
<td>25</td>
<td>66</td>
</tr>
<tr>
<td>0.05</td>
<td></td>
<td>1.3</td>
<td>1.9</td>
<td>22</td>
<td>59</td>
</tr>
<tr>
<td>0.1</td>
<td></td>
<td>1.2</td>
<td>2.1</td>
<td>19</td>
<td>67</td>
</tr>
<tr>
<td>0.2</td>
<td></td>
<td>1.2</td>
<td>1.5</td>
<td>6.4</td>
<td>53</td>
</tr>
<tr>
<td>0.4</td>
<td></td>
<td>0.99</td>
<td>1.1</td>
<td>2.7</td>
<td>20</td>
</tr>
<tr>
<td>0.8</td>
<td></td>
<td>1.0</td>
<td>0.78</td>
<td>0.54</td>
<td>0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nominal Concentration (mg/L)</th>
<th>Growth rates</th>
<th>Relative growth rates (%)</th>
<th>Relative inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.063</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Solvent control</td>
<td>0.055</td>
<td>87.8</td>
<td>12.2</td>
</tr>
<tr>
<td>0.05</td>
<td>0.053</td>
<td>83.8</td>
<td>16.2</td>
</tr>
<tr>
<td>0.1</td>
<td>0.053</td>
<td>84.4</td>
<td>15.6</td>
</tr>
<tr>
<td>0.2</td>
<td>0.052</td>
<td>82.6</td>
<td>17.4</td>
</tr>
<tr>
<td>0.4</td>
<td>0.041</td>
<td>64.4</td>
<td>35.6</td>
</tr>
<tr>
<td>0.8</td>
<td>- 0.013</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>
Growth curves:

<table>
<thead>
<tr>
<th>Nominal Concentration (mg/L)</th>
<th>Area under the curve</th>
<th>Relative growth rates (%)</th>
<th>Relative inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>21,708,000</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Solvent control</td>
<td>13,684,000</td>
<td>63.0</td>
<td>37.0</td>
</tr>
<tr>
<td>0.05</td>
<td>11,984,000</td>
<td>55.2</td>
<td>44.8</td>
</tr>
<tr>
<td>0.1</td>
<td>12,424,000</td>
<td>57.2</td>
<td>42.8</td>
</tr>
<tr>
<td>0.2</td>
<td>7,484,000</td>
<td>34.5</td>
<td>65.5</td>
</tr>
<tr>
<td>0.4</td>
<td>2,752,000</td>
<td>12.7</td>
<td>87.3</td>
</tr>
<tr>
<td>0.8</td>
<td>-247,600</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

Remark: Significant difference in the growth curve was not observed between test concentration group and each control. Added solvent concentration was exceeded 100 mg/l but growth of algae in solvent control was normal.

Reliabilities: (1) Reliable without restrictions

References: National Institute of Environmental Research (NIER), Korea, The toxicity of Benzoyl peroxide to Aquatic plants (algae) (Report No. EG01005, tested by KRICT), 2001

Species: *Pseudokirchneriella subcapitata* (CCAP NO. 278/4)

Endpoint: Biomass, Growth rate

Exposure period: 72 hours

Unit: mg/L

Analytical monitoring: Yes, NPOC (non-purgeable organic carbon) analysis was performed.

$E_{B_{50}}$: 0.44

$E_{C_{50}}$: 0.83

Method: OECD TG 201

Year: 1989

GLP: Yes

Test substance: Lucidol (Benzoyl peroxide), Source- Akzo Chemicals BV, purity = 74.4 %

Remarks: Cultured algae were added to the WAF (Water - Accommodated Fraction) and potassium dichromate was used as positive control. The test concentrations were determined by NPOC analysis that was “indicative” or “representative” of test concentrations but not actually measured. These were performed on the undiluted fraction and control not done on the diluted fractions.

Reliabilities: (2) Reliable with restrictions

### 4.4 TOXICITY TO MICROORGANISMS

<table>
<thead>
<tr>
<th>Type</th>
<th>Aquatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>Secondary activated sludge of a predominantly domestic wastewater</td>
</tr>
<tr>
<td>Exposure period</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Unit</td>
<td>mg/L</td>
</tr>
<tr>
<td>Analytical monitoring</td>
<td>Yes, the respiration rates of activated sludge were measured in a Biological Oxygen Monitor (BOM)</td>
</tr>
<tr>
<td>EC$_{50}$</td>
<td>35</td>
</tr>
<tr>
<td>Method</td>
<td>OECD TG 209 and EEC Part C.Methods for determination of ecotoxicity, biodegradation, activated sludge respiration inhibition test</td>
</tr>
<tr>
<td>Year</td>
<td>1990</td>
</tr>
<tr>
<td>GLP</td>
<td>Yes</td>
</tr>
<tr>
<td>Test substance</td>
<td>Lucidol (Benzoyl peroxide), Source- Akzo Chemicals BV (Lot No.5589076897), purity = 74.4 %</td>
</tr>
<tr>
<td>Remarks</td>
<td>Dichloromethane (DCM) was used as a dispersant.</td>
</tr>
<tr>
<td>Reliabilities</td>
<td>(1) Reliable without restrictions</td>
</tr>
</tbody>
</table>

### 4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

#### 4.5.1 CHRONIC TOXICITY TO FISH

No data

#### 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

No data

### 4.6 TERRESTRIAL ORGANISMS

#### 4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

<table>
<thead>
<tr>
<th>Type</th>
<th>Artificial soil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td><em>Eisenia fetida</em></td>
</tr>
<tr>
<td>Endpoint</td>
<td>Mortality</td>
</tr>
<tr>
<td>Exposure period</td>
<td>14 days</td>
</tr>
<tr>
<td>Unit</td>
<td>mg/kg</td>
</tr>
<tr>
<td>LC$_{50}$</td>
<td>&gt; 1,000 (dry weight of substance)</td>
</tr>
</tbody>
</table>
OECD SIDS BENZOYL PEROXIDE
4. ECOTOXICITY ID 94-36-0
DATE: AUGUST 2002

Year: 2002
GLP: No
Test substance: PEROX-B95 (Benzoyl peroxide), Source – Hansol chemience Co. Ltd (Lot No. 020502), purity = 97.3 %
Remarks: The limit test of 1,000 mg/kg was shown no mortality.
Reliabilities: (2) Reliable with restrictions
References: National Institute of Environmental Research (NIER), Korea, The toxicity of Benzoyl peroxide to earthworm (tested by KRICT), 2002

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

(a)
Species: Chicken Embryo
Exposure period: 14 days
Unit: µmoles/egg
EC_{50}: 0.24
LD_{50} (2d): 0.99
LD_{50}: 0.82
Method: Other: Embryotoxic effect
Year: 1984
GLP: No data
Test substance: Dibenzoyl peroxide, moistened, purum, Fluka
Remarks: Embryotoxic effect of benzoyl peroxide to three-day chicken egg was tested. Acetone was used as solvent for benzoyl peroxide and the solution volume of 5 µl was injected into shell membrane in the air chamber of the egg during 14 days. The eggs were incubated. Malformations, like defects of the right eye of the embryos, were observed.
Reliabilities: (2) Reliable with restrictions

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data

4.8 BIOTRANSFORMATION AND KINETICS

No data
4.9 ADDITIONAL REMARKS

Remarks

: From the chemical structure, benzoyl peroxide is expected that it is hydrolyzed to benzoic acid. Toxicity of aquatic organisms for benzoic acid is as followed. 

Acute toxicity to fish: \( LC_{50} \) (96 hr) of *Lepomis macrochirus* is 44.6 mg/L and *Salmo gairdneri* is 47.3 mg/l in static condition.

Acute toxicity to aquatic invertebrates: \( EC_{50} \) (48 hr) of *Daphnia magna* is 100 mg/L in static condition.

Acute toxicity to aquatic plants: \( EC_{50} \) (3 h) of *Scenedesmus quadricauda* is 75 mg/L by inhibition of photosynthesis.

References

: The OECD HPV program, SIDS Initial Assessment Report for 13th SIAM - Benzoates category
5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a) Preferred Result

<table>
<thead>
<tr>
<th>Type</th>
<th>LD₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species/strain</td>
<td>mouse/ICR</td>
</tr>
<tr>
<td>Sex</td>
<td>male/female</td>
</tr>
<tr>
<td>Number of animals</td>
<td>5 animals/sex/dose</td>
</tr>
<tr>
<td>Vehicle</td>
<td>0.5 % methylcellulose sol.</td>
</tr>
<tr>
<td>Value</td>
<td>&gt; 2,000 mg/kg b.w</td>
</tr>
<tr>
<td>Route of administration</td>
<td>oral (gavage)</td>
</tr>
<tr>
<td>Method</td>
<td>OECD TG 401 (acute oral toxicity)</td>
</tr>
<tr>
<td>Year</td>
<td>2001</td>
</tr>
<tr>
<td>GLP</td>
<td>yes</td>
</tr>
<tr>
<td>Test substance</td>
<td>Benzoyl peroxide, Source – sigma, purity = 79.9 %</td>
</tr>
<tr>
<td>Test condition</td>
<td>- Age : 5 weeks</td>
</tr>
<tr>
<td></td>
<td>- Doses : 0 and 2,000 mg/kg</td>
</tr>
<tr>
<td></td>
<td>- Volume administered or concentration : 10 ml/kg</td>
</tr>
<tr>
<td></td>
<td>- Post dose observation period : 14 days</td>
</tr>
<tr>
<td>Result</td>
<td>Mortality : no animals died following exposure.</td>
</tr>
<tr>
<td></td>
<td>Description, severity, time of onset and duration of clinical signs : the only clinical symptom observed in 2,000 mg/kg dose group was piloerection. After the first day the symptom was recovered in all males and female animals.</td>
</tr>
<tr>
<td></td>
<td>Necropsy findings : no abnormal finding was observed in all dosed animals at necropsy.</td>
</tr>
<tr>
<td>Conclusion</td>
<td>No death animals were observed at limit test exposed to 2000 mg/kg. Rat oral LD₅₀ &gt; 2,000 mg/kg b.w</td>
</tr>
<tr>
<td>Reliability</td>
<td>(1) Reliable without restriction</td>
</tr>
<tr>
<td>References</td>
<td>National Institute of Environmental Research (NIER), Korea, Acute oral toxicity of benzoyl peroxide, (Report No. G01083, tested by KRICT), 2001</td>
</tr>
</tbody>
</table>

(b)

<table>
<thead>
<tr>
<th>Type</th>
<th>LD₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species/strain</td>
<td>rats/albino Spartan weighing 203 - 220 grams</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Number of animals</td>
<td>5 animals</td>
</tr>
<tr>
<td>Vehicle</td>
<td>corn oil</td>
</tr>
<tr>
<td>Value</td>
<td>&gt; 5,000 mg/kg b.w</td>
</tr>
<tr>
<td>Method</td>
<td>Other</td>
</tr>
<tr>
<td>Year</td>
<td>1973</td>
</tr>
<tr>
<td>GLP</td>
<td>no</td>
</tr>
</tbody>
</table>
Test substance: Benzoyl peroxide; purity = 78%; white granules (remainder water)

Test condition: Groups of 5 male albino rats were administered a single oral dose of 5000 mg/kg of test material in a constant volume (20 ml/kg). Rats were grouped housed. Food and water available ad libitum, except for overnight period prior to administration, during which food was withheld but water was available. Test material was administered via gavage (syringe). All rats were observed for mortality for a period of 14 days. Body weights were measured initially and at 14 days.

Result: No mortality occurred at the single dose of 5,000 mg/kg. Rats exhibited normal body weight gain. No toxic symptoms or signs were reported.

Study was conducted in accordance with a recognized scientific procedure for analyzing the acute oral toxicity of a test material in experimental animals conforming to a Limit Dose study. Although only males were tested and no gross pathology results were reported, the study meets minimum scientific standards and provides sufficient information to support the conclusion that.

Conclusion: The acute oral LD$_{50}$ in male albino rats is greater than 5,000 mg/kg.

Reliability: (2) Reliable with restriction

Remark: Study was conducted in accordance with a recognized scientific procedure for analyzing the acute oral toxicity of a test material in experimental animals conforming to a limit dose study. However, only males were tested and no gross pathology results were reported.


