

## **Skin Notation (SK) Profile**

**2-Mercaptobenzothiazole**  
**[CAS No. 149-30-4]**

**Sodium 2-Mercaptobenzothiazole**  
**[CAS No. 2492-26-4]**

**Zinc 2-Mercaptobenzothiazole**  
**[CAS No. 155-04-4]**

**DRAFT**

**Department of Health and Human Services**  
Centers for Disease Control and Prevention  
National Institute for Occupational Safety and Health

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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 assignments and supportive data for 2-mercaptobenzothiazole (MBT), sodium MBT, and zinc MBT. In particular, this document evaluates and summarizes the literature describing the hazard potential for each substance 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 chemicals of interest.

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## Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AOO	acetone-olive oil
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
cm <sup>2</sup>	square centimeter(s)
cm/hour	centimeter(s) per hour
(COR)	subnotation of SK: DIR indicating the potential for a chemical to be corrosive following exposure of the skin
<i>DEREK</i>	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
EC3	Effective concentration inducing a 3-fold increase in proliferation of lymph node cells
GHS	Globally Harmonized System for Labelling and Classification of Chemicals
GPMT	guinea pig maximization test
IARC	International Agency for Research on Cancer
(IRR)	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
<i>kaq</i>	coefficient in the watery epidermal layer
<i>k<sub>p</sub></i>	skin permeation coefficient
<i>k<sub>pol</sub></i>	coefficient in the protein fraction of the stratum corneum
<i>k<sub>p<sub>sc</sub></sub></i>	permeation coefficient in the lipid fraction of the stratum corneum
LD <sub>50</sub>	dose resulting in 50% mortality in the exposed population
LD <sub>Lo</sub>	dermal lethal dose
LLNA	local lymph node assay
log <i>K<sub>OW</sub></i>	base-10 logarithm of a substance's octanol–water partition coefficient
m <sup>3</sup>	cubic meter(s)
MBT	2-mercaptobenzothiazole
MEST	mouse ear swelling test
mg	milligram(s)
mg/kg	milligram(s) per kilogram body weight
mg/m <sup>3</sup>	milligram(s) per cubic meter
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
RF	retention factor
SI ratio	ratio of skin dose to inhalation dose
SK	skin notation
<i>S<sub>w</sub></i>	solubility

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SYS skin notation indicating the potential for systemic toxicity following exposure of the skin  
USEPA United States Environmental Protection Agency  
WEEL workplace environmental exposure limit

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## 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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## 1.0 Introduction

### 1.1 General Substance Information

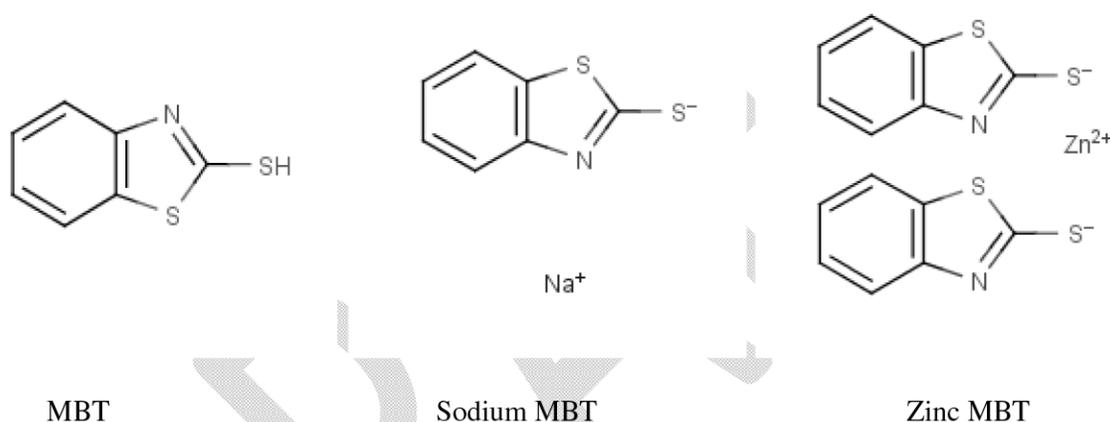
**Chemical(s):** 2-Mercaptobenzothiazole (MBT); Sodium MBT, Zinc MBT

