

6/1/2010

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

**Profile Number:** 04

**Profile Title:** Dinitrotoluene; 2,4-Dinitrotoluene (2,4-DNT); 2,6-Dinitrotoluene (2,6-DNT)

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### Summary

Both reviewers generally agree that the document clearly outlines the systemic health hazards, direct health hazards, and immune-mediated responses associated with exposures of the skin to Dinitrotoluene. Reviewer 2 suggests two studies (referenced below) that should be included as cases of skin absorption. Reviewer 1 has reservations about the SK:SYS assignment. He points to inconsistency between the statement, "No data that specifically estimated the absorption of 2,4-DNT in humans or animals following dermal exposure were identified" and the presentation of studies that do involve estimated absorption, namely Woollen et al [1985] and Reifenrath et al [2002]. Similarly, Reviewer 1 found the presentation of the SK:SEN assignment unclear due to contradictions between the statements in the document and the findings of Emtestam and Forsbeck [1985] and Lee et al [1975].

### Recommendations

- Levine [1985] and Reifenrath [2008] studies should be cited as cases of skin absorption. (Q1, Reviewer 2)
- First sentence on SK:SYS does not seem consistent with what follows. It states, "No data that specifically estimated the absorption of 2,4-DNT in humans or animals following dermal exposure were identified." Following this, several studies (Woollen et al [1985] and Reifenrath et al [2002] that do involve estimated absorption are presented. (Q2, Reviewer 1)
- Rationale for not making SK:SEN assignment is unclear. Justification for "absence of sensitization in workers handling DNT or in guinea pigs" is not adequately provided. Absence of sensitization is contradicted by findings in Emtestam and Forsbeck [1985] and Lee et al. [1975]. (Q6, Reviewer 1)
- In "1.1 General Substances Information" section, the name for the compound with CAS No. 25321-14-6 should be "dinitrotoluene (isomers mixture)". The structural formula for this compound is confusing with the use of "X" to show where the nitro groups will go on the toluene ring. Suggest placing the two nitro groups into the center of the toluene ring, which indicates they can assume of the possible positions in the ring structure, as is done on page 4 of, <http://www.inchem.org/documents/sids/sids/25321146.pdf>. (Q10, Reviewer 1)

### Suggested additional scientific data to review:

- Assessing Exposure to Dinitrotoluene Using a Biological Monitor. Levine, RJ, et al. Journal of Occupational Medicine. (1985), 27(9), 627-38. (Q1/Q12, Reviewer 2)
- Interaction of Hydration, Aging, and Carbon Content of Soil on the Evaporation and Skin Bioavailability of Munition Contaminants. Reifenrath, William G., et al. Journal of Toxicology and Environmental Health, Part A (2008), 71(8), 486-494. (Q1/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:

This document provides a detailed and clear discussion of the evidence for dermal absorption and subsequent systemic effects of DNT in humans. An in vitro study with pig skin and the calculation of the SI ratio are presented as well. Studies showing systemic effects in workers following skin contact are included.

#### Reviewer 2:

In most cases yes.

The below should also be cited as cases of skin absorption.

1. Assessing exposure to dinitrotoluene using a biological monitor. Levine R J; Turner M J; Crume Y S; Dale M E; Starr T B; Rickert D E. Journal of occupational medicine.(1985), 27(9), 627-38. Exposure of workers to dinitrotoluene (DNT) was evaluated at a DNT manufacturing plant. Urine was collected over 72 hours; work diaries were prepared dialy; breathing zone air was sampled; and skin and environmental surfaces were wiped. Chemical analysis was performed using gas chromatography or gas chromatography/mass spectrometry. Proportions of urinary DNT and metabolites deviated substantially from those reported in rats exposed to 2,4-DNT; but as with rats, females appeared to excrete considerably more dinitrobenzyl glucuronide. Between persons on any one day and within persons on different days, considerable variation existed in the proportions of metabolites excreted. The peak rate of excretion was likely to occur toward the end of a work shift or shortly afterward. Most urinary metabolites related to exposure during an eight-hour shift had been excreted by the start of work the following day. Estimates of the maximum one-day exposure incurred by a participant in this study ranged from 0.24 to 1.00 mg of technical-grade DNT per kilogram of body weight. A large proportion of the DNT absorbed by DNT operators and loaders, it is suggested, may have entered through the skin or the gastrointestinal tract.

2. Interaction of Hydration, Aging, and Carbon Content of Soil on the Evaporation and Skin Bioavailability of Munition Contaminants. Reifenrath, William G.; Kammen, Harold O.; Reddy, Gunda; Major, Michael A.; Leach, Glenn J. Journal of Toxicology and Environmental Health, Part A (2008), 71(8), 486-494 Water plays a key role in enhancing the permeability of human skin to many substances. To further understand its ability to potentially increase the bioavailabililty of soil contaminants, artificial sweat was applied to excised pig skin prior to dosing with munition-contaminated soils. Skin was mounted in chambers to allow simultaneous measurement of evapn. and penetration and to control air flow, which changed the dwell time of skin surface water within a l-h period post application of test materials. Addnl. variables included type of compd., aging of spiked soil samples, and carbon content of soil. To this end, the evapn. and skin penetration of C-14 labeled hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX), 2,6-dinitrotoluene (26DNT), and 2,4,6-trinitrotoluene (TNT) were detd. from two soil types, Yolo, having 1.2% carbon, and Tinker, having 9.5% carbon. RDX soil samples aged 27 mo and 62 mo were compared to freshly spiked soils samples. Similarly, 26DNT samples aged 35-36 mo and TNT samples aged 18 mo were compared to freshly spiked samples. Approx. 10 µg/Cm<sup>2</sup> of radiolabeled compd. was applied in 10 mg/Cm<sup>2</sup> of soil. Radiolabel recovered from the dermis and tissue culture media (receptor fluid) was summed to det. percent absorption from the soils. Radiolabel recovered from vapor traps detd. evapn. Mean skin absorption of all compds. was higher for low-carbon soil, regardless of soil age and skin surface water as affected by air flow conditions. For 26DNT, a simultaneous increase in evapn. and