(c)

<table>
<thead>
<tr>
<th>Type</th>
<th>LD$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>Rat</td>
</tr>
<tr>
<td>Number of animals</td>
<td>2 animals/dose</td>
</tr>
<tr>
<td>Value</td>
<td>&gt; 950 mg/kg b.w</td>
</tr>
<tr>
<td>Method</td>
<td>other</td>
</tr>
<tr>
<td>Year</td>
<td>1964</td>
</tr>
<tr>
<td>GLP</td>
<td>No data</td>
</tr>
<tr>
<td>Test substance</td>
<td>Benzoyl peroxide, purity = unknown</td>
</tr>
<tr>
<td>Test condition</td>
<td>Groups of two fasted rats each were given oral doses of benzoyl peroxide placed on a small amount of pea soup concentration at 200, 400 and 950 mg/kg.</td>
</tr>
<tr>
<td>Result</td>
<td>None of the rats died during the study. One of the rats received 400 mg/kg had some vasodilatation, and one that received 950 mg/kg showed slight muscular weakness. The author concluded that the oral LD$_{50}$ of benzoyl peroxide in rats is greater than 950 mg/kg.</td>
</tr>
</tbody>
</table>
5. TOXICITY

Reliability : (4) not assignable


(d)
Type : LD₅₀
Species/strain : Mouse
Value : 5,700 mg/kg
   Discriminating dose : unknown
Method : Not specified
GLP : No data
Test substance : Benzoyl peroxide, purity = unknown
Reliability : (4) not assignable
   No sufficient experimental details

(e)
Type : LD₅₀
Species/strain : Rat
Value : 7,710 mg/kg
   Discriminating dose : unknown
Method : Not specified
GLP : No data
Test substance : Benzoyl peroxide, purity = unknown
Reliability : (4) not assignable

5.1.2 ACUTE INHALATION TOXICITY

(a)
Type : LC₀
Species/strain : Rat/Spartan albino
Exposure time : 4 hours
Number of animals : 10 males ; housed 5/cage
Dose : 24.3 mg/l
Value : 24.3 mg/l
Method : Other (Federal Hazardous Substances Act, Chapter II, Title 16 CFR.)
Year : 1973
GLP : No data
Test substance: Benzoyl peroxide; purity = 78%; white granules (remainder water)

Test condition: A single group of 10 male rats were placed in a sealed 59.1 liter glass chamber and exposed for 4 hours to a dynamic atmosphere of test material. Food and water were available *ad libitum* pre- and post-exposure. Addition of the test material was controlled by two Wright Dust Feeders. Dried, filtered air was passed through the mechanism and directly into the chamber. Airflow was regulated by a flow-meter. Atmospheric concentration was calculated. During exposure rats were separated into 4 units of 2 or 3 each, in order to prevent “piling up”, and to insure adequate exposure to each animal. All animals were observed for 14 days following exposure and then sacrificed.

Result: No mortality was observed at a single dose of 24.3 mg/L.
- Observable signs/symptoms during the 4 hour exposure period included: eye squint, dyspnea, salivation, lacrimation, erythema, increased and decreased respiratory rates, and increased and decreased motor activity.
- Observable signs/symptoms after 24 hours post-exposure: all rats appeared normal.
- Observable signs/symptoms after 48 hours post-exposure included: soft stools.
- All animals appeared normal from day 5 until the end of the study. Body weight gain was determined to be normal throughout study.

Reliability: (2) Reliable with restriction
Study was conducted in accordance with a recognized scientific procedure for analyzing the acute inhalation toxicity of a test material in experimental animals. However, only males were tested and no gross pathology results were reported.

References: Wazeter, F.X., and Goldenthal, E., Acute Inhalation to Rats; 328 - 005 International Research and Development Corporation (IRDC) August 31, 1973

### 5.1.3 ACUTE DERMAL TOXICITY

No data available

### 5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

<table>
<thead>
<tr>
<th>Type</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species/strain</td>
<td>Mouse/R, CBA</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>i.p.</td>
</tr>
<tr>
<td>Exposure time</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Value</td>
<td>20 µmoles/mouse (equivalent to 4.84 mg/mouse or 213 mg/kg b.w)</td>
</tr>
<tr>
<td>Method</td>
<td>Other</td>
</tr>
<tr>
<td>GLP</td>
<td>No data</td>
</tr>
<tr>
<td>Test substance</td>
<td>: Benzoyl peroxide (recrystallized)</td>
</tr>
<tr>
<td>Remarks</td>
<td>: Mice were administered 8 different dose conc. of 5, 10, 15, 20, 25, 30, 40, 50 µmoles/mouse. All animals died within 14 days after injection.</td>
</tr>
<tr>
<td>Reliability</td>
<td>: (2) Reliable with restriction</td>
</tr>
</tbody>
</table>

(b)

| Type | : LD₅₀ |
| Species/strain | : Mouse/'R' hybrid, hairless albino |
| Route of Administration | : i.p. |
| Exposure time | : Not applicable |
| Value | : 17.1 ± 2.1 (SE) µmoles/mouse (Equivalent to 168 mg/kg b.w - calculated) |
| Method | : Other |
| GLP | : No data |
| Test substance | : Benzoyl peroxide, purity = unknown |
| Remarks | : Each mouse was administered 10, 15, 20, 30 µmoles of benzoyl peroxide. All animals died within 8 days after injection. The time of death seemed not very dependent on dose. |
| Reliability | : (2) Reliable with restriction |

(c)

| Type | : LD₅₀ |
| Species/strain | : Mouse |
| Route of Administration | : i.p. |
| Exposure time | : Not applicable |
| Value | : 250 mg/kg |
| Method | : Not specified |
| GLP | : No data |
| Test substance | : Benzoyl peroxide, purity = unknown |
| Remarks | : No experimental information is available |
| Reliability | : (4) not assignable |
5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION

(a)
Test type : *in vivo*
Species/strain : Rabbits/Albino New Zealand
Results : Not irritating
Method : Other
Year : 1973
GLP : No data
Test substance : Benzoyl peroxide, purity = 78% ; white granules (remainder water)
Test condition : Sex : male/female weighting 2643 - 2952 grams
Number of animals : 3 males and 3 females.
Total dose : 500 mg of benzoyl peroxide
Vehicle : Not used.
Exposure time : 4 hours
Grading scale : Draize scale

500 mg of test material was applied to the abraded and intact sites on the shaved backs of rabbits. It was held in place for 4 hours with a gauze bandage. After 4 hours, the bandages were removed and the exposed areas washed with lukewarm water. The skin was examined for any injury or irritation from benzoyl peroxide at 4, 24 and 72 hours.

Result : The skin on the six rabbits appeared unaffected. Due to the absence of skin irritation observed in this study the calculation of primary irritation score was omitted from this reference.

Conclusion : The authors concluded that 78% benzoyl peroxide was neither a primary skin irritant nor a corrosive substance.

Reliability : (2) Reliable with restriction
Study was conducted in accordance with a recognized scientific procedure for analyzing the primary dermal irritation of a test material in experimental animals.

References : Wazeter, F.X., and Goldenthal, E., Primary Skin Irritation and Corrosive Hazard
Test in Albino Rabbits, International Research and Development Corporation (IRDC), August 31, 1973

(b)
Test type : *in vivo*
Species/strain : Rabbit/Mixed breeding, b.w : 2 - 4 kg
Results : Slightly irritating
Year : 1985 (paper accepted)
GLP : No data
Test substance: Benzoyl peroxide, purity = unknown
Test condition:
- Sex: Not specified
- Number of animals: 10 animals/dose
- Total dose: 0.1, 1, 5, 10, 15 and 30 % of benzoyl peroxide
- Vehicle: Yellow soft paraffin
- Control used: negative-vehicle only, positive - 10 % sodium lauryl sulfate
- Exposure time period: 24 hours for determining ID50 and 12 days for IT50
- Grading scale: No grading system applied

Determining irritant potential
- ID50 (irritant dose 50) - concentration which causes an irritant reaction (erythematous reaction) after a single epicutaneous application in 50 % of the animals exposed.
- IT50 (irritant time 50) - number of days necessary to produce an irritant reaction (erythematous reaction) after daily epicutaneous application in 50 % of the animals.

Remarks: Different concentrations of benzoyl peroxide in yellow soft paraffin were applied under occlusion for 24 hours to shaved areas on the back of rabbits to determine ID50 and IT50. The exposure was repeated once daily for a maximum of 10 days to determine IT50. It was stopped when erythematous reactions occurred.

Result: The lowest benzoyl peroxide irritant concentration was 1 % for one animal. All rabbits reacted with 10 %, 15 % and 30 % concentrations without exception. The ID50 was determined as 2.52 % of benzoyl peroxide

<table>
<thead>
<tr>
<th>Animal number</th>
<th>Negative control</th>
<th>Benzoyl peroxide 0.1 %</th>
<th>Benzoyl peroxide 1 %</th>
<th>Benzoyl peroxide 5 %</th>
<th>Benzoyl peroxide 10 %</th>
<th>Sodium lauryl sulfate 15 %</th>
<th>Sodium lauryl sulfate 30 %</th>
<th>Sodium lauryl sulfate 10 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>7</td>
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<td>+</td>
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</tr>
<tr>
<td>8</td>
<td>-</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
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</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
The number of days of exposure necessary to produce an irritant reaction in 50% of the animals with 0.1%, 1% and 5% BP was 8.35 (7.06 - 10.40)d, 4.34 (3.44 - 5.16)d, and 2.31 (1.75 - 2.80)d respectively.

<table>
<thead>
<tr>
<th>Benzoyl peroxide concentration</th>
<th>Days of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1%</td>
<td>0 0 1 1 2 3 3 5 6 6 7 7</td>
</tr>
<tr>
<td>1%</td>
<td>0 0 4 5 6 7 7 8 9 10 10 10</td>
</tr>
<tr>
<td>5%</td>
<td>1 4 8 9 9 10 10 10 10 10 10 10</td>
</tr>
</tbody>
</table>

Reliability: (2) Reliable with restriction

References:
Haustein, U-F, Tegetmeyer, L. and Ziegler, V., Allergic and Irritant Potential of Benzoyl Peroxide, Contact Dermatitis 13, 252 ~ 257, 1985

(c)
Species/strain: Guinea pig
Results: Slightly irritating
Method: Other
GLP: no
Test substance: Benzoyl peroxide, purity = unknown
Remarks: Patches of skin were chemically depilated, and pure benzoyl peroxide, in doses ranging from 0.25 to 1.0 g/kg, was held against the depilated skin under patches for 24 hours. The skin under the benzoyl peroxide was examined for any irritation or other injury. Slight erythema with some delayed scarring of the epidermis resulted. There were no deaths. A similar test was run on guinea pigs with 10% solution of benzoyl peroxide in propylene glycol. The doses ranged from 5 to 20 ml/kg. Only slight erythema was observed; no deaths occurred.

Reliability: (4) not assignable
Experimental details are insufficient.


(d)
Species/strain: Rabbit/New Zealand white
Results: Irritating
Method: Other (cumulative irritation study)
GLP: No data
Test substance: Tritium benzoyl peroxide, purity = 97%; chemical and radiochemical purity

Remarks: The study compared the skin irritation of benzoyl peroxide from topical formulations in which the substance was either freely dispersed or was entrapped in a SOWE (simple oil-in-water emulsion vehicle). Two groups of rabbits received different formulations. 0.025 ml of each formulation was applied to clipped backs of rabbits for 21 days. Irritancy observations were recorded daily with the following scale: Grade 0, no skin reaction; grade 0.5, barely perceptible, spotty erythema; grade 1.0, mild, even erythema covering the whole area of application; grade 2.0, intense erythema with clearly defined edge; grade 3.0, intense erythema plus edema, raised edge; grade 4.0, intense erythema, edema, and bullae; grade 5.0, necrosis. 0.025 ml of each formulation was applied over a previously marked 2 cm² area for 21 days. Cumulative 21-day irritation scores were as follows:

<table>
<thead>
<tr>
<th></th>
<th>Free benzoyl peroxide</th>
<th>Entrapped benzoyl peroxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>vehicle</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2.5 % BP</td>
<td>280</td>
<td>160</td>
</tr>
<tr>
<td>5.0 % BP</td>
<td>520</td>
<td>150</td>
</tr>
</tbody>
</table>

This study shows the entrapped/controlled-released system is less skin irritating.

Reliability: (2) Reliable with restriction


(e)

Species/strain: Mouse/albino

Results: Slightly irritating

Method: Other (cumulative irritation study)

GLP: No data

Test substance: 10 % Benzoyl peroxide

Remarks: Approximately 100 µl of benzoyl peroxide was applied to the entire dorsum for 6 months. Full thickness excisions were made for histological microscopic examination. The keratinocytes showed marked variations in size and shape (atypia). Some are degenerating and separating each other. A focal serous crust lies over the epidermis. Dermal changes were not notable.

Reliability: (2) Reliable with restriction

References: Kligman, A.M. and Kligman, L.H., A Hairless Mouse Model for Assessing the Chronic Toxicity of Topically Applied Chemicals, Food and Chemical Toxicology, 36, 867 ~ 878, 1998
### 5.2.2 EYE IRRITATION/CORROSION

(a) Test type: *in vivo* eye irritation study  
Species/strain: Rabbit/New Zealand White  
Method: OECD TG 405 (1987)  
Year: 2001  
GLP: Yes  
Test substance: Benzoyl peroxide, min., purity = 70 %, remainder water  
Test condition:  
- Sex: male  
- Number of animals per dose: 4 animals/dose  
- Dosed used: 100 mg/site/rabbit  
- Observation period: from 1 hour after dose to 72 hours  
- Tool used to assess score: Hand-slit lamp  
- Scoring method used: OECD method  
- Vehicle and eye washing: eye washed by saline solution at 30 seconds after instillation for 3 animals. No washing for 1 animal  

Result: Corrosiveness was not observed. Slight symptoms of irritation were observed when 100 mg of benzoyl peroxide instilled to an eye of rabbit.

