NIOSH Skin Notation Profile

Diacetyl and 2,3-Pentanedione

SK

- ID^{SK}
- [~~SK~~]
- SYS
- SYS (FATAL)
- DIR
- DIR (IRR)
- DIR (COR)
- SEN

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NIOSH Skin Notation Profile

Diacetyl and 2,3-Pentanedione
[CAS No. 431-03-8; 600-14-6]

Naomi L. Hudson

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 (such as irritant contact dermatitis and corrosion) to induction of immune-mediated responses (such as allergic contact dermatitis and pulmonary responses), or systemic toxicity (such as 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]. 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 (such as skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for diacetyl and 2,3-pentanedione. 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.

John Howard, M.D.
Director, National Institute for
Occupational Safety and Health
Centers for Disease Control and Prevention

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Contents

Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists
AMU	atomic mass unit
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
cm²	squared centimeter(s)
cm/h	centimeter(s) per hour
cm/s	centimeter(s) per second
COR	subnotation of SK: DIR indicating the potential for a chemical to be corrosive to the skin following exposure
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
DSEN	Dermal (skin) sensitization
EC	European Commission
FATAL	subnotation of SK: SYS indicating the potential for the chemical to be fatal during dermal absorption
g	gram(s)
g/L	gram(s)/liter
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
GPMT	guinea pig maximization test
h	hour(s)
IARC	International Agency for Research on Cancer
ID^{SK}	skin notation indicating that a chemical has been evaluated, but insufficient data exist to accurately assess the hazards of skin exposure
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
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
M	molarity
m³	cubic meter(s)
mg	milligram(s)
mg/cm²/h	milligram(s) per square centimeter per hour
mg/kg	milligram(s) per kilogram
mg/m³	milligram(s) per cubic meter
mL	milliliter(s)
mL/kg	milliliter(s) per kilogram
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
RIFM	Research Institute for Fragrance Materials, Inc.
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SK	skin notation
~~SK~~	skin notation indicating that the reviewed data did not identify a health risk associated with skin exposure
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
U.S. EPA	United States Environmental Protection Agency
µg	microgram(s)
µg/cm²	microgram(s) per square centimeter
µg/cm²/h	microgram(s) per square centimeter per hour
µL	microliter(s)
µmol	micromole(s)
w/v	weight/volume

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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- John Cherrie, Ph.D., B.Sc., CFFOH, Professor

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Department of Environmental Sciences and Engineering, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

- Leena A. Nylander-French, Ph.D., CIH

The following individuals contributed to the development or improvement of the skin notation profiles:

- G. Scott Dotson, Ph.D., CIH, DABT, (formerly with NIOSH) Cardno ChemRisk, Cincinnati, OH
- G. Frank Gerberick, Ph.D., The Procter and Gamble Company, Cincinnati, OH
- Dori Germolec, Ph.D., National Toxicology Program, National Institute for Environmental Health Sciences, Research Triangle, NC
- Ben Hayes, M.D., Ph.D., Division of Dermatology, Vanderbilt School of Medicine, Nashville, TN
- Jennifer Sahmel, M.Sc., CIH, ChemRisk, Boulder, CO
- James Taylor, M.D., Industrial Dermatology, The Cleveland Clinic, Cleveland, OH

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1 Introduction

1.1 General Substance Information

Chemical: Diacetyl; 2,3-Pentanedione

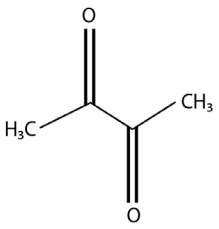
CAS No: 431-03-8; 600-14-6

Molecular weight (*MW*): 86.090; 100.117

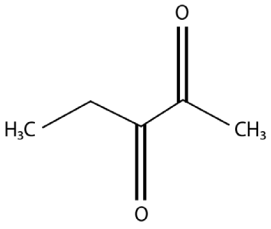
Molecular formula: $C_4H_6O_2$; $C_5H_8O_2$

Structural formula:

Diacetyl



2,3-Pentanedione



The general substance information was obtained from NIOSH [2007a] and the image was obtained from ChemIDplus [NLM, no date].