**CAS No:** 149-30-4; 2492-26-4; 155-04-4

**Molecular weight (MW):** 167.25; 189.23; 397.85

**Molecular formula:** C<sub>7</sub>H<sub>4</sub>NS(SH); C<sub>7</sub>H<sub>4</sub>NS<sub>2</sub>(Na); C<sub>14</sub>H<sub>8</sub>N<sub>2</sub>S<sub>4</sub>(Zn)

**Structural formula:**



**Synonyms:** MBT; 2(3H)-Benzothiazolethione; 2-Benzothiazolethiol; 2-Mercaptobenzothiazole; benzothiazole-2-thiol; Benzothiazolethiol; Dermacid; Mercaptobenzothiazole; sulfadene; Thiotax

**Uses:** MBT and zinc MBT are used primarily as an accelerant during rubber vulcanization and as a fungicide; sodium MBT is utilized as a corrosion inhibitor and fungicide [USEPA 1994; EC 2005].

### 1.2 Purpose

This *Skin Notation Profile* presents (1) a brief summary of technical data associated with skin contact with MBT, sodium MBT, and zinc MBT, in addition to (2) the rationale behind the hazard-specific skin notation (SK) assignments for MBT, sodium MBT, and zinc MBT. 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 MBT, sodium MBT, and zinc MBT. A literature search was conducted through September 2012 to identify information on MBT, sodium MBT,

and zinc MBT, 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 MBT, sodium MBT, and zinc MBT

### 1.3 Overview of SK Assignment for MBT, Sodium MBT, and Zinc MBT

MBT, sodium MBT, and zinc MBT are potentially capable of causing numerous adverse health effects following dermal contact. A critical review of available data has resulted in the following SK assignment for MBT: **SK: DIR (IRR)–SEN**. Sodium MBT has been assigned the following SK assignment: **SK: DIR (COR)–SEN**. Zinc MBT has been assigned the following SK assignment: **SK: SEN**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for MBT and its salts.

**Table 1. Summary of the SK assignment for MBT, Sodium MBT, and Zinc MBT**

<b>MBT</b>		
<b>Skin Notations</b>	<b>Critical Effect(s)</b>	<b>Available Data</b>
SK: DIR (IRR)	Skin irritation	Limited animal data
SK: SEN	Skin allergy	Sufficient human and animal data
<b>Sodium MBT</b>		
<b>Skin Notations</b>	<b>Critical Effect(s)</b>	<b>Available Data</b>
SK: DIR(COR)	Skin corrosivity	Physicochemical property
SK: SEN	Skin allergy	By analogy to 2-mercaptobenzothiazole
<b>Zinc MBT</b>		
<b>Skin Notations</b>	<b>Critical Effect(s)</b>	<b>Available Data</b>
SK: SEN	Skin allergy	Limited animal data

## 2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

Toxicokinetic studies following dermal exposure to MBT were identified. When 0.0361 milligrams (mg) of MBT was applied to the skin of rats and guinea pigs under an occlusive cover for 96 hours, 16.1 to 17.5% and 33.4% of the administered dose was absorbed, respectively [el Dareer et al. 1989]. Nagamatsu et al. [1979] found that 9% of the dose was absorbed in intact guinea pig skin, while 37% was absorbed in abraded guinea pig skin at 48 hours. These results suggest that species differences exist in the toxicokinetics of MBT, with the chemical being more absorbed in the guinea pig than in the rat. The potential of MBT to pose a skin absorption hazard was also evaluated, with use of a predictive algorithm for estimating and evaluating the health hazards of dermal exposure to substances [NIOSH 2009]. The evaluation method compares an