#### - Irritation Score (Cornea/Iris):

<table>
<thead>
<tr>
<th>Observation time</th>
<th>Cornea</th>
<th>Iris</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 24 48 72</td>
<td>1 24 48 72</td>
</tr>
<tr>
<td>M1 (No eye washed animal)</td>
<td>1 1 1 0 1 1 1 0</td>
<td></td>
</tr>
<tr>
<td>M2</td>
<td>0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>M3</td>
<td>0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>M4</td>
<td>0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
</tbody>
</table>

The area of corneal opacity: < 1/4

#### - Irritation Score of Conjunctivae (Redness/Chemosis):

<table>
<thead>
<tr>
<th>Observation time</th>
<th>Redness</th>
<th>Chemosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 24 48 72</td>
<td>1 24 48 72</td>
</tr>
<tr>
<td>M1 (No eye washed animal)</td>
<td>2 2 1 1 2 2 1 0</td>
<td></td>
</tr>
<tr>
<td>M2</td>
<td>1 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>M3</td>
<td>1 1 1 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>M4</td>
<td>0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
</tbody>
</table>
clinical signs: animal survived during the test and no adverse clinical symptom was observed.
No eyes washed animal: opaque cornea was observed until 48 hours after dose in and its area was less than 1/4. Deepened rugae were also found in iris till 48 hours after dose. In the conjunctivae, obvious redness, swelling and excrement were observed till 48 hours after dose but completely recovered after 72 hours. Eyes washed animals: No significant clinical signs were observed.

Reliability: (1) Reliable without restriction

References: National Institute of Environmental Research (NIER), Korea, Acute Eye Irritation/Corrosion Test in Rabbits (Report No. S367, tested by LGCI), 2002

Test type: in vivo eye irritation study
Species/strain: Rabbit/Albino New Zealand
Method: Other (Federal Hazardous Substances Act, Chapter II, Title 16 CFR, US)
Year: 1973
GLP: No data
Test substance: Benzoyl peroxide, purity = 78% ; white granules (remainder water)

Test condition:
- Sex: male and female
- Number of animals: 4 animals/sex. 5 rabbits in Group I and 3 rabbits in Group II.
- Dosed used: 0.1 ml of test material was instilled into the everted lower eye lid of one eye of each rabbit. The average weight of the test material was 111.4 (group I, 5 minute wash) and 120.7 mg (group II, 24 hours wash).
- Exposure time: group I - 5 minutes, group II - 24 hours.
- irritation score: 0-4
- Observation period: Eyes were examined at 1, 24, 48, 72 hours and 7 days after washing.
- Tool used to assess score: fluorescein

Result:
Group I: benzoyl peroxide produced very minor redness (conjunctivitis) and swelling (chemosis) in 1/5 and 2/5 rabbits, respectively, but it was clear in 24 hours. No corneal opacity was observed.
Group II: there was grade 1 opacity in 3/3 at 24 hours; clear in 3/3 at 48 hours. No iritis. There was grade 2 redness in 2/3 at 48 hours, degrading to grade 1 in 1/3 at 72 hours; clear by day 7.

Conclude: Benzoyl peroxide was neither irritating nor corrosive to the eyes of albino rabbits if it was washed out within 5 minutes, but if 78% benzoyl peroxide was not washed out until 24 hours later, it proved to be a strong irritant. It was not considered corrosive because corneal opacity lasted less than 6 days.

Reliability: (2) Reliable with restriction
5. TOXICITY

References

: Wazeter, F.X. and Goldenthal, E., Eye irritation in Albino Rabbits, International Research and Development Corporation (IRDC), August 31, 1973

(c)

Species/strain : Rabbit
Method : Other
GLP : No data
Test substance : Benzoyl peroxide, purity = 50 and 93 % ; powder
Remarks : The eyes were rinsed with water 1 minute after instillation, and any solid residues were removed with a cotton swab.

5.3 SKIN SENSITIZATION

(a)

Type : Cellular proliferation
Species/strain : Mouse, CBA/Ca strain or CBA/JHsd strain
Method : Local lymph node assay (draft OECD TG429)
Year : 1997 (paper received)
GLP : No data
Test substance : Benzoyl peroxide (CAS No. 94-36-0) Source - Sigma, USA, purity = 70 %

Test condition : Sex : Female
Age of animal at study initiation : 6 - 12 weeks
Number of animals per sex per dose : 5 animals/dose
Route of administration : topical application on the dorsum of both ears
Induction concentration : 0.5, 1.0, 2.5, 5.0 and 10.0 % benzoyl peroxide
Induction vehicle : Acetone
Negative control : vehicle only
Volume of material dosed : 25 µl
Duration of exposure for induction : daily for 3 consecutive days.
Length of rest period : 2 days prior to analysis
Grading system used : in vivo \(^{3}\)Hmethylthymidine(or \(^{125}\)I iododeoxyuridine) : incorporation into lymph node cell DNA associated with proliferation induced by application of benzoyl peroxide was an objective and quantifiable response. Stimulation indices (SI) were determined as increase in \(^{3}\)H - TdR incorporation relative to vehicle-treated controls. SI of 3 or greater was considered to have skin sensitizing activity. Based on fitted quadratic regression analyses, estimates of the applied concentration of benzoyl peroxide required to elicit a SI of 3 (EC 3 value) were calculated.
Even at lowest concentration tested (0.5 %), benzoyl peroxide induced stimulation indices of considerably greater than 3, and for this reason it proved impossible to derive mathematically EC₃ values for this chemical.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>4457 (14.6)</td>
<td>9110 (23.4)</td>
<td>8640±953 (18.7)</td>
<td>3581±851 (14.7)</td>
<td>658±86 (24.4)</td>
</tr>
<tr>
<td>1.0</td>
<td>5273 (17.2)</td>
<td>8880 (22.8)</td>
<td>9746±1192 (21.0)</td>
<td>2061±956 (7.9)</td>
<td>598±81 (22.1)</td>
</tr>
<tr>
<td>2.5</td>
<td>5555 (18.1)</td>
<td>8495 (21.8)</td>
<td>11543±1909 (24.9)</td>
<td>2859±1017 (10.9)</td>
<td>909±129 (33.7)</td>
</tr>
<tr>
<td>5.0</td>
<td>6189 (20.2)</td>
<td>8762 (22.5)</td>
<td>11474±1422 (24.8)</td>
<td>5373±1176 (20.5)</td>
<td>849±56 (31.4)</td>
</tr>
<tr>
<td>10.0</td>
<td>6681 (21.8)</td>
<td>6274 (16.1)</td>
<td>8595±971 (18.6)</td>
<td>4522±409 (17.3)</td>
<td>715±62 (26.5)</td>
</tr>
</tbody>
</table>

All concentrations of benzoyl peroxide elicited a statistically significant increase in isotope incorporation in the 3 laboratories (lab C, D, E).

Conclusion: Benzoyl peroxide provoked very vigorous sensitising responses at all test concentration.

Reliability: (1) Reliable without restriction

This substance was evaluated in each of five independent international laboratories using either the standard LLNA protocol (Kimber & Basketter, 1992) or minor modifications of it.


Type: Challenge (Buehler test)
Species/strain: Guinea pig
Number of test animals: 20 test animals in the test group, 10 naive control animals for challenge and 10 separate naive control animals for rechallenge

Result: 42 % of the test group was judged as having positive allergic reactions. It is classified as skin sensitizer according to the threshold defined by EC (> 15 %).
<table>
<thead>
<tr>
<th>Reliability</th>
<th>: (2) Reliable with restriction</th>
</tr>
</thead>
</table>

**Type**
- : Challenge

**Species/strain**
- : human/white young

**Method**
- : Other, Maximization test

**GLP**
- : No data

**Test substance**
- : Benzoyl peroxide (topical preparations for acne)

**Test condition**
- : 4 formulation of benzoyl peroxide, two 5 % and two 10 % gel, were evaluated in a group of 50 white college students. The subjects were challenged 10 - 14 days later by a 48 hours patch test and the responses compared to pretesting with the same materials. The challenge site was evaluated at 48, 72, and 96 hours on a four point scale.

**Result**
- : 38 of 50 subjects developed a ++ or greater reaction. Sensitized subjects reacted to all four formulations.

**Reliability**
- : (2) Reliable with restriction

**References**
- Leyden, J.J., Kligman, A.M, Contact sensitization to benzoyl peroxide, Contact Dermatitis, Vol 3, 273 ~ 275, 1977

**Type**
- : TINA test

**Species/strain**
- : Guinea pig/albino

**Results**
- : Sensitizing

**Method**
- : Other

**GLP**
- : No data

**Test substance**
- : Benzoyl peroxide, purity = unknown

**Remarks**
- : 5 of 25 guinea pigs had a positive reaction after the TINA procedure on 2 consecutive days, while the other animals and controls were negative. The proportion of 20 % positive reactions to Benzoyl peroxide can be interpreted as indicating a relatively weak sensitization rate.

**Reliability**
- : (2) Reliable with restriction

**References**
- Haustein, U-F, Tegetmeyer, L. and Ziegler, V., Allergic and Irritant Potential of Benzoyl Peroxide, Contact Dermatitis, 13, 252 ~ 257, 1985

### 5.4 REPEATED DOSE TOXICITY

(a) **Preferred Result**

**Species/strains**
- : Rat/Sprague-Dawley

**Sex**
- : Male/Female

**Route of administration**
- : Oral (gavage)

**Method**
- : OECD TG 422 (Combined Repeated Dose and Reproduction/Developmental Toxicity Screening Test)

**Year**
- : 2001

**GLP**
- : Yes
**Test substance**: Source - SIGMA, purity = 70 %

**Dose level**: 0, 250, 500, 1,000 mg/kg b.w/day

**Exposure period**: Male : 29 days, female : from 2 weeks before mating to the day 3 of lactation

**Frequency of treatment**: Daily

**Control group**: (-) Concurrent vehicle (+) Cyclophosphamide (4.5 mg/kg/day)

**Post exposure observation period**: 1 day

**Statistical methods**: Dunnett’s multiple comparison test

**Test condition**
- **Test Subjects**
  - *Age*: 7 weeks old for male and female
  - *No. of animals*: 10 animals/sex/dose (5 animals/sex/positive control)
- **Study Design**
  - *Vehicle*: Corn oil
  - *Satellite groups*: Recovery group (5 animals/sex) at 0 and 1000 mg/kg for follow-up observation.
  - *Clinical observations performed and frequency*: General condition and body weight were observed once a day and once a week respectively. For pregnant females, body weight was determined on the day 1, 8, 15 and 20 of gestation and 1 and 3 of lactation. Food consumption was determined on the day 8, 15 and 29 of exposure. Haematology and biochemistry for males only at time of necropsy after 29 days of chemical exposure.
  - *Organs examined at necropsy*:
    - Organ weight: liver, kidney, adrenal gland, testis, epididymis, thymus, spleen, brain, heart, ovary, uterus, thyroid gland, spermary, prostrate gland
    - Microscopic: brain, spinal cord, stomach, pancreas, jejunum, ileum, cecum, colon, rectum, liver, kidney, adrenal gland, spleen, heart, thymus, thyroid, bronchus, lung, pituitary gland, ovary, uterus, vagina, testis, epididymis, spermary, prostrate gland, mammary gland, bladder, nodi lymphatici mesenterici, nodi lymphatici, nervus ischiadicus, femoral marrow and all gross lesion.

**NOAEL**: 500 mg/kg b.w/day

**LOAEL**: 1,000 mg/kg b.w/day
Results

- **Body weight**: Body weight gain was slightly increased (approximately 7% more than controls) in female recovery group exposed to 1,000 mg/kg only after 29 days. No significant body weight changes were observed in all animals except highest dose recovery group.

- **Food/water consumption**: The mean food consumption of 1,000 mg/kg was significantly increased during first and fourth weeks of chemical exposure in male. No other treatment groups were showed abnormal food consumption.

- **Description, severity, time of onset and duration of clinical signs**: Two female rats of depilation and crust were found when exposed to 500 mg/kg. Two female of genital contamination owing to diarrhea and urine were showed in 1,000 kg/mg recovery group. Hematemesis was seen in one male at 500 mg/kg. These findings are not considered to have been related to benzoyl peroxide exposure.

- **Hematological and biochemical findings incidence and severity**:

  Hematological findings: slightly increase in RBC and hematocrit concentration of male and female rats in 1,000 mg/kg recovery group. Slightly decrease in hematocrit in 1,000 mg/kg female recovery group. No other hematological changes were observed in any other animals.