Synonyms: 3-butanedione; biacetyl; dimethyl diketone; dimethylglyoxal; 2,3-diketobutane

Uses: Diacetyl and 2,3-pentanedione are used as synthetic flavoring ingredients in butter, caramel, vinegar, dairy products, and coffee, and are also found in other foods including strawberry, hazelnut, and butterscotch.

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with diacetyl and 2,3-pentanedione and (2) the rationale behind the hazard-specific skin notation (SK) assignment for diacetyl and 2,3-pentanedione. 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 diacetyl and 2,3-pentanedione and the potential for direct skin injuries from diacetyl and 2,3-pentanedione. A literature search was conducted through March 2021 to identify information on diacetyl and 2,3-pentanedione dermal absorption, 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 diacetyl and 2,3-pentanedione. The criteria for the search strategy, evaluation, and selection of data are described in Appendix E in the aforementioned *CIB 61* [NIOSH 2009].

1.3 Overview of SK Assignment for Diacetyl and 2,3-Pentanedione

Diacetyl and 2,3-pentanedione are components in flavoring productions with similar chemical structures (both are diketones). Both are 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 diacetyl: **SK: DIR (IRR)-SEN**. 2,3-Pentanedione was assigned the following SK assignment: **SK: DIR (IRR)-SEN**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for diacetyl and 2,3-pentanedione.

Table 1. Summary of the SK assignment for diacetyl and 2,3-pentanedione

Skin notations	Critical effect	Available data
Diacetyl		
SK: DIR(IRR)	Skin irritation	Limited human and sufficient animal data
SK: SEN	Skin allergy	Sufficient animal data
2,3-Pentanedione		
SK: DIR(IRR)	Skin irritation	By analogy to diacetyl
SK: SEN	Skin allergy	Limited animal data
SK: SEN	Skin sensitization	Sufficient human and animal data

2 Systemic Toxicity From Skin Exposure (SK: SYS)

No toxicokinetic studies were identified that evaluated the potential of diacetyl or 2,3-pentanedione to be absorbed through the skin of humans or animals following dermal exposure.

No estimate of the human dermal lethal dose (LD_{Lo}) was identified for diacetyl or 2,3-pentanedione. A study submitted to the Research Institute for Fragrance Materials, Inc. (RIFM) [1977] reported a LD_{50} of greater than 2,500 milligrams per kilogram of bodyweight (mg/kg) for diacetyl; however, there were only five rabbits in the study and only one dose was tested. Although no newer studies have been identified, the available acute LD_{50} value for rabbits is higher than the critical dermal LD_{50} of 2,000 mg/kg that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009] for diacetyl. Therefore, diacetyl is not considered acutely toxic following dermal exposure. No studies evaluating the LD_{50} for 2,3-pentanedione were identified.

No case reports or epidemiological studies in humans or repeat-dose, sub-chronic, or chronic studies in animals following dermal exposure to diacetyl or 2,3-pentanedione were identified. No standard toxicity or specialty studies evaluating biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to diacetyl or 2,3-pentanedione were identified. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for diacetyl and 2,3-pentanedione.

Table 2. Summary of the carcinogenic designations* for diacetyl and 2,3-pentanedione by numerous governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH [2007]	No designation
NTP [2016]	No designation
U.S. EPA [2021]	No designation
ECHA [2022]	No designation
IARC [2012]	No designation
ACGIH® [2018]	No designation

ACGIH® = American Conference of Governmental Industrial Hygienists; ECHA = European Chemicals Agency; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; U.S. EPA = United States Environmental Protection Agency.

The limited data are insufficient to demonstrate that diacetyl has the potential to be absorbed through the skin and to be systemically available and toxic. An animal study [RIFM 1977] indicated that diacetyl was not acutely toxic following dermal exposure until the dose exceeded 2,000 mg/kg. No studies were found for 2,3-pentanedione. The absence of epidemiological studies in workers or repeat-dose, sub-chronic, or chronic studies in animals following dermal exposure to diacetyl or 2,3-pentanedione precludes adequate evaluation of the potential of diacetyl or 2,3-pentanedione to cause systemic effects following dermal exposure. Therefore, on the basis of the data for this assessment, diacetyl and 2,3-pentanedione are not assigned the SK: SYS notation.

