NIOSH Skin Notation Profiles

Bisphenol A (BPA)
NIOSH Skin Notation (SK) Profile

Bisphenol A (BPA)
[CAS No. 80–05–7]
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Foreword

As the largest organ of the body, the skin performs multiple critical functions, such as serving as the primary barrier to the external environment. For this reason, the skin is often exposed to potentially hazardous agents, including chemicals, which may contribute to the onset of a spectrum of adverse health effects ranging from localized damage (e.g., irritant contact dermatitis and corrosion) to induction of immune-mediated responses (e.g., allergic contact dermatitis and pulmonary responses), or systemic toxicity (e.g., neurotoxicity and hepatotoxicity). Understanding the hazards related to skin contact with chemicals is a critical component of modern occupational safety and health programs.

In 2009, the National Institute for Occupational Safety and Health (NIOSH) published Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations [NIOSH 2009–147]. This document provides the scientific rationale and framework for the assignment of multiple hazard-specific skin notations (SK) that clearly distinguish between the systemic effects, direct (localized) effects, and immune-mediated responses caused by skin contact with chemicals. The key step within assignment of the hazard-specific SK is the determination of a substance’s hazard potential, or its potential for causing adverse health effects as a result of skin exposure. This determination entails a health hazard identification process that involves use of the following:

- Scientific data on the physicochemical properties of a chemical
- Data on human exposures and health effects
- Empirical data from in vivo and in vitro laboratory testing
- Computational techniques, including predictive algorithms and mathematical models that describe a selected process (e.g., skin permeation) by means of analytical or numerical methods.

This Skin Notation Profile provides the SK assignment and supportive data for bisphenol A (BPA; CAS No. 80–05–7). In particular, this document evaluates and summarizes the literature describing the substance’s hazard potential and its assessment according to the scientific rationale and framework outlined in CIB 61. In meeting this objective, this Skin Notation Profile intends to inform the audience—mostly occupational health practitioners, researchers, policy- and decision-makers, employers, and workers in potentially hazardous workplaces—so that improved risk-management practices may be developed to better protect workers from the risks of skin contact with the chemical of interest.

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**Abbreviations**

- **ACGIH**: American Conference of Governmental Industrial Hygienists
- **ATSDR**: Agency for Toxic Substances and Disease Registry
- **BPA**: bisphenol A
- **CIB**: Current Intelligence Bulletin
- **cm²**: squared centimeter(s)
- **cm/hr**: centimeter(s) per hour
- **cm/s**: centimeter(s) per second
- **DEREK™**: Deductive Estimation of Risk from Existing Knowledge
- **DIR**: skin notation indicating the potential for direct effects to the skin following contact with a chemical
- **EC**: European Commission
- **GHS**: Globally Harmonized System of Classification and Labeling of Chemicals
- **GPMT**: guinea pig maximization test
- **IARC**: International Agency for Research on Cancer
- **IMDS**: Integrated Model for the Differentiation of Skin reactions
- **(IRR)**: subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
- **Kaq**: coefficient in the watery epidermal layer
- **Kp**: skin permeation coefficient
- **Kpol**: coefficient in the protein fraction of the stratum corneum
- **Kpsc**: permeation coefficient in the lipid fraction of the stratum corneum
- **LD₅₀**: dose resulting in 50% mortality in the exposed population
- **LD₉₀**: dermal lethal dose
- **log K OW**: base-10 logarithm of a substance’s octanol–water partition
- **M**: molarity
- **m³**: cubic meter(s)
- **mg**: milligram(s)
- **mg/cm²/hr**: milligram(s) per square centimeter per hour
- **mg/kg**: milligram(s) per kilogram body weight
- **mg/m³**: milligram(s) per cubic meter
- **mL**: milliliter(s)
- **mL/kg**: milliliter(s) per kilogram body weight
- **MW**: molecular weight
- **NIOSH**: National Institute for Occupational Safety and Health
- **NTP**: National Toxicology Program
- **OEL**: occupational exposure limit
OSHA  Occupational Safety and Health Administration
ppm  parts per million
REL  recommended exposure limit
RF  retention factor
SEN  skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI ratio  ratio of skin dose to inhalation dose
SK  skin notation
$_{S_{W}}$  solubility
SYS  skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA  United States Environmental Protection Agency
µg  microgram(s)
µg/mL  microgram(s) per milliliter
Glossary

Absorption—The transport of a chemical from the outer surface of the skin into both the skin and systemic circulation (including penetration, permeation, and resorption).

