Skin Notation (SK) Profile

Dinitro-*o*-cresol

[CAS No. 534-52-1]

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 hepatoxicity). 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 the hazard potential of the substance, 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 dinitro-o-cresol. In particular, this document evaluates and summarizes the literature describing the hazard potential of the 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
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
cm^2	square 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
g	gram(s)
g/L	gram(s)/liter
GHS	Globally Harmonized System for Labelling and Classification of Chemicals
GPMT	guinea pig maximization test
hr	hour(s)
IARC	International Agency for Research on Cancer
IPCS	International Program for Chemical Safety
(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
k_p	skin permeation coefficient
kpol	coefficient in the protein fraction of the stratum corneum
k_{psc}	permeation coefficient in the lipid fraction of the stratum corneum
LD_{50}	dose resulting in 50% mortality in the exposed population
LD_{Lo}	dermal lethal dose
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect level
log K_{OW}	base-10 logarithm of a substance's octanol–water partition
M	molarity
m^3	cubic meter(s)
mg	milligram(s)
$mg/cm^2/hr$	milligram(s) per square centimeter per hour
mg/kg	milligram(s) per kilogram body weight
mg/m^3	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
NOAEL	no-observed-adverse-effect level
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/cm^2	microgram(s) per square centimeter
µg/cm^2/hr	microgram(s) per square centimeter per hour
µL	microliter(s)
µmol	micromole(s)

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: Dinitro-o-cresol
CAS No: 534-52-1
Molecular weight (*MW*): 198.1
Molecular formula: $CH_3C_6H_2OH(NO_2)_2$
Structural formula:

Synonyms: 4,6-Dinitro-o-cresol; 3,5-Dinitro-2-hydroxytoluene; 3,5-Dinitro-o-cresol; 4,6-Dinitro-2-methyl phenol; DNC; DN

Uses: Dinitro-o-cresol is used primarily as a herbicide and fungicide, as well as a wood preservative [HSDB 2010].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with dinitro-*o*-cresol and (2) the rationale behind the hazard-specific skin notation (SK) assignment for dinitro-*o*-cresol. 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 dinitro-*o*-cresol. A literature search was conducted through October 2012 to identify information on dinitro-*o*-cresol, 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 dinitro-*o*-cresol

1.3 Overview of SK Assignment

Dinitro-*o*-cresol is potentially capable of causing numerous adverse health effects following skin contact. A critical review of available data has resulted in the following

SK assignment for dinitro-*o*-cresol: **SK: SYS-DIR (IRR)**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for dinitro-*o*-cresol.

Table 1. Summary of the SK Assignment for dinitro-*o*-cresol

Skin Notation	Critical Effect	Available Data
SK: SYS	Acute toxicity	Limited human data; Sufficient animal data
SK: DIR (IRR)	Skin irritation	Limited animal data.

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

Toxicokinetic studies identified in humans or animals following dermal exposure to dinitro-*o*-cresol did not estimate the dermal absorption of the substance. Many of these studies only measured blood levels of dinitro-*o*-cresol in occupational settings that may involve both inhalation and dermal exposures [Bidstrup and Payne 1951; Pollard and Filbee 1951; Steer 1951], although the low vapor pressure of the material provides some rationale for assuming skin as an important contributor to the internal dose. Further evidence for toxicologically meaningful levels of dermal absorption of the substance is provided by an animal study and a case study describing fatality after exposure to dinitro-*o*-cresol. Dow Chemical Company [1992] reported that a single application of 4% solution of dinitro-*o*-cresol on the shaved abdomen killed 3 rabbits within 24 hours. Pollard and Filbee [1951] and Steer [1951] described a case study and Bidstrup and Payne [1951] described a case series, of 8 fatal cases resulting from exposures to unspecified amounts of dinitro-*o*-cresol. King and Harvey [1953] noted that heat (increased environmental temperature) might have a marked effect on the metabolism of dinitro-*o*-cresol. The potential of dinitro-*o*-cresol 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 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, a ratio of the skin dose to the inhalation dose (SI ratio) of 1.08 was calculated for dinitro-*o*-cresol. An SI ratio of ≥0.1 indicates that a chemical is capable of producing systemic toxicity from skin exposure [NIOSH 2009]; therefore dinitro-*o*-cresol is 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 doses (LD_{Lo}) of dinitro-*o*-cresol in humans have been identified although a few cases of occupational exposures (that may have involved both the dermal and inhalation routes) have resulted in death [Steer 1951; Bidstrup and Payne 1951]. The estimated contributions from dermal exposure have generally been lacking in these reports. In guinea pigs, Spencer et al. [1948] reported a dermal LD_{Lo} of 300 mg/kg for

