Captafol/o-Nitrotoluene Expert Panel Report

Part A – Peer Review of the Background Document on o-Nitrotoluene

The Report on Carcinogens (RoC) expert panel for Captafol/o-Nitrotoluene met at the Sheraton Chapel Hill Hotel on October 16, 2007, to peer review the draft background document on o-Nitrotoluene and make a recommendation for its listing status in the 12th Edition of the RoC. Members of the expert panel are as follows:

Lauren Zeise, Ph.D. (Chair)
California Environmental Protection Agency
Office of Environmental Health Hazard Assessment

Michael Elwell, D.V.M., Ph.D.
Covance Laboratories, Inc.
Department of Pathology

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Independent Consultant
(Retired from the International Life Science Institute and the U.S. Environmental Protection Agency)

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Independent Consultant

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Center for the Biology of Natural Systems

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University of Texas Health Science Center
Department of Pharmacology

Alexander W. Teass, Ph.D.
(Retired from the National Institute of Occupational Safety & Health)

One of the charges to this panel was to peer review the draft background document, which includes determining whether the information in the draft background document on captafol is presented in a clear and objective manner, identifying any missing information from the body of knowledge presented in the document, and determining the utility of the body of knowledge in the background document for drawing conclusions about the carcinogenicity of a candidate substance and for applying the RoC criteria for listing. Following the discussion of all sections of the draft background document the expert panel reached a consensus concerning the critique of the draft background document, including its adequacy and any proposed revisions and voted 7 yes/0 no, with 1 absent to accept the draft background document with the proposed changes suggested by the expert panel. Therefore, the expert panel agreed that the background document would be adequate for drawing conclusions about the carcinogenicity of o-nitrotoluene and for applying the RoC listing criteria.

The expert panel proposed revisions for each section of the ortho-Nitrotoluene background document that are appended.
General comments

*Use of foreign language journals.* The panel recommended that publications in foreign language journals should be translated when the studies are relevant for applying the RoC listing criteria. English abstracts from these publications can be used as a source for other types of information (such as exposure levels), if the information in the abstracts is presented clearly.

Executive summary

Mechanistic and Genotoxicity data, Pvi, L16-21: Delete “Based on this proposed …various tissues.” Change to “o-Nitrotoluene caused significantly increased incidences of tumors in tissues other than the liver in both rats and mice, including mammary gland, skin, lung, large intestine, and hemangiosarcomas in various tissues. This suggests that there are other mechanisms of activation for o-nitrotoluene.”
Section 1: Introduction

The expert panel identified additional synonyms for o-nitrotoluene (Table 1-1) and suggested some clarifications for the description of the chemical properties (Table 1-2). The revised tables with the revisions in blue font are below.

Table 1-1. Chemical identification of o-nitrotoluene

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS Registry number</td>
<td>88-72-2</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>( C_7H_7NO_2 )</td>
</tr>
<tr>
<td>Synonyms</td>
<td>1-methyl-2-nitrobenzene</td>
</tr>
<tr>
<td></td>
<td>2-methylnitrobenzene</td>
</tr>
<tr>
<td></td>
<td>2-methyl-1-nitrobenzene</td>
</tr>
<tr>
<td></td>
<td>2-nitrotoluene</td>
</tr>
<tr>
<td></td>
<td>2-nitrotoluel</td>
</tr>
<tr>
<td></td>
<td>benzene, 1-methyl-2-nitro</td>
</tr>
<tr>
<td></td>
<td>o-mononitrotoluene</td>
</tr>
<tr>
<td></td>
<td>o-nitrotoluel</td>
</tr>
<tr>
<td></td>
<td>o-methylNitrobenzene</td>
</tr>
<tr>
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<td>ONT</td>
</tr>
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<td></td>
<td>NSC 9577</td>
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<tr>
<td></td>
<td>RTECs No: XT3150000</td>
</tr>
<tr>
<td></td>
<td>DOT/UN No: 1664</td>
</tr>
</tbody>
</table>