Acute exposure—Contact with a chemical that occurs once or for only a short period of time.

Cancer—Any one of a group of diseases that occurs when cells in the body become abnormal and grow or multiply out of control.

Contaminant—A chemical that is (1) unintentionally present within a neat substance or mixture at a concentration less than 1.0% or (2) recognized as a potential carcinogen and present within a neat substance or mixture at a concentration less than 0.1%.

Cutaneous (or percutaneous)—Referring to the skin (or through the skin).

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

Direct effects—Localized, non-immune-mediated adverse health effects on the skin, including corrosion, primary irritation, changes in skin pigmentation, and reduction/disruption of the skin barrier integrity, occurring at or near the point of contact with chemicals.

Immune-mediated responses—Responses mediated by the immune system, including allergic responses.

Sensitization—A specific immune-mediated response that develops following exposure to a chemical, which, upon re-exposure, can lead to allergic contact dermatitis (ACD) or other immune-mediated diseases such as asthma, depending on the site and route of re-exposure.

Substance—A chemical.

Systemic effects—Systemic toxicity associated with skin absorption of chemicals after exposure of the skin.
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1 Introduction

1.1 General Substance Information

**Chemical:** Bisphenol A (BPA)

**CAS No:** 80–05–7

**Synonyms:**

BPA; 4,4′-(1-Methylethylidene)biphenol; 4,4′-(propan-2-ylidene)di-
phenol; p,p′-isopropylidenebisphenol; 4,4′-isopropylidenediphenol;
2,2-bis(4-hydroxyphenyl)propane

**Molecular weight (MW):** 228.29

**Molecular formula:** C₁₅H₁₆O₂

**Structural formula:**

```
CH₃
HO
CH₃
HO
CH₂
```

**Uses:**

Bisphenol A (BPA) is a high-
production-volume (HPV) chemical
used in the manufacturing of epoxy
resins, plastics, and flame retardants
[NTP-CERHR 2007].

1.2 Purpose

This Skin Notation Profile presents (1) a brief summary of technical data associated with skin contact with BPA and (2) the rationale behind the hazard-specific skin notation (SK) assignment for BPA. The SK assignment is based on the scientific rationale and logic outlined in the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009]. The summarized information and health hazard assessment are limited to an evaluation of the potential health effects of dermal exposure to BPA. A literature search was conducted through July 2010 to identify information on BPA, including but not limited to data relating to its toxicokinetics, acute toxicity, repeated-dose systemic toxicity, carcinogenicity, biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity), irritation, and sensitization. Information was considered from studies of humans, animals, or appropriate modeling systems that are relevant to assessing the effects of dermal exposure to BPA.

1.3 Overview of SK Assignment for BPA

BPA is potentially capable of causing adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for BPA: **SK: SEN**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for BPA.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No studies of BPA in humans or experimental animals following dermal exposure were identified. Morck et al. [2010] conducted a series of in vitro experiments to evaluate the potential adverse effects of BPA exposure during pregnancy. As part of this study, dermal absorption was examined.
using an in vitro diffusion model that employs full thickness human skin. The authors reported that the skin was exposed to 17.5 millimolar BPA for 48 hour in the donor chamber and samples were collected from the receiving chamber at regular time intervals. Among the reported results, 13% of the applied BPA was recovered within 48 hours in the receiving chamber, which represents dermal absorption. Approximately, 7.4% and 17% of the applied dose of BPA were recovered within the epidermis and dermis, respectively. Morck et al. [2010] concluded that more than 1/3 of the applied dose of BPA was dermally absorbed and may be available systemically. Kaddar et al. [2008] investigated the potential for BPA to be percutaneously absorbed through an in vitro diffusion model using pig skin. A solution of radiolabelled BPA, 10 micrograms per milliliter (µg/mL) in physiological serum, was placed on skin samples mounted within modified Franz static diffusion cells. Kaddar et al. [2008] reported that after 2, 5, and 10 hours of exposure, the total BPA skin content was 3%, 6.9%, and 11.4% of the applied dose. After 10 hours, 64.8% of the applied dose remained on the surface of the skin, 5.4 % of the applied dose was located within the epidermis, and 8.8% of the applied dose was contained within the dermis. Kaddar et al. [2008] concluded that BPA remained primarily on the skin surface and the chemical accumulated primarily in the dermis.