  Biochemical findings: In female rats receiving 250 mg/kg a significant decrease in aspartate aminotransferase (AST) was observed and that also showed in 1,000 mg/kg recovery group.

- **Histopathology incidence and severity**: In the 1,000 mg/kg treatment group, testis degenerations were observed microscopically and these pathosis were mainly morphological change in sperm cell such as apoptosis, cellular swelling and multinucleated giant cell. In the female reproductive organ, slight affects were observed in uterus exposed to 1,000 mg/kg.

### Hematology of females (group mean)

<table>
<thead>
<tr>
<th>Treatment (mg/kg/day)</th>
<th>TP  g/dL</th>
<th>ALB g/dL</th>
<th>AST IU/L</th>
<th>ALT IU/L</th>
<th>BUN mg/dL</th>
<th>CREA mg/dL</th>
<th>TCHO mg/dL</th>
<th>GLU mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.9</td>
<td>2.5</td>
<td>145.5</td>
<td>51.1</td>
<td>18.0</td>
<td>0.6</td>
<td>90.8</td>
<td>87.0</td>
</tr>
<tr>
<td>250</td>
<td>6.7</td>
<td>2.5</td>
<td>88.2</td>
<td>59.6</td>
<td>17.0</td>
<td>0.6</td>
<td>90.4</td>
<td>87.4</td>
</tr>
<tr>
<td>500</td>
<td>6.3</td>
<td>2.3</td>
<td>122.6</td>
<td>56.9</td>
<td>18.9</td>
<td>0.6</td>
<td>101.4</td>
<td>82.8</td>
</tr>
<tr>
<td>1,000</td>
<td>6.4</td>
<td>2.4</td>
<td>102.9</td>
<td>61.3</td>
<td>18.3</td>
<td>0.5</td>
<td>92.4</td>
<td>98.6</td>
</tr>
<tr>
<td>recovery</td>
<td>7.5</td>
<td>2.9</td>
<td>118.8</td>
<td>26.9</td>
<td>20.8</td>
<td>0.6</td>
<td>80.8</td>
<td>112.6</td>
</tr>
<tr>
<td>(+)</td>
<td>6.3</td>
<td>2.3</td>
<td>119.8</td>
<td>27.2</td>
<td>17.7</td>
<td>0.6</td>
<td>65.2</td>
<td>102.8</td>
</tr>
</tbody>
</table>
- Mortality and time to death: No deaths were found in all animals including control groups.

- Ophthalmologic findings: Not examined

- Organ weight changes

  mean organ weight of male: Significant decrease in absolute and relative weights of left testes and relative wt of epididymis were observed in 1,000 mg/kg exposure group (p < 0.05), however these changes were not seen in recovery group. No other significant organ changes were found in all male rats.

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>0</th>
<th>250</th>
<th>500</th>
<th>1,000</th>
<th>(+) satellite</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT Testes (g)</td>
<td>1.714</td>
<td>1.645</td>
<td>1.686*</td>
<td>1.496</td>
<td>1.582</td>
</tr>
<tr>
<td>RT Testes (g)</td>
<td>1.734</td>
<td>1.638</td>
<td>1.684</td>
<td>1.589</td>
<td>1.585</td>
</tr>
<tr>
<td>LT Epididymis (g)</td>
<td>0.633</td>
<td>0.609</td>
<td>0.595</td>
<td>0.553</td>
<td>0.578</td>
</tr>
<tr>
<td>RT Epididymis (g)</td>
<td>0.648</td>
<td>0.611</td>
<td>0.595</td>
<td>0.576</td>
<td>0.597</td>
</tr>
<tr>
<td>Liver (g)</td>
<td>1.396</td>
<td>11.887</td>
<td>12.193</td>
<td>11.985</td>
<td>11.299</td>
</tr>
<tr>
<td>Thymus (g)</td>
<td>0.441</td>
<td>0.437</td>
<td>0.437</td>
<td>0.453</td>
<td>0.315</td>
</tr>
<tr>
<td>LT Kidney (g)</td>
<td>1.451</td>
<td>1.419</td>
<td>1.646</td>
<td>1.482</td>
<td>1.468</td>
</tr>
<tr>
<td>RT Kidney (g)</td>
<td>1.476</td>
<td>1.448</td>
<td>1.609</td>
<td>1.521</td>
<td>1.46</td>
</tr>
<tr>
<td>LT Adrenal (g)</td>
<td>0.035</td>
<td>0.032</td>
<td>0.035</td>
<td>0.038</td>
<td>0.032</td>
</tr>
<tr>
<td>RT Adrenal (g)</td>
<td>0.032</td>
<td>0.032</td>
<td>0.034</td>
<td>0.038</td>
<td>0.028</td>
</tr>
<tr>
<td>Spleen (g)</td>
<td>0.765</td>
<td>0.742</td>
<td>0.821</td>
<td>0.77</td>
<td>0.526</td>
</tr>
<tr>
<td>Brain (g)</td>
<td>2.09</td>
<td>2.058</td>
<td>2.033</td>
<td>2</td>
<td>2.066</td>
</tr>
<tr>
<td>Heart (g)</td>
<td>1.419</td>
<td>1.352</td>
<td>1.389</td>
<td>1.295</td>
<td>1.401</td>
</tr>
</tbody>
</table>

mean organ weight of female: increase in absolute and relative liver weights at 1,000 mg/kg, but decrease in relative liver weight at 1,000 mg/kg recovery group.

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>0</th>
<th>250</th>
<th>500</th>
<th>1,000</th>
<th>(+) satellite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (g)</td>
<td>9.088</td>
<td>10.124</td>
<td>10.013</td>
<td>10.15</td>
<td>7.435</td>
</tr>
<tr>
<td>LT kidney (g)</td>
<td>0.878</td>
<td>0.997</td>
<td>0.907</td>
<td>1.023*</td>
<td>0.846</td>
</tr>
<tr>
<td>RT kidney (g)</td>
<td>0.913</td>
<td>0.989</td>
<td>0.929</td>
<td>1.059*</td>
<td>0.868</td>
</tr>
<tr>
<td>LT adrenal (g)</td>
<td>0.039</td>
<td>0.04</td>
<td>0.039</td>
<td>0.044</td>
<td>0.036</td>
</tr>
<tr>
<td>RT adrenal (g)</td>
<td>0.034</td>
<td>0.039</td>
<td>0.037</td>
<td>0.04</td>
<td>0.035</td>
</tr>
<tr>
<td>Thymus (g)</td>
<td>0.244</td>
<td>0.345</td>
<td>0.377</td>
<td>0.342</td>
<td>0.211</td>
</tr>
<tr>
<td>Brain (g)</td>
<td>1.882</td>
<td>1.96</td>
<td>1.924</td>
<td>1.982</td>
<td>1.912</td>
</tr>
<tr>
<td>Spleen (g)</td>
<td>0.579</td>
<td>0.659</td>
<td>0.604</td>
<td>0.662</td>
<td>0.413</td>
</tr>
<tr>
<td>Heart (g)</td>
<td>1.029</td>
<td>0.965</td>
<td>1.022</td>
<td>1.004</td>
<td>1.068</td>
</tr>
</tbody>
</table>
Histopathology incidence and severity: In the 1,000 mg/kg treatment group, testis degenerations were observed microscopically ($p < 0.05$). In the female reproductive organ, slight effects were observed in uterus exposed to 1000 mg/kg.

### Male

<table>
<thead>
<tr>
<th>Treatment (mg/kg/day)</th>
<th>0</th>
<th>250</th>
<th>500</th>
<th>1,000 (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of animals</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Testes Degeneration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>5*</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epididymidis Degeneration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease of spermatocyte</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

### Female

<table>
<thead>
<tr>
<th>Treatment (mg/kg/day)</th>
<th>0</th>
<th>250</th>
<th>500</th>
<th>1,000</th>
<th>C (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineralization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal, minimal</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Focal, slight</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Uterus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial vacuolation</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial hyperplasia</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory cell infiltration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal, minimal</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** Significant decrease in absolute and relative weights of left testes and relative wt of epididymis were observed with testis degenerations in 1,000 mg/kg treated group. This result indicated the NOAEL is 500 mg/kg to male rats.

**Reliability:** (1) Reliable without restriction

**References:** National Institute of Environmental Research (NIER), Korea, Combined Repeated Dose Toxicity with the Reproduction/Developmental Toxicity Screening Testing of Benzoyl peroxide in Rats, (Report No.P049, tested by LGCI), 2001
<table>
<thead>
<tr>
<th>Species/strains</th>
<th>Rat and mouse/albino</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male/Female</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Feeding (p.o) and dermal (subcutaneous injection, skin painting)</td>
</tr>
<tr>
<td>Method</td>
<td>Other (chronic)</td>
</tr>
<tr>
<td>Year</td>
<td>1964</td>
</tr>
</tbody>
</table>

| GLP                | No data              |
| Exposure period    | 80 (mice) and 120 (rat) weeks |
| Frequency of treatment | Daily             |
| Dose               | 0.2826, 0.02826 and 0.002826 % in diet |
| Control group      | No treatment and vehicle only control group |
| NOEL               | 2.8 ppm              |
| LOEL               | N/A                  |
| Test substance     | Novaldelox (commercial powder containing 18 % Benzoyl peroxide) |

**Test condition:**
4 experimental groups (FC, F1, F2 and F3) were maintained on a diet of whole meal flour containing 0, 28.26, 282.6, 2826 ppm of benzoyl peroxide. 25 animals /species/dose/sex were used. Other 3 experimental groups (BC, B1 and B2), composed of 100 and 25 animals/species/dose/sex, were given breadcrumbs made from flour containing 28.26 and 2826 % benzoyl peroxide. 2 groups (SIC, SI) were given subcutaneous injection of 0, 50, 120 mg benzoyl peroxide. Another one group (T), consisting of 25 male and female mice, were painted on the back of the neck on 6 days each week with one drop (50 mg approximately) of 50 % suspension of benzoyl peroxide in flour paste. Group SIC, SI, T and TC were provided with a commercial pellet diet. Body wt gains of rats were noted weekly for 18 weeks, and then monthly. The animals were examined twice daily with regard to their general health. Animals that were moribund were killed. All animals that were killed or that died were autopsied.

**Results:**
The rats consuming the flour diets containing the two highest levels of benzoyl peroxide showed significant decrease in body wt. gain. There were no significant differences in the body weight of the rats given treated breadcrumbs. There was no significant difference between experimental and appropriate control groups in the mortality rate of the animals except F2, in which there was a large number of accidental deaths. There were statistically significant incidence of atrophy of the testicles in the rats given the diet based on flour treated with benzoyl peroxide at 2826 ppm and in the rats receiving diets of breadcrumbs made with flour treated with benzoyl peroxide at 28.26 and 2.826 ppm.
- Pathological finding in rats

<table>
<thead>
<tr>
<th>Infective</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>FC</th>
<th>B1</th>
<th>B2</th>
<th>BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative</td>
<td>138</td>
<td>109</td>
<td>136</td>
<td>159</td>
<td>110</td>
<td>130</td>
<td>104</td>
</tr>
<tr>
<td>Vascular including haemorrhage</td>
<td>53</td>
<td>62</td>
<td>49</td>
<td>48</td>
<td>49</td>
<td>49</td>
<td>56</td>
</tr>
<tr>
<td>Degenerative</td>
<td>16</td>
<td>13</td>
<td>15</td>
<td>28</td>
<td>27</td>
<td>23</td>
<td>49</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>38</td>
<td>30</td>
<td>32</td>
<td>41</td>
<td>41</td>
<td>47</td>
<td>34</td>
</tr>
<tr>
<td>Tumor (ben., mal.)</td>
<td>12</td>
<td>2</td>
<td>3</td>
<td>9</td>
<td>31</td>
<td>11</td>
<td>35</td>
</tr>
<tr>
<td>Ulceration of stomach</td>
<td>2.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.5</td>
<td>2.1</td>
<td>-</td>
</tr>
<tr>
<td>Atrophy of testes</td>
<td>27*</td>
<td>15</td>
<td>15</td>
<td>4</td>
<td>19*</td>
<td>23*</td>
<td>11</td>
</tr>
</tbody>
</table>

* Significant difference from controls P < 0.05

The authors suggested that this atrophy was caused by benzoyl peroxide, which probably marginally decreased the amount of vitamin E in the diet.

The injection of benzoyl peroxide subcutaneously in rats and mice did not result in any tumor formation at the site of injection, or in any increase in tumor incidence elsewhere. Application of a paste made from flour treated with benzoyl peroxide to the skin of rats and mice also caused no tumor formation.

Reliability: (2) valid with restriction
Remark: Exact doses cannot be determined since the actual diet consumption was not reported.