Source: ChemIDplus 2007, Scifinder Scholar

Table 1-2. Physical and chemical properties of o-nitrotoluene

<table>
<thead>
<tr>
<th>Property</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>137.14</td>
</tr>
<tr>
<td>Melting point (°C)</td>
<td>–9.5 (needles); –2.9 (crystals)</td>
</tr>
<tr>
<td>Boiling point (°C)</td>
<td>222 at 760 mm Hg</td>
</tr>
<tr>
<td>Critical temperature (°C)</td>
<td>NA</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.162 at 19°C/15°C</td>
</tr>
<tr>
<td>Solubility in water (at 30°C)</td>
<td>650 mg/L</td>
</tr>
<tr>
<td>Octanol-water partition coefficient (( \log K_{ow} ))</td>
<td>2.30</td>
</tr>
<tr>
<td>Dissociation constant (pK\textsubscript{a})</td>
<td>NA</td>
</tr>
<tr>
<td>Vapor pressure (mm Hg)</td>
<td>0.188 at 25°C</td>
</tr>
<tr>
<td>Vapor density relative to air</td>
<td>4.73</td>
</tr>
<tr>
<td>Henry’s law constant</td>
<td>( 1.25 \times 10^{-5} \ \text{atm-cu m/mole at 25°C} )</td>
</tr>
</tbody>
</table>
Section 2: Human Exposure

1. Section 2.2 Production
   • P8, L29, After “(EPA 2007)”: Delete “One U.S. . . . SRI (2007)” and replace with “SRI (2007) reported that only one U.S. facility produced o-nitrotoluene in 2007, which according to its website has 134 employees, 50 contractors, and 20 retirees (http://www.firstchem.com/).

2. Section 2.3 Environmental occurrence and fate (Page 9)
   • P9, L19: NTP should search the Reporting Center for Hazardous Materials Spills database to see if there is any information on o-nitrotoluene spills.

3. Section 2.3.1 Air (Page 9)
   • P9, L23, After “(see...Exposure)”: insert the following statements from additional studies identified by the expert panel:
     • “Two ambient air samples collected at Boise Idaho in the winter of 1986-1987 contained 3 and 29 ng/m3 of o-nitrotoluene vapor (Nishioka and Lewtas, 1992).”
     • “Smog in Japan and China has been shown to contain o-nitrotoluene (Takahara and Hayakawa, 1984 (Li et al. 2005, Wu et al. 2006).”
     • “o-Nitrotoluene has been found adsorbed to snow (Roth et al. 2004)
     • “In a laboratory investigation, Atkinson et al. (1989) found minor amounts of o-nitrotoluene were formed when toluene vapor and nitrogen oxides were mixed in air: m-nitrotoluene was the major product.”
   • P9, L28, After “2-methyl-4-nitrophenol”: Insert “(Nojima and Kanno 1977).” NTP will confirm HSDB reference for the remainder of sentence.
   • Revise summary to reflect the new information.

4. Section 2.3.2 Water (Pages 10 to 11)
   • P11, L11, After “(Pantex 2006)”: Insert “In contrast with the Ogallala aquifer, Spain et al. (1999) and Best et al. (2000, 2001) studied groundwater highly contaminated with explosives and their impurities and metabolites, including o-nitrotoluene at concentrations greater than 2.1 mg/L (Spain et al. reported 2.9 mg/L). Both research teams were studying remediation of contaminated groundwater at a Tennessee munitions arsenal.” (Additional studies identified by the expert panel).

5. Section 2.3.3 Soil (Page 12)
   • P12, L2: “Delete “No information...however” and replace with the findings of additional studies identified by the expert panel: “A soil contaminated with 39,100 ppm of trinitrotoluene at a historical testing ground in Idaho contained 1.4 ppm of o-nitrotoluene (Radtké et al. 2002a,b).” Continue with “o-Nitrotoluene can result..."
   • P12, L17, After “(GAO 2002, 2003)”: Insert “A similar situation occurs in other countries where munitions manufacture and ammunition testing have been done historically (Toze et al. 1999; Spiegel et al. 2005).”
   • P12, L20, After “HSDB 2007)”: Insert “Obernosterer et al., 2000 used air stripping to remove 20% of o-nitrotoluene from quartz sand and loess loam. [This implies that volatility could be an important transport and remediation mechanism.] A review on sorption, mobility, and biodegradation of nitrotoluenes in soil is available (Toze et al. 1999).”