estimated chemical dose accumulated in the body from skin absorption and an estimated dose from respiratory absorption associated with a reference occupational exposure limit. On the basis of this algorithm, an SI (skin dose to inhalation dose) ratio of 0.062 was calculated for MBT. An SI ratio of  $\geq 0.1$  indicates that a chemical is capable of producing systemic toxicity from skin exposure [NIOSH 2009]; therefore MBT is not considered to be absorbed through the skin following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No dermal lethal dose ( $LD_{Lo}$ ) or data that described the acute dermal toxicity of MBT were located for humans. However, the dermal  $LD_{50}$  value (the dose resulting in 50% mortality in the exposed animals) for the rabbit has been reported to be greater than 7940 milligrams per kilogram body weight (mg/kg) for MBT and zinc MBT and greater than 5010 for sodium MBT [RAPA 2003]. Because the reported dermal  $LD_{50}$  values are greater than the critical dermal  $LD_{50}$  value of 2000 mg/kg body weight that identifies a chemical substance with the potential for acute dermal toxicity [NIOSH 2009], MBT, sodium MBT, and zinc MBT are not considered systemically toxic by the acute dermal route.

No repeat-dose, subchronic, or chronic studies of dermal exposure to MBT, sodium MBT, or zinc MBT were identified. No standard toxicity or specialty studies evaluating biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) or carcinogenicity of MBT were identified following dermal exposure in humans or experimental animals. Table 2 provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for MBT, sodium MBT, and zinc MBT.

**Table 2. Summary of the carcinogenic designations\* for MBT, Sodium MBT, and Zinc MBT by numerous governmental and nongovernmental organizations**

<b>Organization</b>	<b>Carcinogenic designation</b>
NIOSH [2005]	No designation
NTP [2011]	No designation
USEPA [2013]	No designation
GHS [European Parliament 2008]	No designation
IARC [2012]	No designation
EC [2012]**	No designation
ACGIH	No designation

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; GHS = Globally Harmonized System for Labelling and Classification of Chemicals; 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.

\*The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure rather than dermal exposure.

\*\*Date accessed.

Although toxicokinetics data following dermal exposure indicate that MBT has the potential to be absorbed through the skin, studies in rats indicate that MBT, sodium MBT, and zinc MBT are not acutely toxic following dermal exposure. No repeat-dose, subchronic, or chronic studies of dermal exposure to MBT, sodium MBT, or zinc MBT in humans or animals were identified, which further prevents the assessment of the systemic hazards of skin contact with the substances. Therefore, based on insufficient data, this assessment does not assign a SK: SYS notation to MBT, sodium MBT, or zinc MBT.

### 3.0 Direct Effect(s) on the Skin (SK: DIR)

No human or animal *in vivo* studies for corrosivity of MBT or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests for skin integrity using cadaver skin were identified. MBT was irritating to guinea pig skin when the chemical was applied to the shaved flanks of 2 guinea pigs at 5 and 10% concentration in petrolatum under gauze pads for 24 hours, with minimal erythema at 5% concentration of MBT [Wang and Suskind 1988]. The sodium salt of MBT has a high pH of 11.5 [US EPA 1994], and is therefore considered to be corrosive to the skin; this is in line with the protocol outlined within *CIB 61 – A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009-147]. For zinc MBT, the USEPA [1994] reported data from an unpublished dermal irritation study that found slight dermal irritation in one of three rabbits when 500 mg of the substance was applied. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (*DEREK*) for Windows, predicted MBT to be negative for skin irritation.

Based on animal data, MBT does not appear to be not corrosive to the skin, but is a skin irritant at higher concentrations [Wang and Suskind 1988]. The sodium salt is considered corrosive to the skin based on its physico-chemical property (i.e., high pH). While the zinc salt produced irritation in one of three rabbits, the data are insufficient to assign a SK: DIR(IRR) notation based limited information on the study methods and the number of animals tested. Therefore, this assessment assigns the SK: DIR (IRR) notation to MBT, the SK: DIR(COR) notation to sodium MBT and does not assign the SK: DIR (IRR) notation to zinc MBT.