3 Direct Effects on Skin (SK: DIR)

No studies on corrosivity of diacetyl or 2,3-pentanedione or *in vitro* tests for corrosivity using human or animal skin modes or *in vitro* tests of skin integrity using cadaver skin were identified for diacetyl or 2,3-pentanedione. Anderson et al. [2007] performed an irritancy test by measuring the ear thickness of female mice 24 hours following exposure of 1.25–5% diacetyl in a 4:1 acetone and olive oil mixture and observed a significant increase in ear swelling, indicating that diacetyl induced an irritating response. RIFM [1988] reported that diacetyl did not have irritancy potential despite slight erythema on three of four rabbits when 0.5 milliliters (ml) of diacetyl was placed on a 2.5 centimeter (cm) squared of surgical lint and applied to the shaved dorsal skin of four albino rabbits. The test material remained on the rabbits in occluded conditions for four hours [RIFM 1988]. Two of the four rabbits exhibited slight erythema one hour after the dosing period, and a third rabbit exhibited erythema 24 hours post dosing, and skin responses remained 72 hours post dosing period but were resolved after 7 days [RIFM 1988].

Limited occupational exposure data were identified. In an investigation of nine patients exhibiting bronchiolitis obliterans that worked in a popcorn production plant, two of the nine patients reported skin irritation and rashes [Akpinar-Elci et al. 2004]. One of the two patients developed thick keratotic plaques and fissures on the palms and soles, and a skin biopsy showed superficial epidermal necrosis [Akpinar-Elci et al. 2004]. In an earlier study, Kreiss et al. [2002] reported higher rates of skin problems in workers in the microwave popcorn production area than workers in other areas in a popcorn production plant. One of five workers who worked in a pop corn plant in plain-popcorn packaging, bag-printing, in the warehouse offices or outside reported skin irritation as well as 33 of 34 workers who worked in quality control, maintenance, microwave-popcorn packaging, or mixing in a popcorn production plant [Kreiss et al. 2002]. Diacetyl was the predominant compound isolated from air samples in this plant [Kreiss et al. 2002]. NIOSH [2003] reported skin irritation in 12% participants in a health hazard evaluation at a popcorn flavoring plant. Another NIOSH report states 36% of production workers at another popcorn flavoring plant experienced skin irritation [NIOSH 2007b].

The animal [**Anderson et al. 2007; RIFM 1988**][*] and limited occupational exposure data **[Akpinar-Elci et al. 2004; Kreiss et al. 2002]** suggest that diacetyl is a mild skin irritant. Therefore, on the basis of the data for this assessment, diacetyl is assigned the SK: DIR (IRR) notation. 2,3-Pentanedione is assigned the SK: DIR (IRR) notation by analogy, since diacetyl and 2,3-pentanedione are structurally similar alpha-dicarbonyl diketones and have similar inhalation toxic effects via various pathways of exposure [Hubbs et al. 2010].

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

4 Immune-mediated Responses (SK: SEN)

Limited studies were identified that evaluated the potential for diacetyl and 2,3-pentanedione to cause skin sensitization in humans and animals. Akpinar-Elci et al. [2004] reported two cases of skin irritation and rashes in an investigation of nine patients exhibiting obliterative bronchiolitis that worked in a popcorn production plant. Of the two cases, one case was patch tested and showed reactions to butter flavorings, including diacetyl, which was used in the plant [Akpinar-Elci et al. 2004].

Anderson et al. [2007] reported an effective concentration (EC3) value (%) (the concentration of chemical required to induce a stimulation index [SI] of three in the murine local lymph node assay [LLNA]) to be 1.9% for diacetyl. Exposure to higher concentration of diacetyl (24%) elevated total serum IgE; however, it was not deemed biologically significant because of the lack of dose-responsiveness in the IgE + B220 + cell population [Anderson et al. 2007]. However, in a later study, Anderson et al. [2013] reported an EC3 value for diacetyl to be 17.9% and 15.4% for 2,3-pentanedione. The differing results from Anderson et al. [2007] and Anderson et al. [2013] resulted from a contaminant possibly introduced during specific synthesis or storage processes of diacetyl present from different vendors. Roberts et al. [1999] noted positive LLNA results, indicating that diacetyl was a skin sensitizer. Elkama et al. [2018] investigated the sensitizing potential of diacetyl in BALB/c mice using short and long-term protocols. For the short-term protocol, mice were exposed to 25 microliter (µL) of 10% diacetyl in an acetone-olive oil solution on the dorsum of both ears daily for three consecutive days. For the long-term protocol, mice were exposed to 50 µL of 10% diacetyl in an acetone-olive oil solution bilaterally on each shaved flank. This was repeated 5 days later, and 5 days following that, 25 µL of 10% diacetyl was applied to the dorsum of both ears for 3 consecutive days. The SI for the short and long-term protocols were 1.43 and 1.47, respectively [Elkama et al. 2018]. While the SI is indicative that diacetyl is not a strong dermal sensitizer, there were statistically significantly increased levels of interleukin (IL)-2, IL-4, and IL-13 as well as statistically significantly increased levels of IgE in diacetyl-exposed groups [Elkama et al. 2018].