6. Section 2.4 General population exposure (Page 12)

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1 Note: Section number, page numbers and line numbers refer to the location in the draft background document.
• P12, L25, After "(HSDB 2007)" : Insert "[as well as via skin contact with contaminated surfaces and via oral ingestion of contaminated food, water, or dust.]" NTP will confirm the accuracy of this information.

• P12, L28-29: "No exposure to o-nitrotoluene was documented” contradicts the finding of o-nitrotoluene detected in 19.1% of air samples. NTP will clarify this statement.

• P12, L29, After (Krotosynski et al. 1979): Insert “Since o-nitrotoluene has a fish log BCF (bioconcentration factor) of 1.30 (Guo et al. 2004), [human exposure via fish residues should not be very important as a source.] Accumulation and depletion of o-nitrotoluene in carp (cyprinus carpio) has been modeled (Hou et al. 1997).” (Additional studies identified by the expert panel).

• P12, L 29, insert after (Krotoszynski et al. 1979), information from P10, L19-21 “At a former production site in Wisconsin between1999 and 2002, o-nitrotoluene was detected in offsite, private well-water at a maximum concentration of 0.095 μg/L”

7. Section 2.6 Biological indices of exposure (Pages 13 and 14)

• P13, L12, After “alcohol”: Insert “[probably present as o-nitrobenzyl glucuronide]”

• P14, L3-5: The units of measure should be "nmol/g creatinine."

• P14, L7, After “metabolites”: Insert “The importance of skin exposure was unknown.”

• P14, L13, After “bioactivation-system”: Insert “; however, work in other animal species such as rabbit and rat has shown that o-nitrotoluene has low methemoglobin-activating potency (Akahori 1954, Vasilienko 1976, Mlynarczyk and Sadowski, 2001). [Where exposures are to technical grade nitrotoluene, most of the methemoglobin activity will be related to the concentration of the para- and meta-nitro- isomers rather than the ortho- nitro- isomer.” (Additional studies identified by the expert panel).

8. Regulations (Pages 14 and 15)

• P14, L21, After “transporting.”: Insert “Safety measures after spills or leaks are prescribed in accordance with o-nitrotoluene being a combustible toxic hazardous material.”

• P15, L5: After “skin]”: Insert “Biological Exposure Index (BEI): 1.5% of methemoglobin during or at the end of the shift”

9. Summary (Page 15)

• P15, L19, After “Netherlands” : Delete “and Germany” and replace with “Germany, and the United States.”

• P19, L24, After “grounds”: Insert “o-Nitrotoluene has been detected in workplace and ambient air, surface water, ground water, fish, and soils.”

Modify summary to reflect other changes listed above.
Section 3: Human Cancer Studies

The human exposure study subgroup reviewed the description of human cancer studies reported in Sections 3 (magenta manufacturing workers who were or may have been exposed to o-nitrotoluene) and in section 5 (workers exposed to dinitrotoluenes or ortho-toluidine).

1. General Comments
   - Create a new Section 3.2: Studies of workers exposed to dinitrotoluenes or ortho-toluidine.
   - Move the description of studies on workers exposed to dinitrotoluenes (Section 5.5.2) and ortho-toluidine (Section 5.5.3) to this new Section (3.2) and summarize these studies in the discussion and summary. (The discussion and summary will become Section 3.3).