### 4.0 Immune-mediated Responses (SK: SEN)

MBT has been extensively tested in human elicitation studies, in addition it is included in standardized patch test as a common allergen used to diagnose mercapto-sensitive patients or patients presenting with suspected allergic contact dermatitis [Diepgen et al. 2006]. A human maximization test conducted found positive reactions in 9 out of 24 volunteers at induction and challenge concentrations of 25% and 10% in petrolatum, respectively, following a pre-treatment of skin with a 5% solution of sodium lauryl sulfate [Kligman 1966]. Chowdhuri and Ghosh [2007] patch tested 155 patients with footwear dermatitis using the Indian Standard Battery of allergens. The reported results indicated that 12.9% (n=20) of the study participants had positive allergic reactions to MBT, which may be present within rubber components of footwear. Warshaw et al. [2008] conducted an analysis of the results of standard patch testing conducted by the North American Contact Dermatitis Group in 2003 through 2004, and found that allergic

reactions to MBT were more common, with 69 (1.3%) of the 5143 patients patch tested exhibiting positive allergic reactions to 1% MBT in petrolatum.

Numerous animal studies were identified in which the sensitization potential of MBT was investigated using the array of experimental designs. Magnusson and Kligman [1969] examined the ability of MBT to act as a sensitizing agent via the guinea pig maximization tests (GPMTs) and the Landsteiner-Draize test. The authors reported positive responses from the GPMT within 8 out of 20 of test animals following induction with 1.0% MBT in adjuvant (intradermal) for the L-D test and 25% MBT in petrolatum (topical) and challenge with 15% MBT in petrolatum (topical); however, MBT did not elicit a positive response in guinea pigs in the Landsteiner-Draize test [Magnusson and Kligman 1969]. Goodwin et al. [1981] observed positive responses in 60% of guinea pigs in a GPMT following induction with 0.4% (injection) and 10% (patch) concentrations and challenge with 10% (patch) concentration. The authors classified MBT as a moderate sensitizer [Goodwin et al. 1981]. Wang and Suskind [1988] appraised the sensitization potential of MBT using a modified Buehler test. A solution of 0.5% MBT in petrolatum resulted in 20% of the treated guinea pigs experiencing positive reactions, while a 2% solution resulted in positive reactions in 70% of the treated guinea pigs. The National Toxicology Program (NTP) [1990] used the mouse ear swelling test (MEST) to investigate the dermal sensitizing potential of 0.1, 3.0, or 7.5% MBT for 5 consecutive days and challenged 7 days later with a 7.5% solution, and concluded that under the experimental conditions, a statistically significant contact hypersensitivity response to MBT was observed. Basketter et al. [1992] compared the results generated from the GPMT and local lymph node assay (LLNA) and found that 80% of the test animals treated with MBT during the GPMT responded positively resulting in the substance being classified as a strong sensitizer. For the LLNA test, positive results were reported [Basketter et al. 1992]. Ikarashi et al. [1993] studied the sensitizing abilities of rubber additives, including MBT at concentrations of 2.5, 5.0, or 10.0%, using the murine LLNA test and found that none of the applied doses of MBT resulted in a significant EC3 value (the effective concentration inducing a 3-fold increase in proliferation of lymph node cells). De Jong et al. [2002a] reported that MBT was a weak sensitizer using a modified LLNA test to examine the sensitizing activity of four compounds used to produce natural rubber products, including MBT. The test animals were treated on three consecutive days with six doses ranging from 0.1 to 25.0% concentrations of MBT in AOO, and an EC3 value of 6.4 and 7.8 at MBT concentrations of 10 and 17.5%, respectively was calculated [De Jong et al. 2002a]. In a second study, De Jong et al. [2002b] used a modified LLNA test to study and rank the allergenic potential of 15 rubber chemicals, including MBT and zinc MBT. The EC3 values for MBT and zinc MBT were reported as 9.9 and 30.3%, respectively. MBT was identified as a moderate sensitizer, while zinc MBT was classified as a weak sensitizer [De Jong et al. 2002b]. Ahuja et al. [2009] investigated the sensitizing potential of MBT using a bisphasic LLNA test, where female mice were treated with 3, 10, or 30% concentrations of MBT in DMSO on days 1 to 3 followed by application at the same concentration on days 15 to 17. The authors reported that a significant increase in cell and lymph node weight along with a decrease in C8+ cells in the animals treated with 3 and 10% MBT solutions suggesting that MBT was a mild to moderate allergen [Ahuja 2009].