No dermal lethal concentration (LD_{10}) for humans or dermal LD_{50} (the dose required to produce mortality in 50% of the exposed population) has been identified for BPA. The absence of these data precludes adequate evaluation of the acute dermal toxicity of BPA.

No epidemiological studies that evaluated the potential of BPA to cause systemic effects were identified. A single study investigating the transfer of BPA to the skin during the handing of thermal printing paper containing BPA was identified [Beidermann et al. 2010]. The findings of the study demonstrate the contamination of the skin with BPA, which was highly variable based on the condition of the skin and exposure scenario. Beidermann et al. [2010] concluded that BPA was transferred to the skin during the handing of the thermal printing paper, but due to the nature of the study, its ability to penetrate the skin and contribute to systemic dose could not be defined.

No information was available on potential systemic effects in animals following repeat-dose (21-day or 28-day), subchronic (90-day), or chronic (at least 12-month) dermal exposure to BPA. DuPont [1962] stated that results of experimental studies and actual experience with BPA elicited no systemic effect from occasional contact with the chemical; however, details of these studies were not provided.

No standard toxicity or specialty studies evaluating biological system/function-specific effects (including reproductive and developmental effects and immunotoxicity) of BPA following dermal exposures were identified. No epidemiological studies or studies that evaluated the human or animal carcinogenic potential of BPA
following dermal exposure were identified. Table 2 provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for BPA.

Insufficient data were identified to adequately evaluate the potential for dermal uptake of BPA or its contribution to the onset of systemic toxic effects in humans or animals following skin contact. Therefore, on the basis of the data for this assessment, BPA is not assigned the SK: SYS notation.

3 Direct Effects on Skin (SK: DIR)

No data on the corrosivity of BPA from in vitro tests with human or animal skin models or on skin integrity from in vitro tests with cadaver skin were identified. However, a limited number of skin irritation studies involving animals have been conducted. Shumskaya [1961] evaluated the local effect of BPA on the skin by applying an unspecified amount of the pure BPA powder or 10% ointment in Vaseline to shaved areas (4 × 4 cm) of skin on the backs of rabbits. One application of the pure powder did not produce a pronounced skin reaction. However, repeated dermal applications (30 times in 37 days) of the powder caused moderate swelling and redness, which began after the 7th application and lasted for 12 days. After day 15, the skin turned yellow, followed by dark pigmentation. The investigator reported that the skin of rabbits became dry and began to desquamate and pigment 1 week after repeated application of the 10% ointment in Vaseline. Shumskaya [1961] concluded, however, that BPA had an insignificant local irritating effect on the skin. DuPont [1962] observed only a very slight, simple irritation on the skin of rabbits following continuous contact with the dry powder under a bandage, over a 2-week period. In this study, three similar applications of dry powder to abraded skin produced practically no irritation, whereas application of a 10% aqueous solution under occlusion was slightly irritating to the rabbits. Thorgeirsson and Fregert [1977] observed no irritation to guinea pig skin following a 24-hour occlusive exposure in acetone. In a more recent study, Vohr et al. [2004] found no irritating potential for BPA when they exposed mice to BPA up

Table 2. Summary of the carcinogenic designations* for BPA by numerous governmental and nongovernmental organizations

<table>
<thead>
<tr>
<th>Organization</th>
<th>Carcinogenic designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIOSH [2005]</td>
<td>None</td>
</tr>
<tr>
<td>NTP [2009]</td>
<td>None</td>
</tr>
<tr>
<td>USEPA [2009]</td>
<td>None</td>
</tr>
<tr>
<td>IARC [2009]</td>
<td>None</td>
</tr>
<tr>
<td>EC [2010]</td>
<td>None</td>
</tr>
<tr>
<td>ACGIH</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; USEPA = United States Environmental Protection Agency.

*Note: The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure rather than dermal exposure.
to its solubility limit (reported as 30%); the investigators used a modified local lymph node assay (LLNA) and the Integrated Model for the Differentiation of Skin reactions (IMDS). No predictions from the structure-activity relationship model, Deductive Estimation of Risk from Existing Knowledge (DEREK™) for Windows, were available for BPA. Hulzebos and Gerner [2010] evaluated the potential of BPA to act as a skin irritant using the Integrated Assessment Scheme (IAS). This evaluation tool is designed to critically assess multiple lines of toxicological data to determine the potential of a substance to cause skin irritation. Hulzebos and Gerner [2010] predicted that BPA is not a skin corrosive or irritant based on the results of the IAS analysis.

