

Skin Notation (SK) Profile

Arsenic and inorganic arsenic containing compounds

[CAS No. 7440-38-2]

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 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 arsenic and inorganic arsenic containing compounds. 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	squared centimeter(s)
cm/hour	centimeter(s) per hour
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
DMBA	7,12-dimethylbenz(a)anthracene
EC	European Commission
GHS	Globally Harmonized System for Classification and Labelling 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
k_p	skin permeation coefficient
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
mg	milligram(s)
mg/hour	milligram(s) per hour
mg/kg	milligram(s) per kilogram body weight
mL	milliliter(s)
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SK	skin notation
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA	United States Environmental Protection Agency
μL	microliter(s)
μg/cm ²	microgram(s) per square centimeter
μg/cm ² -hour	microgram(s) per square centimeter per hour

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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: (Elemental) Arsenic and inorganic arsenic containing compounds¹

CAS No: 7440-38-2 (elemental arsenic)

Molecular weight (MW): 74.9 (elemental arsenic)

Molecular formula: As (elemental arsenic)

Structural formula: As (elemental arsenic)

Synonyms: Arsenic metal; arsenia

Uses: Arsenic is used as a wood preservative and pesticide [ATSDR 2007].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with arsenic and (2) the rationale behind the hazard-specific skin notation (SK) assignment for arsenic. 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 arsenic. A literature search was conducted through February 2013 to identify information on arsenic, 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 arsenic.

1.3 Overview of SK Assignment

Arsenic is potentially capable of causing skin irritation following skin contact. A critical review of available data has resulted in the following SK assignment for arsenic: **SK: DIR (IRR)**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for arsenic.

Table 1. Summary of the SK Assignment for arsenic

¹ This document summarizes the health risks associated with skin contact with inorganic arsenic and other substances that contain inorganic arsenic, including, but not limited to, arsenic metal; arsenic acid (CAS No. 7778-39-4), arsenic trioxide (CAS No. 1327-53-3), arsenite (i.e., potassium), and arsenates (i.e, calcium, lead, magnesium, sodium).

Skin Notation	Critical Effect	Available Data
SK: DIR (IRR)	Skin irritation	Sufficient human data; limited animal data

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

Toxicokinetic studies following dermal exposure to arsenic and its inorganic compounds were identified. Although no *in vivo* studies in humans were identified, *in vivo* toxicokinetic studies in monkeys and rats demonstrate that arsenic is absorbed following dermal exposure. Wester et al. [1993] reported that 6.4% and 2.0% of the applied arsenic dose were absorbed through the skin when radioactive water solutions of arsenic-73 as arsenic acid at a low (trace) level of 0.000024 micrograms per square centimeter ($\mu\text{g}/\text{cm}^2$), and a higher dose of 2.1 $\mu\text{g}/\text{cm}^2$, respectively, were applied in a volume of 5 microliters (μL)/ cm^2 to the skin of Rhesus monkey for 24 hours. In rats, skin application of sodium arsenate aqueous solutions for one hour caused the initial accumulation of arsenic in the skin, with the absorption rate of 1.14-33.1 $\mu\text{g}/\text{cm}^2$ -hour for 0.01 to 0.2 molar (M) concentrations, followed by a slow and continuous distribution to the blood stream and to other tissues [Dutkiewicz 1977]. Thirty percent of the absorbed dose was eliminated in the urine and feces at 10 days after the skin application. Dutkiewicz [1977] calculated that this absorption rate would result in an overall absorption rate of 0.8 to 23.2 milligrams (mg)/hour in humans, assuming the surface area of the hands to be 700 cm^2 . Wester et al. [1993] reported a percutaneous absorption of 1.9% of the applied dose (when receptor fluid and skin concentrations were added) when the low level radioactive water solution of arsenic-73 of 0.000024 $\mu\text{g}/\text{cm}^2$, as used in the Rhesus monkey study, was applied to human skin *in vitro* for 24 hours. The value from the *in vitro* study was less than the *in vivo* percutaneous absorption of 6.4% in the Rhesus monkey. When arsenic-73 was applied to 0.64 cm^2 dermatosed pig skin samples for 16 hours, Turkall [2003] reported total penetration (sum of the radioactivity of the initial dose in the receptor fluid of 0.4% and the remaining dose of 44.2% bound to skin) as 44.6% of the initial dose recovered at the end of the 16-hour study. This study indicated that more arsenic bound to the skin following topical application than penetrated into receptor fluid. The potential of arsenic to pose a skin absorption hazard was not evaluated with 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 (OEL). The ratio of the skin dose to the inhalation dose (SI ratio) could not be calculated because this method is not validated to determine skin absorption for inorganic compounds. More information about the SI ratio can be found in the appendix.