Based on the human and animal data, MBT has been identified as a skin sensitizer using multiple experimental design, test species, and concentrations of applied MBT [Kligman 1966; Goodwin

et al. 1981; De Jong et al. 2002a, b; Basketter et al. 1992, 2005; Diepgen et al. 2006; Chowdhurl and Ghosh 2007; Warshaw et al. 2008; Ahuja et al. 2009]. *DEREK* predicted MBT to be a plausible skin sensitizer. No sensitization tests were identified for sodium MBT or zinc MBT. However, because sodium MBT is completely soluble in water and is expected to dissociate into sodium and MBT [USEPA 1994], it is predicted to be a sensitizer. Limited evidence in mice suggest that zinc MBT is a weak sensitizer [De Jong et al. 2002b]. Overall, the available studies in humans [Kligman 1966; Diepgen et al. 2006; Chowdhurl and Ghosh 2007; Warshaw et al. 2008], animals [Kligman 1966; Magnusson and Kligman 1969; Goodwin et al. 1981; Wang and Suskind 1988; Basketter et al. 1992; De Jong et al. 2002a, 2002b; Ahuja et al. 2009] provide sufficient evidence that MBT is a skin sensitizers. By analogy to MBT, sodium MBT is identified as a skin sensitizer. In addition, zinc MBT is classified as a weak skin sensitizer based on limited animal data [De Jong et al. 2002b]. Therefore, this assessment assigns a skin notation of SK: SEN to these substances.

## 5.0 Summary

Toxicokinetics data following dermal exposure to MBT and prediction of a mathematical model indicate that the chemical has the potential to be absorbed through the skin. However, studies in rats indicate that MBT, sodium MBT, and zinc MBT are not acutely toxic following dermal exposure. No repeat-dose or prolonged dermal exposure studies were identified in humans or animals, precluding identification of the potential systemic effects and effect levels following such exposures. For this reason, the SYS notation is not assigned to MBT. The available data in animals indicates that MBT is not corrosive to the skin, but is a skin irritant at higher concentrations [Wang and Suskind 1988]. Sodium MBT is considered corrosive to the skin based on its high pH of 11.5, while there is insufficient evidence to assign the SK:DIR(IRR) notation to zinc MBT [USEPA 1994]. MBT has been identified as a weak to strong sensitizing agent depending on the experimental design, test species, and applied concentrations of MBT [Goodwin et al. 1981; Basketter et al. 1992, 2005; De Jong et al. 2002a, b; Ahuja et al. 2009]. Diagnostic human patch tests and predictive tests in animals including GMPT, a Buehler test, murine and modified LLNA tests, and MEST provide evidence of MBT's ability to act as a skin sensitizer [Kligman 1966; Magnusson and Kligman 1969; Goodwin et al. 1981; Wang and Suskind 1988; Basketter et al. 1992; De Jong et al. 2002a, 2002b; Diepgen et al. 2006; Chowdhurl and Ghosh 2007; Warshaw et al. 2008; Ahuja et al. 2009]. By analogy to MBT, sodium MBT is also identified as a skin sensitizer. Limited evidence in mice suggests that zinc MBT is a weak skin sensitizer [De Jong et al. 2002b]. Therefore, on the basis of this assessment, MBT is assigned a composite skin notation of **SK: DIR (IRR)–SEN**, while sodium MBT is assigned a composite skin notation of **SK: DIR (COR)–SEN** and zinc MBT is assigned a composite skin notation of **SK: SEN**.