Anderson et al. [2007] also evaluated diacetyl using the software packages TOPKAT 6.2, *DEREK*® for windows, and a NIOSH logistic regression model. The TOPKAT model and the NIOSH logistic regression models predicted diacetyl as an indeterminate skin sensitizer, and *DEREK*® predicted diacetyl to be a skin sensitizer. 2,3-Pentanedione was not evaluated.

There was only one case report identified that investigated the skin sensitization potential of diacetyl using diagnostic (human patch test) methods **[Akpinar-Elci et al. 2004]**.* However, results from animal studies **[Elkama et al. 2018]** and LLNAs **[Anderson et al. 2007; Anderson et al. 2013; Roberts et al. 1999]**, supported by the structure-activity relationship model predictions from TOPKAT 6.2, *DEREK* for MS Windows, and the NIOSH logistic regression models, demonstrate that diacetyl is a potential skin sensitizer. Results from an animal study using LLNAs **[Anderson et al. 2013]** indicate that 2,3-pentanedione is a skin sensitizer. Additionally, diacetyl and 2,3-pentanedione are structurally similar alpha-dicarbonyl diketones and have similar toxic effects via different pathways of exposure [Hubbs et al. 2010]. Therefore, on the basis of the data for this assessment, diacetyl and 2,3-pentanedione are assigned the SK: SEN notation.

5 Summary

There are insufficient data to indicate that diacetyl and 2,3-pentanedione are acutely toxic following dermal exposure. Limited data from epidemiological studies in workers or repeat-dose, sub-chronic, or chronic studies in animals following dermal exposure to diacetyl or 2,3-pentanedione preclude adequate evaluation

of the potential of these chemicals to cause systemic effects following dermal exposure. Additionally, diacetyl and 2,3-pentanedione are structurally similar alpha-dicarbonyl diketones and have similar toxic effects via different pathways of exposure [Hubbs et al. 2010]. Although no studies evaluated corrosivity of diacetyl or 2,3-pentanedione, animal data [**Anderson et al. 2007; RIFM 1988**] and limited occupational exposure data [**Akpinar-Elci et al. 2004; Kreiss et al. 2002**] suggest that diacetyl is a mild skin irritant. A report from an epidemiological study in workers exposed to diacetyl [**Akpinar-Elci et al. 2004**], supported by predictive tests in animal studies [**Elkama et al. 2018**] and LLNAs [**Anderson et al. 2007, 2013; Roberts et al. 1999**] and mathematical models demonstrate that diacetyl is a potential skin sensitizer. Results from an animal study using LLNAs [**Anderson et al. 2013**] indicate that 2,3-pentanedione is a skin sensitizer. Therefore, on the basis of these assessments, diacetyl and 2,3-pentanedione are each assigned a composite skin notation of **SK: DIR (IRR)-SEN**.

Table 3 summarizes the skin hazard designations for diacetyl and 2,3-pentanedione issued by NIOSH and other organizations.

Table 3. Summary of previous skin hazard designations for diacetyl and 2,3-pentanedione from NIOSH and other organizations

Organization	Skin hazard designation
NIOSH [2007a]	No designation
OSHA [2018]*	No designation
ACGIH® [2018]	No designation

ACGIH® = American Conference of Governmental Industrial Hygienists; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.
*Year accessed.

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Note: Asterisks (*) denote sources cited in text.

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