### 5.5 GENETIC TOXICITY IN VITRO

#### A. BACTERIAL TEST

**(a) Preferred Result**

- **Type**: Bacterial reverse mutation assay
- **Species/Strain**: *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, *Escherichia coli* WP2 uvrA
- **Method**: OECD TG 471, 472
- **System of testing**: Bacterial
- **Year**: 2001
- **GLP**: Yes
- **Metabolic activation**:
  - Species and cell type: Rat Sprague Dawley strain, male, liver homogenate
  - Quantity: 4 % S9 in the S9 mix
  - Induced: Aroclor-1254 induced
- **Concentrations tested**: 0.247, 0.74, 2.22, 6.67, 20 and 60 µg/plate
- **Statistical Methods**: Dunnett’s test (p < 0.01)
- **Test substance**: Benzoyl peroxide, source – Sigma (B-2030), Purity = approx. 71.8 %
Test condition:
- Number of replicates: one time
- Frequency of Dosing: 3 plates/dose
- Positive and negative control groups and treatment: Negative control - solvent control (Dimethyl sulfoxide), Positive control - 2-aminoanthracene with S9, 2-nitrofluorene, sodium azide, 9-aminoacridine, 4-nitroquinoline 1-oxide
- Number of metaphases analyzed: not analyzed
- Solvent: Dimethyl sulfoxide
- Description of follow up repeat study: A preliminary test was performed at the concentrations of 1.6, 8, 40, 200, 1,000 and 5,000 µg/plate.
- Criteria for evaluating results: counting the number of revertant colonies in the plate after 2-day-incubation at 37 celcius.

Results:

Cytotoxicity conc:
- With metabolic activation: not observed
- Without metabolic activation: not observed

Genotoxic effects:
- With metabolic activation: negative
- Without metabolic activation: negative

Conclusion:
Benzoyl peroxide did not induce mutation in the Salmonella typhimurium TA98, TA100, TA1535, TA1537, Escherichia coli WP2 uvrA strains with or without metabolic activation.

Reliability:
(1) Reliable without restriction
This study was well conducted by GLP laboratory based on OECD test guideline.

References:
National Institute of Environmental Research (NIER), Korea, Bacterial Reverse Mutation Test, Test No. S350, tested by LGCI, 2001
(c)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA97a, TA100, TA102, TA104
Concentration: 1 - 100 µg/plate
Metabolic activation: With and Without
Results:
- Cytotoxicity conc: Not mentioned
- Precipitation conc: With metabolic activation: negative
- Genotoxic effects: Without metabolic activation: negative
Method: Other (Ames, 1973)
GLP: No data
Test substance: Benzoyl peroxide, Source - Aldrich Chemical Co., purity = unknown
Remarks: Method: Preincubation method modified by Ames
Benzoyl peroxide was non-mutagenic when tested using *Salmonella typhimurium* TA97a, TA100, TA102, TA104 strains with or without metabolic activation.
Reliability: (2) Reliable with restriction

(d)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA97, TA98, TA100, TA1535, TA1537
Concentration: A half log dose intervals up to a dose that elicited toxicity, five doses and a maximum dose of 10 µg/plate
Metabolic activation: With and Without
Results:
- Cytotoxicity conc: Judged by a preliminary test, but no data
- Precipitation conc: With metabolic activation: negative
- Genotoxic effects: Without metabolic activation: negative
Method: Other (Haworth, et al., 1983)
GLP: No data
Test substance: Benzoyl peroxide, Source - Aldrich Chemical Co., purity = unknown
Remarks: Method: Preincubation method
Reliability: (4) not assignable
Insufficient experimental details
B. NON-BACTERIAL TEST

(a) Type
System of testing
Concentration
Metabolic activation
Results
Cytotoxicity conc
Precipitation conc
Genotoxic effects
Method
GLP
Test substance
Remarks
Reliability
References

5.6 GENETIC TOXICITY IN VIVO

(a) Preferred Result
Test substance:
Benzoyl peroxide, source - Sigma (B-2030), purity = 71.8 %

Test condition:
- Age at study initiation : 7 weeks
- No. of animals per dose : 6
- Vehicle : Pluronic F-68 solution (5 %)
- Duration of test : 2 days
- Frequency of treatment : one daily treatment
- Sampling times and number of samples : 24 hours after last administration, 6 samples/dose
- Control groups and treatment : negative control (Pluronic F-68 solution), Positive control (2 mg/kg of Mitomycin C)
- Clinical observations performed : mortality, general clinical observations
- Organs examined at necropsy : not examined

Results:

Effect on mitotic index or PCE/NCE ratio by dose level

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Group mean (PCE/PCE+NCE)</th>
<th>Group mean frequency of MNPCE (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0.54</td>
<td>1.33</td>
</tr>
<tr>
<td>50</td>
<td>0.57</td>
<td>0.75</td>
</tr>
<tr>
<td>100</td>
<td>0.52</td>
<td>0.83</td>
</tr>
<tr>
<td>200</td>
<td>0.45</td>
<td>1</td>
</tr>
<tr>
<td>Positive control</td>
<td>0.43</td>
<td>59.7</td>
</tr>
</tbody>
</table>

Genotoxic effects:
Negative
- statistical results : Only positive control group showed statistically increased frequency of micronucleated cells (p < 0.01).
- Description, severity, time of onset and duration of clinical signs : On the 2nd day, hypoactivity was observed at the concentration of 200 mg/kg.
- Body weight changes by dose and sex : On the 3rd day for the sacrifice, there was a decrement of body weight at the concentration of 100 and 200 mg/kg (p < 0.05).
- Food/water consumption changes by dose and sex : none

Conclusion:
Benzoyl peroxide showed negative result in micronucleus test in vivo up to the test concentration of 200 mg/kg.

Reliability:
(1) Reliable without restrictions
This study was conducted by GLP lab based on OECD test guideline.

References:
National Institute of Environmental Research (NIER), Korea ; Micronucleus test of Benzoyl peroxide in mouse (test No.S349, tested by LGCI), 2001

Type:
A dominant lethal assay
Species/Strains:
Mouse/ICR (Ha Swiss)
Sex:
Male/Female
Route of Administration:
i.p
Exposure period:
8 weeks (total weeks of mating)
Doses:
7 males at the lower dose (54 mg/kg), 9 males at the higher dose (62 mg/kg), 10 males for the control group (solvent)
Results:
Negative
Method:
Modified dominant lethal mouse assay
5. TOXICITY

5.7 CARCINOGENICITY

(a) Preferred Result

<table>
<thead>
<tr>
<th>Test type</th>
<th>2-year dermal carcinogenicity study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>Mouse</td>
</tr>
<tr>
<td>Strain</td>
<td>B6C3F1/CrlBR</td>
</tr>
<tr>
<td>Sex</td>
<td>Male and female</td>
</tr>
<tr>
<td>Vehicle</td>
<td>aqueous carbopol gel (0 % BP)</td>
</tr>
<tr>
<td>Method</td>
<td>Covance Protocol 6711 - 100 (US FDA)</td>
</tr>
<tr>
<td>Year</td>
<td>2001</td>
</tr>
<tr>
<td>GLP</td>
<td>Yes</td>
</tr>
<tr>
<td>Test substance</td>
<td>Benzoyl peroxide in carbopol gel (1, 5 and 25 - 15 %)</td>
</tr>
<tr>
<td>Test Conditions</td>
<td></td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Dermal</td>
</tr>
<tr>
<td>Exposure period</td>
<td>at least 104 weeks</td>
</tr>
<tr>
<td>Frequency of treatment</td>
<td>once daily</td>
</tr>
<tr>
<td>Post exposure observation period</td>
<td>none</td>
</tr>
<tr>
<td>Doses</td>
<td>0, 1, 5, 25 mg/mouse/day</td>
</tr>
<tr>
<td>Control group</td>
<td>Yes, vehicle control, untreated control, sentinels (not received treatment)</td>
</tr>
<tr>
<td>Area covered</td>
<td>ca. 2 × 3 cm of dorsal skin</td>
</tr>
<tr>
<td>Occlusion</td>
<td>semi-occlusive</td>
</tr>
<tr>
<td>Concentration in vehicle</td>
<td>1, 5, 15 and 25 % BP</td>
</tr>
<tr>
<td>Total volume applied</td>
<td>0.1 mL</td>
</tr>
</tbody>
</table>

Remarks:

All females were sacrificed at 13 days after mating. Each male mouse was treated with a test chemical or with the solvent alone, and subsequently caged with 3 untreated virgin female mice, which were replaced weekly for 8 consecutive weeks. All females were sacrificed at 13 days after the midweek of their caging and presumptive mating, without being checked for vaginal plugs. Each female was scored for pregnancy, and for numbers of total implants, as comprised by live implants, early fetal deaths and late fetal deaths. Total implants, early fetal deaths (brown or black containing necrotic and hemorrhagic material but no embryo), late fetal deaths (implantation sites containing a subnormal fetus and placenta which may be white or pale) were used as criteria for evaluating results. This test was a modified dominant lethal mouse assay and benzoyl peroxide was proved to be not meeting any screening criteria for mutagenic effects.

Reliability:

(2) Reliable with restriction

References:

Test conditions: Mice in Group 1 serve vehicle controls and received daily topical applications of the carbopol gel vehicle at a dose volume of 0.1 mL. Mice in Group 6 served as negative controls; the hair on the backs of these mice was clipped at the same intervals as the other mice on study; however, these mice were not treated. Sixty mice/sex were assigned to Groups 1, 2, 3, 4, and 6, with the first 10 mice/sex/group designated for interim sacrifice during week 53 and the remaining 50 mice/sex/group designated for terminal sacrifice after 104 weeks of treatment. Fifty mice/sex in Group 5 served as recovery animals, in that they were treated with 25% benzoyl peroxide for 52 weeks, then treated with the vehicle for the remainder of the study. Twenty mice/sex in Group 7 served as sentinel animals for pathogen screening at Weeks 26, 52, 78, and 104.

Diet and water were provided *ad libitum*. Once weekly, each animal was removed from its cage and examined for abnormalities and signs of toxicity, specifically noting the location, size, and appearance of any grossly visible or palpable masses. The treated skin for analogous site on the untreated control) was graded for irritation once weekly. Body weights were recorded weekly from weeks 1 through 14 and every fourth week thereafter and at weeks 53 and 5. Group 4 had additional body weights taken at weeks 57 and 59. Food consumption was measured and recorded weekly for weeks 1 through 13 and every fourth week thereafter and at weeks 52 and 104. Blood smears were prepared from all moribund-, interim-, and terminal sacrifice animals for possible evaluation of hematopoietic neoplasia.

After 52 weeks (interim-sacrifice animals) or 104 weeks (terminal sacrifice animals) of treatment the animals were anesthetized, weighed, exsanguinated, and necropsied. At necropsy, macroscopic observations were recorded, and selected tissues were collected and preserved. The liver with gallbladder, kidneys, and brain were weighed from all animals at interim sacrifice. Selected tissues (treated skin, untreated skin, and livers) were examined microscopically from all interim-sacrifice mice (Groups 1, 2, 3, 4, and 6).

All collected tissues were examined microscopically from all terminal-sacrifice mice in Groups 1, 2, 3, 4, and 6, whereas only treated and untreated skin was examined microscopically from the mice in Group 5 (high-dose-discontinued). Tumors were statistically analyzed separately and combined for relationship to treatment.
Results: With the exception of the findings of ulcerations at the application site, there were no treatment-related differences in clinical observations among any of the groups. Treatment did not affect survival, body weights, or food consumption. The major microscopic findings were observed at the application site. At the interim (Week 53) sacrifice, these findings consisted of hyperkeratosis (1, 5, and 25 % benzoyl peroxide), subepidermal subacute inflammation (5 and 25 % benzoyl peroxide), and sebaceous gland hyperplasia (males: 5 and 25 % benzoyl peroxide; females: 1, 5, and 25 % benzoyl peroxide). These findings were dose-dependent with regards to incidence and/or group mean severity. Similar findings were noted at the terminal (Week 105-106) sacrifice with the exception that there were no findings for treated or untreated skin in the high-dose and high-dose-discontinued animals. The high-dose-discontinued animals, after being treated with 25 % benzoyl peroxide for 1 year, were allowed 52 weeks of recovery.

Although the high-dose animals were not originally intended to be a recovery group, they were not treated with benzoyl peroxide for the final 13 weeks of study since the 25 - 15 % benzoyl peroxide concentrations had been found to exceed the maximum tolerated dose. In both of these cases there was no residual effect of treatment.

Conclusion: Under the condition of this study, there were no histologic findings indicative of oncogenicity resulting from daily topical exposure of mice to benzoyl peroxide gels at concentration up to 25 % (dose level 25 mg/mouse/day). The spectrum of neoplasms observed in this study was typical for aging B6C3F1 mice.