Wester et al. [1993] demonstrated that the presence of other chemicals significantly enhanced the dermal bioavailability of arsenic. The partition coefficient (k_p) of arsenic chloride from water to powdered human stratum corneum was reported as 1.1×10^4 [Wester et al. 1993]. It is important to note that lead arsenate compounds have low solubility in water [Liu et al. 2009], and would not be as hazardous as some of the other inorganic compounds of arsenic described in this document. Based on the available toxicokinetic studies in both humans and animals, arsenic has limited potential to be absorbed through human skin compared to animal skin.

No estimated dermal lethal doses (LD_{Lo}) of arsenic for humans have been identified. However, a dermal LD₅₀ (the dose resulting in 50% mortality in the exposed animals) value of greater than 2,400 milligrams per kilogram body weight (mg/kg) was reported for female rats for arsenic as lead or calcium arsenate [Gaines 1960]. Because the reported acute dermal LD₅₀ value for the rat is greater than the critical dermal LD₅₀ value of 2000 mg/kg that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009], arsenic and its inorganic compounds are not considered acutely toxicity following dermal exposure.

No epidemiological or occupational exposure studies or repeat-dose, sub-chronic or chronic toxicity studies in animals were identified that evaluated system effects following dermal exposure to arsenic or its inorganic compounds. No specialty studies were identified that evaluated biological system/function specific effects (including reproductive effects and immunotoxicity) following dermal exposure to arsenic. A case report by Robinson [1975] described peripheral neuropathy in a man who was dermally treated with arsenic; however detailed information was not provided.

No studies that evaluated the carcinogenic potential of arsenic or its inorganic compounds following the dermal exposure route were identified. The classification of carcinogenicity of arsenic following dermal exposure has not been done, but several organizations have developed such classifications based on data from other exposure routes. It should be noted that skin cancers in the form of Bowen’s disease, a squamous cell carcinoma *in situ*, and basal cell carcinomas, are commonly associated with the chronic ingestion and inhalation of arsenic [ATSDR 2007]. The relationship between skin contact with arsenic-containing compounds and these diseases could not be determined because of the absence of quality data on the subject. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for arsenic.

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

Organization	Carcinogenic designation
NIOSH [2005]	Potential occupational carcinogen
NTP [2014]	Known human carcinogen
USEPA [2014]	Group A: Human carcinogen
European Parliament [2008]	No GHS designation
IARC [2012]	Group 1: Carcinogenic to humans
EC [2013] [†]	No designation
ACGIH [2001]	Group A1 : Confirmed human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; GHS = Globally Harmonized System for Classification and Labelling 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 since studies using the dermal route of exposure were unavailable.

[†]Date accessed.

There is some indication from toxicokinetic studies that arsenic has measurable but limited potential to be absorbed through the skin of humans and animals [Dutkiewicz 1977; Wester et al. 1993; Turkall 2003]. The limited availability by the dermal route is consistent with the results of the acute dermal toxicity study identified in animals [Gaines 1960] that indicates that arsenic is not acutely toxic despite its known acute toxicity via other routes. In addition, the lack of case reports, epidemiological studies, prolonged or repeat-dose studies in animals precludes adequate evaluation of the potential of arsenic to cause systemic effects following dermal exposure. Therefore, on the basis of the data for this assessment, arsenic is not assigned the SK: SYS notation.

3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on corrosivity of arsenic or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. However, several occupational cases or human studies have reported irritant contact dermatitis or cutaneous effects in patients or workers exposed to arsenic [Pinto and McGill 1953; Bourrain 1998; Mohamed 1998]. Skin reactions were mostly in the form of itching, dryness, hyperpigmentation, folliculitis, superficial ulceration, erythema, swelling, and papules, with vesicle formation in severe cases. In mice treated twice daily with 50 μ L of 0.4% potassium arsenite solution in 80% ethanol extensive ulceration was observed [Boutwell 1963].

