

6/2/2010

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**Review:** NIOSH Skin Notations Review - Group A

**Profile Number:** 14

**Profile Title:** Nitroglycerin

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### Summary

For the most part, both reviewers agreed that the systemic health hazards, direct health hazards, and immune-mediated responses associated with exposures of the skin to Nitroglycerin were clearly outlined. Reviewer 1 did not feel that an adequate explanation for not assigning the SK:SYS (FATAL) notation was provided. Though the document describes the development of tolerance to the vasodilating action of nitroglycerin and the subsequent risk of sudden death when these individuals are removed abruptly from long-term exposures, the reviewer questions why this risk is not justification for assigning an SK:SYS (FATAL) notation. Additionally, Reviewer 2 suggests that the document would benefit from a quantitative assessment of data validity, utilizing the Benezra (J Invest Derm) criteria.

### Recommendations

- More adequately account for why the SK:SYS (FATAL) notation is not assigned in light of the risk of sudden death subsequent to the abrupt withdrawal of long-term nitroglycerin exposure. (Q2, Q13, Reviewer 1)
- A quantitative assessment of data validity, utilizing the Benezra (J Invest Derm) criteria. (Q5, Reviewer 2)

### Suggested additional scientific data to review:

- Benezra (J Invest Derm) (Q5, Reviewer 2)
- Contact patch manufacturers for their adverse effect files. (Q12, Reviewer 2)

### Verbatim Reviewer Comments

**1. Does this document clearly outline the systemic health hazards associated with exposures of the skin to the chemical? If not, what specific information is missing from the document?**

#### Reviewer 1:

As presented in this document, there are numerous human dermal studies involving nitroglycerin, so its absorption into the blood of exposed workers and the occurrence of systemic effects are completely understood. The calculation of the SI ratio of 4.97 for nitroglycerin is explained, providing an indication that skin absorption may contribute to the body burden of this compound. Dermal absorption quantitation studies are described in monkeys and mice. Several epidemiological studies report chronic vascular effects in workers exposed to nitroglycerin. Therefore, this document provides a clear description of how nitroglycerin causes systemic effects following dermal exposure.

#### Reviewer 2:

Yes

**2. If the SYS or SYS (FATAL) notations are assigned, is the rationale and logic behind the assignment clear? If not assigned, is the logic clear why it was not (e.g., insufficient data, no identified health hazard)?**

Reviewer 1:

Although the rationale and logic for assigning the SK:SYS notation is clearly explained, an adequate explanation for not assigning the SK:SYS (FATAL) notation is not provided. This document does describe the development of tolerance to the vasodilating action of nitroglycerin in workers subchronically or chronically exposed and the subsequent risk of sudden death in some of these individuals when they are removed abruptly from long-term exposures. Why this risk is not justification for assigning the SK:SYS (FATAL) needs to be provided, since there are documented cases of death due to exposure to nitroglycerin (although it is actually the withdrawal of exposure that precipitates sudden death).

Reviewer 2:

NA

**3. Does this document clearly outline the direct (localized) health hazards associated with exposures of the skin to the chemical? If not, what specific information is missing from the document?**

Reviewer 1:

This document does provide a clear discussion of case reports that demonstrate irritant contact dermatitis following dermal exposures to nitroglycerin. In addition, animal studies are mentioned that provide supporting evidence of the mild irritating effect of nitroglycerin on the skin.

Reviewer 2:

Yes

**4. If the DIR, DIR (IRR), or DIR (COR) notations are assigned, is the rationale and logic behind the assignment clear? If not assigned, is the logic clear why it was not (e.g., insufficient data, no identified health hazard)?**

Reviewer 1:

The rationale and logic is clear for the assignment of SK:DIR (IRR) to nitroglycerin.

Reviewer 2:

NA

**5. Does this document clearly outline the immune-mediated responses (allergic response) health hazards associated with exposures of the skin to the chemical? If not, what specific information is missing from the document?**

Reviewer 1:

This document presents information about case studies that link dermal exposure to nitroglycerin with skin sensitization. Also, incidences of nitroglycerin patch testing in humans resulting in allergic contact dermatitis are described.

Reviewer 2:

Partially. These papers would benefit from a quantitative assessment of data validity, utilizing the Benezra

(J Invest Derm) criteria

**6. If the SEN notation is assigned, is the rationale and logic behind the assignment clear? If not assigned, is the logic clear why it was not (e.g., insufficient data, no identified health hazard)?**

Reviewer 1:

Adequate rationale and logic are given for the assignment of the SK:SEN notation to nitroglycerin.

Reviewer 2:

Partially. see #5 (above).

**7. If the ID<sup>(SK)</sup> or SK were assigned, is the rationale and logic outlined within the document?**

Reviewer 1:

These notations were not assigned to nitroglycerin in this document.

Reviewer 2:

NA

**8. Are the conclusions supported by the data?**

Reviewer 1:

Other than not accounting for why the SK:SYS (FATAL) notation is not assigned due to the risk of sudden death subsequent to nitroglycerin exposure, all other conclusions made in this document are supported by the data presented. I agree with the notations assigned to nitroglycerin in this document.

Reviewer 2:

Yes

**9. Are the tables clear and appropriate?**

Reviewer 1:

The tables in this document are clear and appropriate.

Reviewer 2:

Yes

**10. Is the document organized appropriately? If not, what improvements are needed?**

Reviewer 1:

This document is well organized.

Reviewer 2:

Yes

**11. Is the language of the manuscript acceptable as written? If not, what improvements are needed?**

Reviewer 1:

The language used in this manuscript is both clear and concise.

Reviewer 2:

Yes

**12. Are you aware of any scientific data reported in governmental publications, databases, peer reviewed journals, or other sources that should be included within this document?**

Reviewer 1:

I am not aware of any additional scientific data that should be included in this document.

Reviewer 2:

Yes. Contact patch manufacturers for their adverse effect files.

**13. What is your final recommendation for this manuscript? (Do you agree with the scientific rationale that serves as a basis for the skin notation assignments?)**

Reviewer 1:

After providing a clearer justification for not assigning the SK:SYS (FATAL) notation to nitroglycerin, I recommend that this document be accepted as the SK Profile for Nitroglycerin.

Reviewer 2:

Acceptable. See above

NB Add statement re data (or lack of) on:

- a) Photoirritation
- b) Photoallergic Contact Dermatitis
- c) "Validity" of penetration algorithm