Reliability: (1) Reliable without restriction

References:
Consumer Healthcare Products Association (CHPA), Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice, Covance study No.6711-100, Vol 1of 7, 2001

(b)
Test type: initiation/promotion
Species/Strains: Mouse/SENCAR
Sex: Female
Route of Administration: Skin
Method: Other (one year skin tumor induction test)
Year: 1981 (paper received)
GLP: Not mentioned
Test substance: Benzoyl peroxide (CAS No. 94-36-0)
Test Conditions:
Exposure period: 53 weeks
Frequency of treatment: 2 times a week
Post exposure observation period:
Doses: 1, 10, 20, 40 mg of Benzoyl peroxide in 0.2 ml of acetone
Control group:
Yes, Concurrent vehicle
Dose applied

1) tumor promoting activity (Group 1 - 4) : single topical application of 10 nmole of DMBA in 0.2 ml of acetone. After one week, topical applications of various dose levels of benzoyl peroxide was applied twice weekly for 52 weeks.
2) tumor initiating activity (Group 6 - 9) : one topical application of various dose levels of benzoyl peroxide in 0.2 ml of acetone. After one week, 2 µg of TPA was applied twice weekly for 52 weeks.
3) Complete carcinogenic activity (Group 11 - 14) : topical applications of various dose levels of benzoyl peroxide in 0.2 ml of acetone twice weekly for 52 weeks
4) control (Group 5, 10, 15) : acetone only, 0.2 ml twice weekly for 52 weeks

Age at study initiation: 7 - 9 weeks
No. of animals: 30 animals/dose
clinical observations performed and frequency: number and incidence of papillomas and carcinomas were recorded weekly.

Results:

Although benzoyl peroxide is not a complete skin carcinogen or a skin tumor initiator, it is an effective promoter of both papillomas and squamous cell carcinomas. Even at a dose of 40 mg given twice weekly for 1 year, benzoyl peroxide was not effective as a complete carcinogen. Benzoyl peroxide did not show any tumor-initiating activity when it was applied once at various dose levels, with subsequent repetitive applications of the known promoter TPA. However, when benzoyl peroxide was applied topically twice weekly after initiation of tumors with DMBA, it proved to be an effective promoter with a reasonable dose-response relationship. As little as 1 mg given twice weekly produced a significant number of papillomas and carcinomas. The tumor response appeared to plateau at a dose level of 20 mg, with 79 percent of the mice developing papillomas (average of 5.2 papillomas per mouse at 30 weeks). At the same dose level, 43 percent of the mice developed squamous cell carcinomas at 52 weeks.
### Skin tumor induction of benzoyl peroxide in SENCAR mice

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg)</th>
<th>Mice Alive at 30 weeks</th>
<th>Papillomas/mouse at 30 weeks</th>
<th>Mice with papillomas at 30 weeks (%)</th>
<th>Mice with carcinomas at 52 weeks (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>29</td>
<td>0.8</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>28</td>
<td>3.8</td>
<td>72</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>27</td>
<td>5.2</td>
<td>79</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>24</td>
<td>5.4</td>
<td>85</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Acetone (only 0.2ml)</td>
<td>28</td>
<td>0.03</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>29</td>
<td>0.1</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>28</td>
<td>0.1</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>28</td>
<td>0.1</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>27</td>
<td>0.2</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Acetone (only 0.2ml)</td>
<td>29</td>
<td>0.2</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

Benzoyl peroxide promoted both papillomas and carcinomas when it was topically applied to mice after DMBA initiation. Benzoyl peroxide was inactive on the skin as a complete carcinogen or as a tumor initiator.

Reliability: (2) Reliable with restriction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of treatment</td>
<td>Oral- ad libitum; Subcutaneous-single injection/week; Dermal-6 times a week</td>
</tr>
<tr>
<td>Post exposure observation period</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Doses</td>
<td>Oral - 28, 280, 2,800 mg/kg diet; Subcutaneous - 120 mg/rat, 50 mg/mouse; 50 mg (50% suspension)</td>
</tr>
<tr>
<td>Control group</td>
<td>Yes</td>
</tr>
<tr>
<td>Concurrent no treatment, Concurrent vehicle</td>
<td></td>
</tr>
<tr>
<td>Test substance</td>
<td>Benzoyl peroxide, purity = unknown</td>
</tr>
<tr>
<td>Results</td>
<td>The overall tumor incidence was not significantly different between the experimental and control groups in rats or mice</td>
</tr>
<tr>
<td>Reliability</td>
<td>(2) Reliable with restriction</td>
</tr>
</tbody>
</table>

**Species/Strains**
- Mouse/SENCAR

**Sex**
- Female

**Route of Administration**
- Dermal

**Method**
- GLP

**Exposure period**
- Dermal - 100 weeks

**Frequency of treatment**
- 2 times a week

**Post exposure observation period**
- Not mentioned

**Doses**
- 0.1, 0.3, 0.6, 2.0 and 20 mg

**Control group**
- Benzoyl peroxide, purity = unknown

**Results**
- Benzoyl peroxide is a mouse skin promoter but was inactive as a complete carcinogen or as a tumor initiator.

**Reliability**
- (2) Reliable with restriction

**References**

**Species/Strains**
- Mouse/hr/hr Oslo strain and SENCAR

**Sex**
- Male/Female

**Route of Administration**
- Skin

**Method**
- GLP

**Exposure period**
- 52 Weeks

**Frequency of treatment**
- Twice a week

**Post exposure observation period**
- None

**Doses**
- 5% Benzoyl peroxide in a gel (Panoxyol)

**Control group**
- Yes
  - Concurrent vehicle, Historical
### Test substance
- Benzoyl peroxide, purity = unknown

### Results
- No induction of carcinoma

### Reliability
- (2) Reliable with restriction

### References
- Iversen, O.H., Skin Tumorigenesis and Carcinogenesis Studies with 7,12-dimethylbenzene[a]anthracene, ultraviolet Light, Benzoyl Peroxide (Panoxy gel 5 %) and Ointment Gel Carcinogenesis, 9 (5), 803 ~ 809, 1988

#### (f) Species/Strains
- Mouse/SENCAR

#### Sex
- Female

#### Route of Administration
- Skin

#### Method
- GLP: No data

#### Exposure period
- 20 Weeks

#### Frequency of treatment
- 2 times a week

#### Doses
- 20 mg of Benzoyl peroxide in 0.2 ml of acetone

#### Control group
- Yes

### Test substance
- Benzoyl peroxide, purity = unknown

### Results
- Benzoyl peroxide enhanced the progression of preexisting papillomas.

### Reliability
- (2) Reliable with restriction

### References

#### (g) Species/Strains
- Mouse/Uscd (Hr) stock albino

#### Sex
- No data

#### Route of Administration
- Skin

#### Method
- GLP: No data

#### Exposure period
- 70 Weeks

#### Frequency of treatment
- 5 times a week

#### Doses
- 5 % Benzoyl peroxide lotion in an aqueous vehicle

#### Control group
- Yes, Concurrent vehicle

### Test substance
- Benzoyl peroxide, purity = unknown

### Results
- Benzoyl peroxide did not act as skin tumor promoters under this condition in which croton oil promoted skin tumors following initiation by UV radiation.

### Reliability
- (2) Reliable with restriction

### References
- Epstein, J., Photocarcinogenesis Promotion Studies with Benzoyl Peroxide and Croton Oil, J. Investigative Dermatology, 91(2), 114 ~ 116, 1988
(h) Species/Strains: Hamster/Pathogen-free Syrian golden  
Sex: Male  
Route of Administration: Skin  
Method: GLP: No data  
Exposure period: 64 weeks  
Frequency of treatment: 3 times a week  
Post exposure observation period:  
Doses: 80, 160 mg of benzoyl peroxide in 1 ml of acetone  
Control group: Yes, Concurrent vehicle  
Test substance: Benzoyl peroxide, purity = unknown  
Results: Benzoyl peroxide is able to promote the formation of dermally located Melanotic tumors.  
Reliability: (2) Reliable with restriction  
References: Schweizer, J., Loehrke, H., Edler, L. and Goerttler, K., Benzoyl Peroxide promotes the Formation of Melanotic Tumors in the Skin of 7, 12-dimethylbenz[a]anthracene-initiated Syrian Golden Hamsters, Carcinogenesis, 8 (3), 479 ~ 482, 1987

(i) Species/Strains: Hamster/Syrian golden  
Sex: Male/Female  
Route of Administration: Skin (painting of the hamster buccal pouch)  
Method: GLP: No data  
Exposure period: 6 weeks  
Frequency of treatment: 3 times a week  
Post exposure observation period: none  
Doses: 40 % solution of Benzoyl peroxide in acetone (equivalent to 20 mg of benzoyl Peroxide per single brush application)  
Control group: Yes  
Concurrent no treatment, Concurrent vehicle  
Test substance: Benzoyl peroxide, purity = unknown  
Results: Benzoyl peroxide is noncarcinogenic, but it in a 40 % solution of benzoyl peroxide in acetone acts as a promoter after initiation with a subthreshold dose of 0.1 % DMBA in oil.  
Reliability: (2) Reliable with restriction  

(j) Species/Strains: Mouse/SENCAR  
Sex: Female  
Route of Administration: Skin  
Method: GLP: No data
<table>
<thead>
<tr>
<th>Exposure period</th>
<th>51 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of treatment</td>
<td>2 times a week</td>
</tr>
<tr>
<td>Post exposure observation period</td>
<td>none</td>
</tr>
<tr>
<td>Doses</td>
<td>10 mg of benzoyl peroxide in 0.2 ml of acetone (equivalent to 2mg benzoyl Peroxide)</td>
</tr>
<tr>
<td>Control group</td>
<td>Yes, Concurrent vehicle</td>
</tr>
<tr>
<td>Test substance</td>
<td>Benzoyl peroxide, purity = unknown</td>
</tr>
<tr>
<td>Results</td>
<td>Benzoyl peroxide is a potent promoter and has possible carcinogenic action.</td>
</tr>
<tr>
<td>Reliability</td>
<td>(2) Reliable with restriction</td>
</tr>
</tbody>
</table>

(k)
| Species/Strains | Mouse/Swiss Albino |
| Sex | Female |
| Route of Administration | Skin |
| Method | |
| GLP | No data |
| Exposure period | 46 weeks |
| Frequency of treatment | 2 times a week |
| Post exposure observation period | |
| Doses | 20 mg/300 µl |
| Control group | Yes, Concurrent no treatment |
| Test substance | Benzoyl peroxide, purity = unknown |
| Results | Iron overload augments Benzoyl peroxide-mediated tumor promotion in 7,12-dimethylbenzen[a]anthracene (DMBA)-initiated mouse skin. |
| Reliability | (2) Reliable with restriction |
| References | Rezazadeh, H., and Athar, M., Effect of Iron Overload on the Benzoyl Peroxide Mediated Tumor Promotion in Mouse Skin, Cancer Letters, 126, 135 ~ 142, 1998 |

(l)
| Sex | Male/Female |
| Route of Administration | Dermal |
| Method | |
| GLP | No data |
| Exposure period | 164 days in Car-S (Carcinogenesis-susceptible) strain, 253 days in Car-R (Carcinogenesis-resistant) strain |
| Frequency of treatment | 2 times a week |
| Post exposure observation period | Promotion by exposure with chemicals was continued as long as the increase of papilloma number was a linear function of time, at least in the most susceptible line. |
| Doses | 3.7, 7.5 and 15.0 mg Benzoyl peroxide |
OECD SIDS  BENZOYL PEROXIDE

5. TOXICITY  ID 94-36-0

DATE: AUGUST 2002

Control group : Yes
Test substance : Benzoyl peroxide, purity = unknown
Test condition : Mouse/Car-R and Car-S mice produced by 16 consecutive generation of bi-directional selective breeding at the ENEA (Rome, Italy)

Results : Benzoyl peroxide is also able to promote carcinoma development in Car-S mice
Reliability : (2) Reliable with restriction

Test type : Tumor promotion using human bronchial epithelial cell culture
Species/Strains : Normal human bronchial epithelial cell
Method : GLP : No data
Exposure period : 6 hours exposed to Benzoyl peroxide and followed by 7 - 9 days of incubation for the tests of cell proliferation and morphological changes; one hour for DNA damage test.
Frequency of dosing : single dosing
Number if replicates : duplicate dishes or well were measured and each experiment was repeated 3 times for the tests of cell proliferation and morphological changes.
Doses : 0.003, 0.03 and 0.3 mM in cell proliferation test ; 0.056 mM in morphological Change test ; 0.1 mM in DNA damage test
Control group : Yes
Concurrent no treatment
Test substance : Benzoyl peroxide, purity = unknown
Results : The 50 % of control concentration (growth rate) for the 6-hr exposure was found to be 0.065 mM Benzoyl peroxide ; Benzoyl peroxide–exposed cells were smaller than controls (median cell planar area, 620 sq µm versus 1,150 sq µm) ; Benzoyl peroxide caused detectable amounts of both single strand breaks and DNA-protein cross-links.
Reliability : (2) Reliable with restriction