2. Section 3.1 Studies of magenta manufacturing workers
   - P17 L25, After “deaths): Insert “Larynx, esophageal and lung cancer also showed statistically significant elevations in the entire cohort, but the small sample in the magenta/safranine sub-cohort did not permit evaluation of these other cancer types.”
   - P17 to 18: Incorporate the following text in the description of the study reported by Rubino et al.: “The study had an excellent follow-up rate (96%). However, like all occupational cohort SMR-based studies, the effect estimates utilize an external comparison group (to determine expected disease rates). Rubino et al. used expected death rates in all Italy, in order to give more precise estimates, but the workers were males from Northern Italy. A strength of the study is the fact that the authors studied a group of workers who were specifically exposed to o-nitrotoluene, although also exposed to o-toluidine and 4,4’-methylene bis(2-methylene aniline) (but not to naphthylamines or benzidines)."
   - Page 18, L11, Before “mortality”: Insert “bladder cancer”
   - P18 L11, After “study.” Insert “The authors observed an earlier age at diagnosis, as well as an excess of bladder cancer mortality, in the cohort compared to the general population.”
   - P18, L17, Before “case-control study”: Insert “hospital-based” before
   - P18, L21, After “literature.”: Insert “Vineis and Magnani (1985) looked at 74 chemicals as part of a job exposure matrix. No adjustments were made for multiple comparisons”

3. Section 5.5.2 Dinitrotoluenes
   - P72, L21: Replace “450” workers with “457” workers
   - P72, L23: Replace “observed” with “expected.”, then insert “The numbers of observed deaths for specific cancer sites were small. However, the authors did observe a non-significant excess of colon cancer (SMR = 186).”
   - P72, L25: Replace “(some of which…)” with “(< 10% of whom ….)"
   - P73, L1, After “this”: Insert “Potential exposure to carcinogens other than dinitrotoluenes was a concern.”
   - P73, L3, After “dinitrotoluenes”: Insert “through inhalation and direct skin contact”
   - P73, L4, After “dinitrotoluenes”: Insert “(75% 2,4 DNT and 20% 2,6 DNT)”
   - P73, L5, After “renal-cell cancer”: Insert “Confidence intervals were not provided.”
   - P73, L6, After “humans”: Insert “Harth (2006) reported a cluster of 3 urothelial cancers among 60 workers exposed to 2,4 dinitrotoluene, with a calculated SIR = 15.9 (confidence intervals were not provided)". (Harth is a study identified by the expert panel)

4. Section 5.5.3 o-Toluidine hydrochloride

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2 Note: Section number, page numbers and line numbers refer to the location in the draft background document.
P73, L 29: After “(CI=2.13 to 5.73)”: Insert “The SIR for bladder cancer among the definitely exposed was 6.48 (95% CI: 3.0 to 12.2), which increased to 27.2 (95% CI: 11.8-53.7) for workers who were employed in the department with o-toluidine and aniline exposure for ≥ 10 years.”

P74, L2, After “used”: Insert “The authors collected smoking history on a 5% sample of workers using company medical records, and used modeling techniques to estimate that only a small proportion of the elevated SIR (1.05) could be attributed to higher smoking in the cohort versus the general population. This study has the advantage of calculating SIRs (using incidence rates) rather than SMRs (using death certificates). The authors concluded that o-toluidine was more likely than aniline to be responsible for the bladder cancer excess, in view of the greater carcinogenic potency of o-toluidine than aniline in animals. Stasik (1988) found excess bladder cancer incidence (SIR=72.7, 95% CI: 31.4 to 153.3) among workers exposed to 4-chloro-o-toluidine, o-toluidine and two other monocyclic amines.” (Stasik is a study identified by the expert panel).

5. Section 3.2 Discussion and Summary

P19, L3, After “Workers”: Insert ”Most of the aforementioned studies did not address other potential confounders such as cigarette smoking or genetic acetylator phenotype (e.g. NAT1, NAT2 genotypes.) But the relative risks associated with smoking and genetic susceptibility as well as other risk factors are small relative (RR= 2 to 4) to those associated with the dye manufacture.”