dinitro-*o*-cresol, and a dermal LD_{50} value (the dose resulting in 50% mortality in exposed animals) of 400 mg/kg. Because the reported acute dermal LD_{50} values are lower than the critical dermal LD_{50} value of 2,000 mg/kg body weight that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009], dinitro-o-cresol is considered acutely toxic following dermal exposure.

No epidemiological studies or occupational exposure studies were identified following dermal exposure to dinitro-*o*-cresol. No repeat-dose, subchronic, or chronic studies in animals were identified. Ambrose [1942] did not observe any systemic effect following application of 2% aqueous dinitro-*o*-cresol solution (sodium salt) to the shaved arm pits and to the anterior cubital surface of each arm of two human volunteers for 30 days or to the depilate skin of 10 rats and 6 rabbits. This study provided insufficient data to calculate an applied dose for both humans and animals.

No standard reproductive toxicity studies or specialty studies evaluating biological system/function specific effects (including immunotoxicity) following dermal exposure to dinitro-*o*-cresol were identified. No studies were identified that evaluated the carcinogenic potential in humans or animals from dermal exposure to dinitro-*o*-cresol. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for dinitro-*o*-cresol.

Table 2. Summary of the carcinogenic designations for dinitro-*o*-cresol by numerous governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2011]	No designation
USEPA	No designation
GHS [European Parliament 2008]	No designation
IARC [2012]	No designation
EC [2012]*	No designation
ACGIH [2001]	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
*Date accessed.

Several studies were identified that showed that dinitro-*o*-cresol is absorbed through the skin following dermal exposure. Dermal acute toxicity studies **[Spencer 1948]**[1] and fatality post dermal exposure to dinitro-*o*-cresol animal studies **[Dow Chemical Company 1992]** demonstrated that the substance is systemically available and toxic.

[1]References in **bold** text indicate studies that serve as the basis of the SK assignments.

Therefore, on the basis of the data for this assessment, dinitro-*o*-cresol is assigned the SK: SYS notation.

3.0 Direct Effects on Skin (SK: DIR)

Numerous human and animal studies were identified for dinitro-*o*-cresol that reported direct effects on the skin. One study reported the staining of the skin following contact with dinitro-*o*-cresol [Bidstrup and Payne 1951]. Several dermal studies were identified in which repeated application of dinitro-*o*-cresol resulted in no skin irritation in human volunteers. For example, no signs of dermal irritation were observed when the hands of two workers were exposed to a 20% solution of dinitro-*o*-cresol in oil for a period of two weeks to 17 days [Stott 1956] or when 0.5% or 1% dinitro-*o*-cresol solutions were applied to the backs of workers for patch testing [Lisi et al. 1987]. Repeated application of 2% dinitro-*o*-cresol solution to the shaved arm pits and to the anterior cubital surface of each arm of human volunteers for 30 days produced no dermal irritation [Ambrose 1942]. In contrast, technical grade dinitro-*o*-cresol was shown to be a dermal irritant in animal studies. Spencer et al. [1948] observed slight irritation on the abdomen of rabbits after administration of 7 applications of a 3% alcohol solution of dinitro-*o*-cresol. However, no signs of dermal irritation were observed when a 2% aqueous solution of dinitro-*o*-cresol was applied daily to the depilated dorsal surface of rats and rabbits for 30 days [Ambrose 1942]. Twenty repeat applications of 4% dinitro-*o*-cresol solution in Dormant oil to the ears of rabbits produced slight irritation and a slight hyperplastic reaction and 5% dinitro-*o*-cresol solution in olive oil produced very slight simple irritation [Dow Chemical Company 1992]. The conflicting results on the irritation potential of dinitro-*o*-cresol may be explained by differences in applied concentration among the studies. Predictions using the structure activity relationship model Deductive Estimation of Risk from Existing Knowledge (*DEREK*) for Windows indicate that the substance was negative for skin irritation.