5.8  TOXICITY TO REPRODUCTION
(a) Preferred Result

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species/strains</td>
<td>Rat/Sprague-Dawley</td>
</tr>
<tr>
<td>Sex</td>
<td>Male/Female</td>
</tr>
<tr>
<td>Method</td>
<td>Combined Repeated Dose and Reproduction/Developmental Toxicity Screening Test OECD TG 422</td>
</tr>
<tr>
<td>Year</td>
<td>2001</td>
</tr>
<tr>
<td>GLP</td>
<td>Yes</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral (gavage)</td>
</tr>
<tr>
<td>Dose level</td>
<td>0, 250, 500, 1,000 mg/kg b.w/day</td>
</tr>
<tr>
<td>Exposure period</td>
<td>Male : 29 days, female : from 2 weeks before mating to the day 3 of lactation</td>
</tr>
<tr>
<td>Frequency of treatment</td>
<td>Daily</td>
</tr>
<tr>
<td>Control group</td>
<td>(-) Concurrent vehicle (+) Cyclophosphamide (4.5 mg/kg/day)</td>
</tr>
<tr>
<td>Post exposure</td>
<td>1 day</td>
</tr>
<tr>
<td>Premating exposure period</td>
<td>14 days</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>Dunnett’s multiple comparison test</td>
</tr>
<tr>
<td>Test substance</td>
<td>Source : SIGMA, purity : 70 %</td>
</tr>
<tr>
<td>Test condition</td>
<td>- Test Subjects Age : 7 week old for male and female</td>
</tr>
<tr>
<td></td>
<td>- Weight at study initiation : 323.38 - 356.63 g for males, 212.21 - 237.18 g for females</td>
</tr>
<tr>
<td></td>
<td>- No. of animals : 10 animals/sex/dose (5 animals/sex/positive control)</td>
</tr>
<tr>
<td></td>
<td>- Vehicle : Corn oil</td>
</tr>
</tbody>
</table>
- Dosing schedule: males – premating period (2 weeks) and mating period; 29 days females – premating period (2 weeks), mating, pregnant and lactation period; 41 ~ 51 days
- Mating procedures: M/F ratios per cage; 1/1, proof of pregnancy; sperm detection in vagina
- Clinical observations performed and frequency: General condition was observed once a day. Body weight and food consumption of pregnant animals were determined on the day 1, 7, 14, 20 of pregnancy and the day 1, 3 of lactation. Haematology and biochemistry for males only at the time of necropsy after 28 days of chemical exposure
- Sperm examination: concentration, motility, morphology was observed at necropsy.
- Parameters assessed during study P and F1: copulation index (matings/pairs x 100), fertility index (Pregnancies/matings x 100), gestation index (live litters/pregnancies x 100), viability index (No. of live offspring at day1 or day3/No. of live offspring at birth × 100), body weight of live pups (on day 0 and 4), No. of corpora lutea, No. of female mated, abortion, premature birth, gestation period, sex ratio (Total No. of male pups/Total No. of female pups)

<table>
<thead>
<tr>
<th>NOAEL parental</th>
<th>NOAEL F1 Offspring</th>
<th>NOAEL F2 Offspring</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>= 500 mg/kg/day</td>
<td>= 500 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>= N/A</td>
<td>= N/A</td>
<td></td>
</tr>
</tbody>
</table>

**Results**

Significant decrease in absolute and relative weights of left testes and relative wt of epididymis was observed in male animals exposed to 1000 mg/kg (p < 0.05). Severe testis atrophy was seen in the highest exposure male group but these changes were not seen in recovery animals. The pups which exposure to highest levels of benzoyl peroxide showed significant decrease in body wt. Gain (p < 0.01). There was no significant difference between experimental and control groups in the precoital time, copulation, fertility and gestation rate.
<table>
<thead>
<tr>
<th>DOSE (mg/kg)</th>
<th>0</th>
<th>250</th>
<th>500</th>
<th>1000</th>
<th>Cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of mated males</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Copulation index (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100 (5/5)</td>
</tr>
<tr>
<td>Fertility index (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>90 (9/10)</td>
<td>100 (5/5)</td>
</tr>
<tr>
<td>No. of mated females</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Copulation index (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100 (5/5)</td>
</tr>
<tr>
<td>Fertility index (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>90 (9/10)</td>
<td>100 (5/5)</td>
</tr>
<tr>
<td>Gestation index (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>40 (2/5)</td>
</tr>
<tr>
<td>No. of dams</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>No. of corpora lutea</td>
<td>169</td>
<td>182</td>
<td>171</td>
<td>157</td>
<td>90</td>
</tr>
<tr>
<td>Mean±S.D</td>
<td>16.9±4.1</td>
<td>18.2±2.3</td>
<td>17.1±1.9</td>
<td>17.4±2.5</td>
<td>18±1.9</td>
</tr>
<tr>
<td>No. of implantations</td>
<td>150</td>
<td>150</td>
<td>161</td>
<td>136</td>
<td>81</td>
</tr>
<tr>
<td>Mean±S.D</td>
<td>15.0±1.8</td>
<td>15.0±2.9</td>
<td>16.1±1.9</td>
<td>15.1±2.1</td>
<td>16.2±1.6</td>
</tr>
<tr>
<td>Mean % preimplantation loss</td>
<td>9</td>
<td>16.1</td>
<td>5.8</td>
<td>12.9</td>
<td>9.9</td>
</tr>
<tr>
<td>No. of embryo/fetal death</td>
<td>10/3</td>
<td>9/3</td>
<td>7/3</td>
<td>3/0</td>
<td>54/9</td>
</tr>
<tr>
<td>No. of live pups born</td>
<td>Mean±S.D</td>
<td>13.7±2.7</td>
<td>13.8±2.5</td>
<td>15.1±2.1</td>
<td>14.8±2.2</td>
</tr>
<tr>
<td>Mean pregnancy period (day)</td>
<td>20.4</td>
<td>20.8</td>
<td>20.6</td>
<td>20.8</td>
<td>22</td>
</tr>
<tr>
<td>Viability index on day 1 pp</td>
<td>97.5</td>
<td>98.1</td>
<td>100</td>
<td>100</td>
<td>53.3*</td>
</tr>
<tr>
<td>Viability index on day 3 pp</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>90*</td>
</tr>
<tr>
<td>Body weights of pups (g)</td>
<td>Male 1 DAY</td>
<td>6.88±0.53</td>
<td>7.22±0.81</td>
<td>5.91±0.64</td>
<td>6.72±0.79</td>
</tr>
<tr>
<td>3 DAY</td>
<td>8.93±0.91</td>
<td>9.10±1.03</td>
<td>8.69±0.79</td>
<td>8.12±1.01*</td>
<td>7.16±0.88</td>
</tr>
<tr>
<td>Female 1 DAY</td>
<td>5.51±0.53</td>
<td>5.93±0.76*</td>
<td>5.73±0.59</td>
<td>5.21±0.79</td>
<td>4.33±0.74</td>
</tr>
<tr>
<td>3 DAY</td>
<td>8.60±0.99</td>
<td>8.79±1.03</td>
<td>8.48±0.89</td>
<td>7.49±1.03*</td>
<td>5.48±0.89</td>
</tr>
<tr>
<td>Precoital time</td>
<td>Mean±S.D (day)</td>
<td>2.2±1.2</td>
<td>3.2±1.3</td>
<td>2.4±1.2</td>
<td>2.3±1.2</td>
</tr>
</tbody>
</table>
- Mortality and day of death: No deaths were found in all animals including control groups.
- Body weight: Body weight gains were slightly increased (approximately 7% more than controls) in female recovery group exposed to 1,000 mg/kg only after 29 days. No significant body weight changes were observed in all treatment animals except highest dose recovery group. Low body weight gain of pups showed in 1,000 mg/kg dose.
- Food/water consumption: The mean food consumption of 1,000 mg/kg was significantly increased at first and fourth weeks of chemical exposure in male. No other treatment groups were showed abnormal food consumption.
- Organ weight changes: Significant decrease in absolute and relative weights of left testes and relative wt of epididymis were observed in 1000 mg/kg exposure group, however these changes were not seen in recovery group.
- Histopathology incidence and severity: In the 1,000 mg/kg treatment group, testis degenerations were observed microscopically and these pathosis were mainly morphological change in sperm cell such as apoptosis, cellular swelling and multinucleated giant cell. In the female reproductive organ, slight affects were observed in uterus exposed to 1,000 mg/kg.
- Grossly visible abnormalities, external, soft tissue and skeletal abnormalities.

In the 1000 mg/kg dose group, the incidence of runts was significantly higher than control group.

<table>
<thead>
<tr>
<th>Treatment (mg/kg/day)</th>
<th>0</th>
<th>250</th>
<th>500</th>
<th>1000</th>
<th>Cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. with major abnormalities</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean % of pups examined</td>
<td>0</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No. of females affected</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No. with minor abnormalities</td>
<td>20</td>
<td>20</td>
<td>18</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>Mean % of pups examined</td>
<td>14.2</td>
<td>12.4</td>
<td>11.5</td>
<td>41.4*</td>
<td>100.0*</td>
</tr>
<tr>
<td>No. of females affected</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>No. with variants</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Statistically significant difference from control group (p < 0.01)

Conclusion: Significant toxic effect was found in P0 and F1 exposed to 1,000 mg/kg. This result indicated that the NOAEL for both reproduction and developmental toxicity was 500 mg/kg b.w/day.

Reliability: (1) Reliable without restriction


5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

(a) Preferred Result
Species/strains : Rat/Sprague-Dawley
Sex : Male/Female
Route of administration : Oral (gavage)

Method : Combined Repeated Dose and Reproduction/Developmental Toxicity Screening Test OECD TG 422
Year : 2001
GLP : Yes
Dose level : 0, 250, 500, 1,000 mg/kg b.w/day
Exposure period : Male : 29 days, female : from 2 weeks before mating to the day 3 of lactation
Frequency of treatment : Daily
Control group : (-) Concurrent vehicle (+) Cyclophosphamide (4.5 mg/kg/day)
Post exposure : 1 day
Statistical methods : Dunnett’s multiple comparison test
NOAEL for developmental : = 500 mg/kg/day
Test substance : Benzoyl peroxide, Source-SIGMA, purity = 70 %
Results : The body weight gain of pups on the day 3 after birth decreased at 1,000 mg/kg. Benzoyl peroxide has adverse effects on development of pups with high birthrate of runt at 1000 mg/kg dose level. No significant differences appeared between the treatment and control group in any other observation.

Reliability : (1) Reliable without restriction
References : National Institute of Environmental Research (NIER), Combined Repeated Dose Toxicity with the Reproduction/Developmental Toxicity Screening Testing of Benzoyl peroxide in Rats (Report No.P049, tested by LGCI), 2001

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities
No data

B. Toxicodynamics, toxicokinetics
(a) Type: Metabolism
Remarks: The transepidermal penetration and metabolic disposition of \(^{14}\text{C}\)-benzoyl peroxide were assessed \textit{in vitro} (excised human skin) and \textit{in vivo} (rhesus monkey). \textit{In vitro}, the benzoyl peroxide penetrated into the skin, through the stratum corneum or the follicular openings, or both, and was recovered on the dermal side as benzoic acid. \textit{In vivo}, benzoic acid was recovered from urine in amounts equivalent to 45 \% and 98 \% of the radiolabel following topical and i.m. administration, respectively, of \(^{14}\text{C}\)-benzoyl peroxide. Authors concluded that benzoyl peroxide penetrates as such into the skin layers and is converted therein to benzoic acid, which, in turn is absorbed into the systemic circulation. Renal clearance of the metabolite is sufficiently rapid as to preclude its hepatic conjugation with glycine, since following topical administration to rhesus monkeys, no hippuric acid was found in the urine, as could have been expected had a significant amount of benzoic acid passed through the liver.

Reliability: (2) Reliable with restriction

(b) Type: Metabolism
Remarks: The effect of drug concentrations of 2.5, 5 and 10 \% upon the transepidermal penetration of \(^{14}\text{C}\)-benzoyl peroxide in a lotion vehicle was assessed in excised human skin and \textit{in vivo} in the rhesus monkey. \textit{In vitro}, penetration of benzoyl peroxide was dose-dependent, both as to rate and to amount, as measured by hourly recovery of the metabolite, benzoic acid, from the dermal side of the model. \textit{In vivo}, the higher the concentration of benzoyl peroxide absorbed was excreted rapidly in urine as benzoic acid; no hippuric acid was detected at any time. Authors concluded that the transepidermal delivery of benzoyl peroxide, but not its metabolic disposition, is concentration-dependent, and the renal clearance of the systemically absorbed drug is so rapid that it precludes passage through the liver – therefore, no systemic toxicity due to the substance accumulation can be expected.