P19, L20, New paragraph: Insert “Limited epidemiologic studies on dinitrotoluenes are available and suggest elevations in hepatobiliary, urothelial, renal, and possibly colon cancer. Two studies of o-toluidine reported excess bladder cancer incidence.”
Section 4: Studies of Cancer in Experimental Animals

1. General
   - The background document should indicate that the NTP studies represent a high quality data set for making conclusions about potential carcinogenicity of o-nitrotoluene.
   - Treatment-related hemangiosarcomas in mice were listed in various sites, which were in the subcutis/skeletal muscle and mesentery. The specific sites should be noted in the document, preferably in a table, with associated statistics.
   - ‘The description of each study should (1) include the age of the animals at start of the study; (2) include the purity of the substance; (3) include more details (in the footnotes to the tables or noted in the text) on characteristics, such as laboratory, chronological time window, that the historical control share with the concurrent controls; (4) report significance values for trend tests in the tables, and (5) distinguish $P$ values that are highly significant (e.g., $P < .001$ from those that are $P < .05$ or $< .01$). Tumor effects are quite striking and the current report does not reflect that.

2. Section 4.1 Rats
   - P 21-22 Section 4.1.1: Move the discussion of the toxic effects observed in the 13-week study to the toxicity section (Section 5.6). Delete all entries except that for the epididymis-mesothelium findings from Table 4-1.
   - P 24 L12-14 “slightly greater mean body weight than those in the 26-week-exposure group, but still weighted less than the controls”: Were these weight differences statistically different? If yes say so; if not, delete. Magnitude of the effect not defined in paper. It can be noted that the rats in both the stop exposure and the 26 week study weighed more that the control.
   - P 25, L9: Emphasize the consistencies of the mesothelomia findings in the altered and non-altered fluora study.
   - P 26, L28: If the low survival of the high-dose and/or mid-dose animals is due to malignancy it should be noted.
   - P 27, L 8-23: Delete parenthetical for malignant mesothelioma (“mainly large, papillary or solid areas of pleomorphic mesothelial cells”) and replace with site-specific information, e.g. tunica vaginalis of the testis epididymis or surface of abdominal wall. Also, delete the detailed description of tumors for the lung and liver lesions (i.e., at line 18 and 19 – “which were usually papillary and distorted the alveolar architecture” and the sentence at line 20-23 “The hepatocellular adenomas consisted... three or more cells thick.”).
   - P 29, Table 4-3a: Delete heading, “various tissues” from the heading for Malignant Mesotheliomas.
   - P 30 Table 4-3b: Add adenoma/carcinoma to column heading for the lung tumors.

3. Section 4.1 Mice
   - P 31, Section 4.2.1: Move the 13-week mouse study (subchronic toxicity) to Section 5.6.
   - P 33, Table 4-5: Add the following footnote for the incidence of large-intestine carcinoma (0%) in the 5000-ppm male mice. “Dunnick et al. (2003; NTP 2002b) suggested that the 5000-ppm male mice did not survive long enough for tumors to develop in the large intestine.”

3 Note: Section number, page numbers and line numbers refer to the location in the draft background document.
4. Section 4.3 Summary, Table 4-6 (page 34)
   - Change “Mesothelium” to “Malignant Mesothelium” to be consistent with the text.
   - Insert a row under Liver for “Hepatocholangiocarcinoma”, Insert new footnote (b) “Only 2 tumors were observed but they are very rare and the NTP used them as part of their call.”
   - Notation (+=) for colon tumors in female mice, After “different”: Insert “from concurrent controls but highly significant (p>0.001) compared to historical controls”.
   - Footnote “a”: Change “Only adenomas (no carcinomas) were found in female F344/N rats” to “Based on adenomas found in female F344N rats.”
Section 5: Other Relevant Data

1. Section 5.1.1 ADME: Human data (Pages 35-36)
   - P35, L27-29, After “alcohol: Insert “[probably present as o-nitrobenzyl glucuronide],”
   - P35, L25: Delete “indirect” before “evidence”

2. Section 5.1.2 ADME: Rodent data (page 36-37)
   - P37 L12, Before “NTP 2002b”: Insert the following new references: “Sabbioni 1994; Sabbioni and Sepai 1995;”.
   - P37 L13, After “tissues”: Insert findings from a new reference, “The hemoglobin binding index for o-nitrotoluene in female Wistar rats was measured to be 0.72±0.19 mmol compound/mol Hb)/(mmol compound/kg body weight (Sabbioni 1994)