penetration with conditions that favored enhanced soil hydration of freshly prepd. samples was consistent with a mechanism that involved water displacement of 26DNT from its binding sites. A mean penetration of 17.5% was obsd. for 26DNT in low-carbon soil, which approached the value previously reported for acetone vehicle (24%). 26DNT penetration was reduced to 0.35% under dryer conditions and to 0.08% when no sweat was applied. When soil hydration conditions were not varied from cell to cell, air flow that favored a longer water dwell time increased penetration, but not evapn., consistent with a mechanism of enhanced skin permeability from a higher hydration state of the stratum corneum. Profiles of 26DNT penetration vs. air flow conditions were exponential for freshly prepd. soil samples, suggesting strong and weak binding sites; corresponding profiles of 26DNT penetration from aged samples were linear, suggesting a conversion of weak to strong binding sites. Absorption and evapn. was less than 5% for TNT and less than 1% for RDX, regardless of soil type and age. Fresh preps. of RDX in Tinker soil and aged samples of TNT in Yolo soil showed a significant decrease in skin absorption with loss of surface moisture. The penetration rate of radiolabel into the receptor fluid was highest during the 1-2 h interval after dosing with 26DNT or TNT. HPLC anal. of 26DNT in receptor fluid at max. flux indicated no metab. or breakdown. For TNT, however, extensive conversion to monoamino derivs. and other metabolites was obsd. Relatively little radioactivity was found in the dermis after 26DNT and TNT applications, and dermal exts. were therefore not analyzed by HPLC. RDX was not sufficiently absorbed from soils to allow HPLC anal. This study has practical significance, as the use of water for dust control at remediation sites may have the unintended effect of increasing volatilization and subsequent absorption of soil contaminants. Soil in contact with sweaty skin may give the same result. Skin absorption of 26DNT from soil was over 50-fold higher than the value for dryer skin and over 200-fold higher than the value obtained when there was no sweat application. While the hydration effect was less dramatic for RDX and TNT, soil contaminants more closely matching the phys. properties of 26DNT may be similarly affected by hydration.

**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:

The rationale and logic for assigning the SK:SYS notation are clearly expressed in this document. Be that as it may, the first sentence in paragraph 2.0, "Systemic Toxicity from Skin Exposure (SK:SYS)" does not seem to be consistent with what follows. The first sentence states "No data that specifically estimated the absorption of 2,4-DNT in humans or animals following dermal exposure were identified." Following this opening sentence, the paragraph presents several studies that do involve the estimated absorption of 2,4-DNT (Woollen et al [1985]; Reifenrath et al. [2002].

Reviewer 2:

Insufficient data for SYS (FATAL).

**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 clearly presents case reports of dermatitis in workers and a study in rabbits showing dermal irritation.

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 justifying the assignment of the SK:DIR (IRR) notation to DNT are clearly stated in this document.

Reviewer 2:

Insufficient data

**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:

The evidence for and against skin sensitization or photosensitization in humans are both discussed in this document.

Reviewer 2:

Yes

**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:

The rationale and logic presented for not making the assignment of the SK:SEN notation are unclear. The sentence "These predictions of negative or weak activity are consistent with the absence of sensitization in workers handling DNT or in guinea pigs." is confusing. Justification for "predictions of negative or weak activity" is provided in the discussion, but justification for "absence of sensitization in workers handling DNT or in guinea pigs" is not. In fact, the absence of sensitization is contradicted by the findings of Emtestam and Forsbeck [1985] and Lee et al. [1975]. Perhaps this sentence should be rewritten to more clearly summarize the data presented.

Reviewer 2:

SK: SEN notation was not assigned on an adequate basis.

**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 in this document.

Reviewer 2:

SK: DIR (IRR) and SK: SYS notations were each assigned on an adequate basis.

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

Reviewer 1:

Other than in paragraphs 2 (SK:SYS) and 4 (SK:SEN), as noted above, the conclusions throughout this document support the data presented.

Reviewer 2:

Yes

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

Reviewer 1:

The tables are clear and appropriate.

Reviewer 2:

Yes

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

Reviewer 1:

The document is organized very well. In the "1.1 General Substances Information" section, the name for compound with CAS No. 25321-14-6 should be "dinitrotoluene (isomers mixture)". The structural formula given for this compound is somewhat confusing and misleading since it uses "X" to show where the nitro groups will go on the toluene ring. The following structural formula is suggested: place the two nitro groups into the center of the toluene ring, which indicates they can assume all the possible positions on the ring structure, as shown on page 4 of the following document, <http://www.inchem.org/documents/sids/sids/25321146.pdf>.

Reviewer 2:

Yes

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

Reviewer 1:

The language of the manuscript is very acceptable.

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 other scientific data that should be included in this document.

Reviewer 2:

See the 2 abstracts in #1.

**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:

I recommend that the first sentence in paragraph 2 be rewritten and that the rationale and logic presented in paragraph 6 be revised. I agree with the skin notation assignments made in this document based on the data presented.

Reviewer 2:

Acceptable