Reliability: (2) Reliable with restriction
OECD SIDS

5. TOXICITY

ID 94-36-0

DATE: AUGUST 2002

(c) Type: Metabolism

Remarks: The greatest amount of penetrating BP (9 to 14 % of the applied
dose) was found in the horny layer, which forms a reservoir and
where biotransformations were reduced. Small quantities of BP
diffused toward the epidermis down to the deeper dermis, where
benzoic acid represented 74 % of the radioactivity. Distribution
gradients of the radioactivity and conversion rates to benzoic acid
were stable between 3 and 24 hours of application in all parts of the
skin. This result showed that diffusion of BP from the vehicle was
in balance with the dissociation processes and the blood resorption
as benzoic acid throughout the experiment.

Reliability: (2) Reliable with restriction

References: Wepierre, J., Corroller, M. and Didry, J. R., Distribution and
Dissociation of Benzoyl Peroxide in Cutaneous Tissue after
Application on Skin in the Hairless Rat, International Journal of
Cosmetic Science 8, 97-104, 1986

(d) Type: Metabolism

Remarks: The percutaneous penetration and the metabolism of benzoil
peroxide (BPO) were assessed in vitro on human skin and in vivo on
5 patients with leg ulcers. The BPO in vitro absorbed by the skin
was converted to benzoic acid preferably in the dermis. The portion
penetrated through the skin was benzoic acid only. Also in patients
treated with BPO, no BPO could be detected in the serum. These
findings show that BPO as such is absorbed by the skin, but is
systemically absorbed only after the metabolisation to benzoic acid.
Therefore, a systemic-toxic effect in local therapy with BPO can be
excluded.

Reliability: (2) Reliable with restriction

References: Morsch, B. and Holzmann, H., Untersuchungen zur perkutanen
Resorption von Benzoyl peroxid, Arzneim.-Forsch./Drug Res., 32
(1), Nr.3, 1982

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(a) Type: Epidemiological case-control study (using medical records)

Results: There is no evidence that acne suffers (who may have used
benzoyl peroxide without prescription) or individuals prescribed
benzoyl peroxide, have an increased risk of malignant melanoma.

Reliability: (2) Reliable with restriction

Melanoma, Benzoyl Peroxide and Acne: A Pilot Epidemiological
Case-Control Investigation, British J, Derm., 118, 239-242, 1988
(b)
Type: Epidemiological case-control study (using cancer registry)
Results: No statistically significant association between the prescribed use of benzoyl peroxide and skin cancer was found in 931 cases and 7630 controls.
Remarks: Limitations were that the nonprescription use of benzoyl peroxide by cases and controls was not considered, and the Drug Prescription Plan records did not cover the full period during which benzoyl peroxide containing medications were available.
Reliability: (2) Reliable with restriction
References: To. T, Hogan D, Wilson, E, Miller, A, Benzoyl peroxide and facial skin cancer, Am. J. Epidemiol., 134:772

(c)
Type: Epidemiological case-control study (using cancer registry)
Results: No statistically significant association was found between the use of acne medications containing benzoyl peroxide and skin cancer of the head and neck in 964 cases and 3856 controls. Also acne was not associated with increased risk of skin cancer.
Remarks: This study covered all prescription and nonprescription use of benzoyl peroxide containing acne medications.
Reliability: (2) Reliable with restriction

(d)
Type: Contact dermatitis
Results: Two cases were reported of allergic contact dermatitis to acne preparations containing benzoyl peroxide. Both patients had positive patch tests to 5% Benzoyl peroxide in petrolatum while 40 of 41 control patients had no reaction.
Reliability: (2) Reliable with restriction

(e)
Type: Skin irritation
Results: Two cases were reported in which topical application of benzoyl peroxide resulted in an unusual pattern of reticulate hyperpigmentation of the skin, most likely as a sequela of an irritant contact dermatitis.
Reliability: (2) Reliable with restriction
(f) Type: Skin allergy
Results: After 4 months of use, a patient with acne developed allergic contact urticaria to 5% topical benzoyl peroxide. The observed symptoms were the increased hive-like lesions occurred about 20-30 minutes after topical application.
Reliability: (2) Reliable with restriction
References: Tkach, J.R., Allergic Contact Urticaria to Benzoyl Peroxide, Cutis 29, 187 ~ 188, 1982

(g) Type: Allergic contact dermatitis
Results: Benzoyl peroxide is an irritant but has only infrequently been reported as a sensitizer. Non-medical exposures include its use as a component of acrylates and as a bleach and preservative for flour and oil. As such it has caused allergic contact dermatitis in patients in whom it was present in an acrylic bone cement and in dental acrylates. In the occupational setting it has produced allergic contact dermatitis in bakers.
Reliability: (2) Reliable with restriction
References: Mosby Year Book, Contact and Occupational Dermatology, St. Louis, MO/Marks, J.G., V.A. DeLeo, 164 ~ 164, 1992

(h) Type: Sensitization
Results: The investigation of patients with leg ulcers, treated with a concentrated benzoyl peroxide solution, revealed a sensitization to the substance in nearly half of the probands. Therefore and because of the probable promotion of neoplastic epidermal proliferation, benzoyl peroxide-containing solutions
Reliability: (2) Reliable with restriction
References: Von Bahmer F.A., A. Schulze-Dirks und H.Zaun, Sensibilisierende Wirkung einer fur die behandlung des Ulcus cruris verwendeten 20% igen Benzoylperoxid-Zubereitung, Dermatosen, 32, Nr 1, 21 ~ 24, 1984

(i) Type: Skin irritation
Results: 63 patients with papulopustular acne had been treated by mean of 10% benzoyl peroxide gel daily twice for 8 weeks at times of little insolation. Only in a few patients transient redness, burning, dryness and scaling occurred. Allergic sensitization was not observed.
Reliability: (2) Reliable with restriction
(j) Type: Patch test
Results: A 23 years old woman with cystic acne was treated with a 5% topical solution (Peroxiben 5% gel). After 7 days she noted intolerance with redness and scaling and severe itching. She was patch tested with a standard series, benzoyl peroxide 1% pet., vehicle and wood tars. The result showed a strong positive response. Another recent preparation of 1% benzoyl peroxide in neutral gel was also positive.
Remarks: There have been many attempts to explain contact allergy to benzoyl peroxide in patients with acne is rather uncommon compared to its capacity to sensitize. The pilosebaceous unit may generate an intermediate metabolite, the allergen being a metabolite seldom formed in facial skin, or perhaps degrade the drug more rapidly. Sweating could dilute the compound and wash away the product. Treatment without occlusive techniques would minimize the likelihood of sensitization. The presence of inflammation in acne could interfere with the induction of an allergic response. Several other reports have suggested that in many cases, the symptoms of sensitization are mild and they may be regarded merely as irritants; thus a patch test is not performed.
Reliability: (2) Reliable with restriction

(k) Type: Patch test
Results: A 25 years old man had been an electrician for the last 4 years. Benzoyl peroxide may have acted as a contactant allergen after plastic particles became airborne when sawing plastic material, or perhaps after being melted during soldering. A positive patch test to benzoyl peroxide was obtained at the recommended concentration of 1%.
Remarks: Allergic contact dermatitis due to benzoyl peroxide may develop as a consequence of occupational exposure, affecting mainly workers in the electronics and plastics (epoxy resins and catalysts) industries, electricians, dentists, bakers, and laboratory technicians. Airborne allergic contact dermatitis from this agent has also been reported due to molten candle wax. When benzoyl peroxide is used for therapeutic purposes, leg ulcers are more prone to develop sensitization than acneic skin.
Reliability: (2) Reliable with restriction
References: Santiago, Q., J.M., Olaguibel, B.E., Garcia and Tabar, A.I., Occupational airborne contact dermatitis due to benzoyl peroxide, Contact Dermatitis. 29, 165 ~ 166, 1993
OECD SIDS

BENZOYL PEROXIDE

5. TOXICITY

DATE: AUGUST 2002

(1)

Type: Patch test
Results: Positive
Remarks: 272 children up to the age of 14 years were patch tested during 10 years period. An unusual feature was the finding of 10 patients patch test positive to benzoyl peroxide 1 % pet. The positivities to this allergen were classified as relevant.

Reliability: (2) Reliable with restriction
References: Sevila, A., Romaguera, C., Vilaplana, J., Botella, R., Contact dermatitis in children, Contact Dermatitis, 30, 292 ~ 294, 1994

(m)

Type: Patch test
Results: 791 patients including 59 dental technician were tested with the denture material series. Benzoyl peroxide ranked 2nd in patch test positivity. The result in dental technicians showed that positive reaction to benzoyl peroxide were observed in 9.8 % of patients. Positive and questionable reactions to benzoyl peroxide were observed in 37 and 57 other patients respectively.

Remarks: Reactions were more frequent in dental technicians, who might be exposed to benzoyl peroxide in working environment.

Reliability: (2) Reliable with restriction
References: Gebhardt, M., Geier, J., Evaluation of patch test results with denture material series, Contact Dermatitis, 34, 191 ~ 195, 1996

(n)

Type: Patch test
Results: Positive
Remarks: It is reported that a 62 year-old man with total hip prosthesis developed a recurrent sterile fistula and loosening of his prosthesis due to allergy to the bone cement component benzoyl peroxide.

Reliability: (2) Reliable with restriction

(o)

Type: Patch test
Results: Positive
Remarks: For investigation of the sensitizing activity, several series of patients were patch tested. 11 subjects were tested with 1 % benzoyl peroxide only; 9 were positive. 30 patients were tested with 1 %, 0.5 % and 0.25 %. In 16 cases, all levels produced positive reactions; only 8 patients in this group showed no positive reaction. 31 of 41 patients treated, who had been negative before treatment, showed positive reaction, at least to benzoyl peroxide 1 %.

Reliability: (2) Reliable with restriction
References: Agathos, M., Bandmann, H.J., Benzoyl peroxide contact allergy in leg ulcer patients, Contact Dermatitis, 17, 316 ~ 317, 1984
Type: Patch test

Results: Positive

Remarks: Benzoyl peroxide patch testing was performed on 60 young adults who had participated in a double-blind acne study. 25% of those who had used a benzoyl peroxide product showed reactivity of +1 or greater.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>+2</th>
<th>+1</th>
<th>±</th>
<th>0</th>
<th>+2</th>
<th>+1</th>
<th>±</th>
<th>0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Benzoyl-peroxide</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

The positive patch tests did not correlate with acne treatment responses. 2 of 44 individuals in the acne study group developed clinical allergy and had dramatically positive patch tests, while the majority of individuals with positive patch tests could use products containing benzoyl peroxide daily without significant adverse effects.

Reliability: (2) Reliable with restriction

References:
Rietschel, R.L. and Duncan, S.H., Benzoyl peroxide reactions in an acne study group, Contact Dermatitis, 8, 323 ~ 326, 1982

Type: Patch test

Results: Positive (allergic contact dermatitis)

Remarks: A 60 years old former joiner having served for about 15 yr as a sacristan suffered from eczema on his face, neck and hands. He had had ‘allergy of face’ at the age of 22 yrs, when busy staining veneer with a special was preparation. There were no reactions to airborne allergens on prick testing. Patch testing was performed on the upper neck with candle waxes and burned candle wicks. Benzoyl peroxide gave a strong crescendo reaction at 0.5 % pet. All candles lit in cathedral were made from a 9:1 mix. of paraffin and beeswax with cotton wicks. Wax bleaching with benzoyl peroxide and shaping candles were performed for several hours.

Reliability: (2) Reliable with restriction

References:
Bonnekoh, B. and Merk, H.F., Airborne allergic contact dermatitis from benzoyl peroxide as a bleaching agent of candle wax, Contact Dermatitis, 24, 367 ~ 368, 1984
6. REFERENCES

Agathos, M., Bandmann, H.J., Benzoyl peroxide contact allergy in leg ulcer patients, Contact Dermatitis, 17, 316~317, 1984

Akzo Nobel, The Netherlands, Effects of the Wate - Accomodated Fraction of Lucidol on the Growth of the Freshwater Green Alga Pseudokirchneriella subcapitata, 1989

Aldrich, Catalog handbook of fine chemicals, Milwaukee, WI, Aldrich chem. Co., 163, 2000~2001

Autoxidized Squalene and Linoleic Acid, and of Simpler peroxides, in Relation to Toxicity of Radiation, Biochem. J. 67, 551~558, 1957

Baker, J., Material Safety Data Sheet (MSDS) Number, B1831, Effective Date, 11/02/01 by Mallinckrodt chemicals


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Bonnekoh, B. and Merk, H.F., Airborne allergic contact dermatitis from benzoyl peroxide as a bleaching agent of candle wax, Contact Dermatitis, 24, 367~368,1984


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Consumer Healthcare Products Association (CHPA), Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice, Covance study No.6711-100, Vol 1 of 7, 2001

Dillon, D., Combes, R. and Zeiger, E., The Effectiveness of Salmonella strains TA100, TA102 and
6. REFERENCES

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