Although case reports in humans and non-standard skin irritation studies in animals found dinitro-*o*-cresol to be non-irritating, the studies by **Spencer et al. [1948]** and **Dow Chemical Company [1992]** provided evidence that dinitro-*o*-cresol may act as a weak skin irritant. Therefore, on the basis of the data for this assessment, dinitro-*o*-cresol is assigned the SK: DIR (IRR) notation.

4.0 Immune-mediated Responses (SK: SEN)

No studies were identified that evaluated the potential of dinitro-*o*-cresol to cause skin sensitization in humans. No predictive tests in animals (guinea pig maximization tests, Buehler tests, murine local lymph node assays or mouse ear swelling tests) were also identified. Based on structure activity relationship, *DEREK* for Windows predicted dinitro-*o*-cresol to be negative for sensitization. Therefore, on the basis of the data for this assessment, dinitro-*o*-cresol is not assigned the SK: SEN notation.

5.0 Summary

Although no estimates of dermal absorption of dinitro-*o*-cresol in humans or animals were identified, there is ample evidence from human exposure experience and animal data that show that the substance can be absorbed through the skin following dermal exposure. The substance was systemically available and toxic based on dermal acute toxicity studies **[Spencer 1948; Dow Chemical Company 1992].** Although case reports in humans and non-standard skin irritation studies in animals found dinitro-*o*-cresol to be non-irritating, the studies by **Spencer et al. [1948]** and **Dow Chemical Company [1992]** provided evidence that dinitro-*o*-cresol, at higher concentrations, may act as a weak skin irritant. No data were identified to evaluate the skin sensitization potential of dinitro-*o*-cresol. Therefore, on the basis of these assessments, dinitro-*o*-cresol is assigned a composite skin notation of **SK: SYS-DIR (IRR)**.

Table 3 summarizes the skin hazard designations for dinitro-*o*-cresol previously issued by NIOSH and other organizations. The equivalent dermal designations for dinitro-*o*-cresol, according to the Global Harmonization System (GHS) of Classification and Labelling of Chemicals, are Acute Toxicity Category 2 (Hazard statement: Fatal in contact with the skin), Skin Irritation Category 2 (Hazard statement: Causes skin irritation), and Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction [European Parliament 2008]. In addition, dinitro-*o*-cresol has been classified as a Mutagenicity Category 2 (Hazard Statement: Suspected of causing genetic defects) [European Parliament 2008].

Table 3. Summary of previous skin hazard designations for dinitro-*o*-cresol

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2012]*	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: Potential for dermal absorption that provides a significant contribution to systemic toxicity
EC [2012]*	R27: Very toxic by contact with skin R38: Irritating to skin 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.

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

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Appendix: Calculation of the SI Ratio for Dinitro-*o*-cresol

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for dinitro-*o*-cresol. 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 found 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 *kp* 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 centimeters per hour (cm/hr), 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

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

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 milligrams (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 [cm^2]).

Equation 2: Determination of Skin Dose

Skin dose = $k_p \times S_w \times$ Exposed skin surface area × Exposure time
= k_p(cm/hr) × S_w (mg/cm^3) × 360 cm^2 × 8 hr

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 (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

Inhalation dose = OEL × Inhalation volume × RF
= OEL (mg/m^3) × 10 m^3 × 0.75

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 dinitro-*o*-cresol. The calculated SI ratio was 1.08. On the basis of these results, dinitro-*o*-cresol is predicted to represent a skin absorption hazard.

Table A1. Summary of Data used to Calculate the SI Ratio for Dinitro-*o*-cresol

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	0.0029
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	1.0791×10^{-5}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.1776
Molecular weight (MW)[a]	amu	198.14
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})[a]	None	2.13
Calculated skin permeation coefficient (k_p)	cm/hr	0.0028
Skin dose		
Water solubility (S_w)[a]	mg/cm^3	0.198
Calculated skin permeation coefficient (k_p)	cm/hr	0.0028
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	1.619
Inhalation Dose		
Occupational exposure limit (OEL)[b]	mg/m^3	0.2
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	1.5
Skin dose–to–inhalation dose (SI) ratio	None	1.08

[a]Variables identified from SRC [2009].
[b]The OEL used in calculation of the SI ratio for dinitro-*o*-cresol was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

Appendix References

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