Boutwell [1963] evaluated the tumor initiation and promotion potential of topical applications of potassium arsenite in ethanol. In an 18-week initiation study, mice received a total of 1.24 mg of potassium arsenite divided into 8 applications over 5 days. The tumor-promoting agent, croton oil (25 μ L of 2.0% concentration in benzene) was then applied twice weekly to the skin beginning 2 days after application of the test material. No increase in tumorigenicity was observed [Boutwell 1963]. In a 30-week tumor-promotion study, 20 mice were given a single application of 75 μ g of 7,12-dimethylbenz(a)anthracene (DMBA) in 25 μ L of acetone to a shaved area on the skin, followed by twice daily (11 times a week) application with 50 μ L of 0.4% potassium arsenite solution in 80% ethanol. The exposure resulted in a weekly cumulative dose of 2.2 mg potassium arsenite [Boutwell 1963]. Although hyperplasia and external ulceration were observed, no tumors were identified. Boutwell [1963] concluded potassium arsenite was neither a tumor initiator nor promoter.

Case reports and human studies [**Pinto and McGill 1953; Bourrain 1998; Mohamed 1998**]² demonstrate that chronic or high-dose dermal exposure to arsenic can result in irritant contact dermatitis. Some of the irritant symptoms observed could possibly reflect other ingredients. Moreover, some of the observed skin effects could arise from arsenic uptake via other routes of exposure (e.g., oral, inhalation) in the occupational setting. However, the effects are consistent with irritation and are supported by the finding that prolonged exposure to arsenic following dermal application resulted in extensive ulceration at the site of application in mice [**Boutwell 1963**]. Therefore, on the basis of the data for this assessment, arsenic is assigned the SK: DIR (IRR) notation.

4.0 Immune-mediated Responses (SK: SEN)

²References in **bold** text indicate studies that serve as the basis of the SK assignments.

Several studies were identified that evaluated the potential of arsenic to cause skin sensitization in humans and animals. Wahlberg and Boman [1986] reported two out of 379 (0.5%) eczema patients patch tested with arsenic compounds [0.1% sodium arsenate in distilled water (pH 8.5) and 0.05% sodium arsenite in distilled water (pH 10.0)] that showed positive test results. The patients had no known previous exposure to arsenic compounds and the positive response might have been due to a cross reactivity with nickel. In a guinea pig maximization test (GPMT), arsenic compounds (1.0% sodium arsenate and 0.1% sodium arsenite) were not sensitizing to the skin, and were not rated as Grade I Allergens [Wahlberg and Boman 1986].

An *in vivo* animal study using the GPMT did not support the weak skin sensitization data in humans [Wahlberg and Boman 1986]. This assessment concludes that data are too limited to conclude that arsenic and its inorganic compounds have the potential to cause skin sensitization in humans. Therefore, on the basis of the data for this assessment, arsenic is not assigned the SK: SEN notation.

5.0 Summary

There is some indication from toxicokinetic studies that arsenic and its inorganic compounds have measurable, but limited potential to be absorbed through the skin of humans and animals [Dutkiewicz 1977; Wester et al. 1993; Turkall 2003]. The limited availability by the dermal route is consistent with the results of the acute dermal toxicity study identified in animals [Gaines 1960] that indicates that arsenic is not acutely toxic despite its known acute toxicity via other routes. These data are insufficient to adequately evaluate the potential of arsenic and its inorganic compounds to cause systemic effects, including skin cancers, following dermal exposure. Case reports and human studies [Pinto and McGill 1953; Bourrain 1998; Mohamed 1998] and data from animals [Boutwell 1963] indicate that chronic or high-dose dermal exposure to arsenic can result in irritant contact dermatitis. An *in vivo* animal study using the GPMT did not support the weak skin sensitization data in humans [Wahlberg and Boman 1986]. Therefore, on the basis of these assessments, arsenic is assigned a composite skin notation of **SK: DIR (IRR)**.

Table 3 summarizes the skin hazard designations for arsenic previously issued by NIOSH and other organizations. There is not an equivalent dermal designation by the Globally Harmonized System (GHS) [European Parliament 2008].

Table 3. Summary of previous skin hazard designations for arsenic

Organization	Skin hazard designation
NIOSH [2005]	No designation
OSHA [2015]*	No designation
ACGIH [2001]	No designation
EC [2013]*	No designation

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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DRAFT

Appendix: Calculation of the SI Ratio

This appendix presents an overview of the SI ratio. 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 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 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 squared centimeters [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 (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.

Appendix References

NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2009-147, <http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf>. Accessed: 01-27-15.

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