Table 3 summarizes the skin hazard designations for MBT, sodium MBT, and zinc MBT previously issued by NIOSH and other organizations. The equivalent Global Harmonization System (GHS) of Classification and Labelling of Chemicals dermal designation for Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction) [European

Parliament 2008]. Equivalent GHS classifications for sodium MBT and zinc MBT were not available.

**Table 3. Summary of previous skin hazard designations for MBT, Sodium MBT, and Zinc MBT**

<b>Organization</b>	<b>Skin Hazard Designation</b>
NIOSH [2005]	No designation
OSHA	No designation
AIHA [2010]	Skin and DSEN notations, indicating that the chemical might be absorbed in toxicologically significant amounts through the skin and can cause dermal sensitization.
ACGIH	No designation
EC [2012] <sup>*</sup>	R43 – May cause sensitization by skin contact

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.

\*Date accessed.

## References

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

\*Ahuja V, Wanner R, Platzek, Stahlmann R [2009]. Appraisal of the sensitizing potential of orally and dermally administered Mercaptobenzothiazol by a biphasic protocol of the local lymph node assay. *Arch Toxicol* 83: 933–939

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## Appendix: Calculation of the SI Ratio for MBT

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for MBT. Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended only to serve as supportive data during the assignment of the NIOSH SK. An in-depth discussion on the rationale and calculation of the SI ratio can be located in Appendix B of the *Current Intelligence Bulletin (CIB) #61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

### Overview

The SI ratio is a predictive algorithm for estimating and evaluating the health hazards of skin exposure to substances. The algorithm is designed to evaluate the potential for a substance to penetrate the skin and induce systemic toxicity [NIOSH 2009]. The goals for incorporating this algorithm into the proposed strategy for assigning SYS notation are as follows:

- (1) Provide an alternative method to evaluate substances for which no clinical reports or animal toxicity studies exist or for which empirical data are insufficient to determine systemic effects.
- (2) Use the algorithm evaluation results to determine whether a substance poses a skin absorption hazard and should be labeled with the SYS notation.

The algorithm evaluation includes three steps:

1. determining a skin permeation coefficient ( $k_p$ ) for the substance of interest,
2. estimating substance uptake by the skin and respiratory absorption routes, and
3. evaluating whether the substance poses a skin exposure hazard.

The algorithm is flexible in the data requirement and can operate entirely on the basis of the physicochemical properties of a substance and the relevant exposure parameters. Thus, the algorithm is independent of the need for biologic data. Alternatively, it can function with both the physicochemical properties and the experimentally determined permeation coefficient when such data are available and appropriate for use.

The first step in the evaluation is to determine the  $k_p$  for the substance to describe the transdermal penetration rate of the substance [NIOSH 2009]. The  $k_p$ , which represents the overall diffusion of the substance through the stratum corneum and into the blood capillaries of the dermis, is estimated from the compound's molecular weight ( $MW$ ) and base-10 logarithm of its octanol-water partition coefficient ( $\log K_{ow}$ ). In this example,  $k_p$  is determined for a substance with use of Equation 1. A self-consistent set of units must be used, such as outlined in Table A1. Other model-based estimates of  $k_p$  may also be used [NIOSH 2009].

**Equation 1: Calculation of Skin Permeation Coefficient ( $k_p$ )**

$$k_p = \frac{1}{\frac{1}{k_{psc} + k_{pol}} + \frac{1}{k_{aq}}}$$

where  $k_{psc}$  is the permeation coefficient in the lipid fraction of the stratum corneum,  $k_{pol}$  is the coefficient in the protein fraction of the stratum corneum, and  $k_{aq}$  is the coefficient in the watery epidermal layer. These components are individually estimated by

$$\begin{aligned} \log k_{psc} &= -1.326 + 0.6097 \times \log K_{ow} - 0.1786 \times MW^{0.5} \\ k_{pol} &= 0.0001519 \times MW^{-0.5} \\ k_{aq} &= 2.5 \times MW^{-0.5} \end{aligned}$$