Taken together, the results of the reviewed study indicate that BPA has limited or no potential of causing direct effects of the skin, including corrosion or irritation. Therefore, on the basis of the data for this assessment, BPA is not assigned the SK: DIR notation.

4 Immune-mediated Responses (SK: SEN)

Several cases were identified in which patients presented with contact dermatitis or skin lesions. Diagnostic patch-tests with 1% BPA revealed that these patients were allergic to BPA [Romaguera et al. 1981, 1986; Freeman and Warin 1984; Van Joost et al. 1988, 1990; Srinivas et al. 1989]. Several workers, patients, or volunteers with or without dermatitis have also been patch-tested to evaluate the potential of BPA to cause skin sensitization or photoallergenicity. Standard patch-testing of some of these subjects with 1% or 2% BPA produced allergic reactions in some [Jolanki et al. 1990], but not in others [Freeman and Warin 1984; Prens et al. 1986; Van Joost 1988; Van Joost et al. 1990]. No cross-reactivity was reported between BPA and epichlorohydrin when patients with confirmed allergic contact dermatitis due to epichlorohydrin were tested [Van Joost et al. 1988]. It should be noted that positive results noted in these studies may be caused by cross-reactivity with BPA resins.

One study evaluated the skin sensitization potential of BPA. In this study, Thorgerinson and Fregert [1977] observed no skin sensitization reaction in a guinea pig maximization test (GPMT) when animals were induced with a 5% solution of BPA in acetone, followed by a challenge with a 1% solution. These investigators found no cross-reactions between BPA and its diglycidyl ether-BPA-based epoxy resins and epichlorohydrin. Several studies have also evaluated the photoallergenicity of BPA in predictive animal models. For example, Gerberick and Ryan [1990] confirmed that BPA is a photoallergen in the mouse ear-swelling test. Vohr et al. [2004] investigated the sensitizing or photoallergenic potential of BPA with a modified murine local lymph node assay, the IMDS, to distinguish skin sensitization from acute irritation. Those investigators also used a UV-IMDS assay to test for photoreactivity of BPA. In their study, dermal application of 3%, 10%, or 30% (solubility limit) BPA to mice did not result in any skin sensitization. UV irradiation of mice after each application did not result in photoallergic reactions. On the basis of these results, Vohr et al. [2004] did not consider BPA to be a skin sensitizer or photosensitizer. DEREK™ predicted BPA to be positive for skin sensitization.

Van Joost et al. 1990 and a predictive test in animals (mouse ear-swelling test) [Gerberick and Ryan 1990] is sufficient to conclude that BPA is a skin sensitizer and photoallergen. Therefore, on the basis of the data for this assessment, BPA is assigned the SK: SEN notation.

5 Summary

Lack of relevant toxicokinetic and toxicity data on BPA precludes adequate evaluation of the potential of the chemical to be absorbed through the skin and to cause systemic effects in humans or animals following dermal exposure. In vitro studies indicate that BPA may be readily absorbed by the skin [Kaddar et al. 2008; Morck et al. 2010]. Review of available animal studies and predictive tools indicate that BPA has limited or no potential to cause direct effects of the skin including corrosion and irritation. The skin sensitization potential of the chemical has been evaluated in several case reports and predictive animal studies (mouse ear-swelling test). The weight of evidence indicates that BPA is a skin sensitizer and can cause photoallergy [Romaguera et al. 1981, 1986; Freeman and Warin 1984; Van Joost 1988; Srinivas et al. 1989; Gerberick and Ryan 1990; Jolanki et al. 1990; Van Joost et al. 1990]. Therefore, on the basis of this assessment, BPA is assigned a composite skin notation of SK: SEN.

Table 3 summarizes the skin hazard designations for BPA previously issued by NIOSH and other organizations. The equivalent dermal designation for BPA, according to the Globally Harmonized System (GHS) of Classification and Labeling of Chemicals, is Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction) [European Parliament 2008]. BPA has been identified as a Category 2 Reproductive toxicant (Hazard statement: Suspected of damaging fertility) [European Parliament 2008].

References

Note: Asterisks (*) denote sources cited in text; daggers (†) denote additional resources.

Bisphenol A (BPA)

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