The second step is to calculate the biologic mass uptake of the substance from skin absorption (skin dose) and inhalation (inhalation dose) during the same period of exposure. The skin dose is calculated as a mathematical product of the  $k_p$ , the water solubility ( $S_w$ ) of the substance, the exposed skin surface area, and the duration of exposure. Its units are mg. Assume that the skin exposure continues for 8 hours to unprotected skin on the palms of both hands (a surface area of 360 square centimeters [ $\text{cm}^2$ ]).

**Equation 2: Determination of Skin Dose**

$$\begin{aligned} \text{Skin dose} &= k_p \times S_w \times \text{Exposed skin surface area} \times \text{Exposure time} \\ &= k_p (\text{cm}/\text{hour}) \times S_w (\text{mg}/\text{cm}^3) \times 360 \text{ cm}^2 \times 8 \text{ hours} \end{aligned}$$

The inhalation dose (in mg) is derived on the basis of the occupational exposure limit (OEL) of the substance—if the OEL is developed to prevent the occurrence of systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assume a continuous exposure of 8 hours, an inhalation volume of 10 cubic meters ( $\text{m}^3$ ) inhaled air in 8 hours, and a factor of 75% for retention of the airborne substance in the lungs during respiration (retention factor, or RF).

**Equation 3: Determination of Inhalation Dose**

$$\begin{aligned} \text{Inhalation dose} &= \text{OEL} \times \text{Inhalation volume} \times \text{RF} \\ &= \text{OEL} (\text{mg}/\text{m}^3) \times 10 \text{ m}^3 \times 0.75 \end{aligned}$$

The final step is to compare the calculated skin and inhalation doses and to present the result as a ratio of skin dose to inhalation dose (the SI ratio). This ratio quantitatively indicates (1) the

significance of dermal absorption as a route of occupational exposure to the substance and (2) the contribution of dermal uptake to systemic toxicity. If a substance has an SI ratio greater than or equal to 0.1, it is considered a skin absorption hazard.

### Calculation

Table A1 summarizes the data applied in the previously described equations to determine the SI ratio for MBT. The calculated SI ratio was 0.062. On the basis of these results, MBT is predicted not to represent a skin absorption hazard.

**Table A1. Summary of Data used to Calculate the SI Ratio for MBT**

Variables Used in Calculation	Units	Value
<b>Skin permeation coefficient</b>		
Permeation coefficient of stratum corneum lipid path ( $k_{psc}$ )	cm/hour	0.00691
Permeation coefficient of the protein fraction of the stratum corneum ( $k_{pol}$ )	cm/hour	$1.17456 \times 10^{-5}$
Permeation coefficient of the watery epidermal layer ( $k_{aq}$ )	cm/hour	0.19331
Molecular weight ( $MW$ ) <sup>a</sup>	amu	167.25
Base-10 logarithm of its octanol–water partition coefficient ( $\text{Log } K_{ow}$ ) <sup>a</sup>	None	2.42
Calculated skin permeation coefficient ( $k_p$ )	cm/hour	0.00669
<b>Skin dose</b>		
Water solubility ( $S_w$ ) <sup>a</sup>	mg/cm <sup>3</sup>	0.12
Calculated skin permeation coefficient ( $k_p$ )	cm/hour	
Estimated skin surface area (palms of hand)	cm <sup>2</sup>	360
Exposure time	hour	8
Calculated skin dose	mg	2.311
<b>Inhalation Dose</b>		
Occupational exposure limit (OEL) <sup>b</sup>	mg/m <sup>3</sup>	5
Inhalation volume	m <sup>3</sup>	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	37.5
<b>Skin dose–to–inhalation dose (SI) ratio</b>	None	0.062

<sup>a</sup>Variables identified from SRC [2010].

<sup>b</sup>The OEL used in calculation of the SI ratio for MBT was the AIHA WEEL value.

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