3. Section 5.1.3 ADME: in vitro data (Page 37 to 38)
   - P38, L11: Insert new paragraph describing findings of Kedderis and Rickert 1985.  
     (Additional study identified by the expert panel.)
     Rat liver microsomal cytochromes P450 oxidized the isomeric aminobenzyl alcohols, metabolites of the nitrotoluenes, to hydroxylamine and/or aminophenol metabolites (Kedderis and Rickert, 1985). The metabolites were extractable into ethyl acetate and capable of reducing ferric iron, consistent with the formation of hydroxylamines and/or aminophenols. The oxidation rates of the aminobenzyl alcohols were five times lower than those of the aminonitrobenzyl alcohols (metabolites of dinitrotoluenes). The rate of aminobenzyl alcohol oxidation varied as 2- > 3- > 4-.. Thus the 2-aminobenzyl alcohol metabolite of o-nitrotoluene (0.5 mM) was oxidized at a greater rate (0.29 ± 0.01 nmol formed/min/mg protein) than the aminobenzyl alcohol metabolites of m-nitrotoluene (0.18 ± 0.00) or p-nitrotoluene (0.04 ± 0.00). These results are consistent with the toxic potency of the mononitrotoluene isomers.

4. Section 5.1.4 ADME: In vivo metabolism of o-nitrotoluene in rodents (Pages 39 to 43)
   - P41, 1st Paragraph: Add a sentence to note that minor metabolites can be converted into major metabolites.
   - P41, L14-16: Replace “non-pretreated” with “untreated”.
   - P41, L22-25: Delete sentence beginning with “Presumably.”

5. Section 5.2 (pages 49 to 52)
   - Page 52, L18-20: Delete “Although hemoglobin… to rats and” since this has nothing to do with DNA adduct formation. Begin new sentence with “DNA adducts are formed…”
   - Page 52 L26-29: Delete sentence beginning with “Jones, et al. (2005a)…concentrations.”

3. Section 5.3.2: Genetic damage and related effects: Mammalian systems (Pages 53 to 55)
   - P54, L6, After “(CHO)”: Insert “and lung (CHL/IU)”
   - P55: Add to text and Table 5-5, results from the following new studies identified by the expert panel:
     - Matsushima et al. (1999): o-nitrotoluene (2 to 50 μg/ml) caused micronuclei in Chinese hamster lung cells.
     - Ishidate et al. 1988: o-nitrotoluene caused chromosomal aberrations in CHL
     - Huang 1996: o-nitrotoluene caused chromosomal aberrations in human peripheral lymphocyte

4 Note: Section number, page numbers and line numbers refer to the location in the draft background document.
5. Section 5.3.3: Genetic damage and related effects: Gene expression studies
   - P59–68: Consolidate and integrated this text with the text on page 5.4.2. Add findings from Iida et al. 2007, that o-nitrotoluene did not down regulate TSC -22.

6. Section 5.4.1: Genetic damage and related effects Mechanistic studies and Considerations:
   - bioactivation of o-NT
     - P 62, L4-9: Delete text from “However, there appears…o-nitrotoluene administration.”.
     (which states that female rats should be more resistant to the hepatocarcinogenic effects of o-nitrotoluene if only the bioactivation factors were considered). Begin last sentence with “The significantly….“

6. Section 5.5 Carcinogenicity and genotoxicity of o-nitrotoluene analogues and metabolites
   - P68, L10, After “male rats”; Insert text stating that the bioactivation of 2,4 dinitrotoluene is similar to that of o-nitrotoluene

7. Section 5.5.2 Dinitrotoluenes (Pages 70-73)
   - P71, L7-23: Correct mistakes in defining the isomers.
     - L8, “2,4-“ should be “2,6-“
     - L9, “2,6-“ should be “2,4-“
     - L13, “2,6-“ should be “2,4-“ and “2,4” should be “2,6-“
   - P 72, L9, Insert new paragraph describing findings in Kedderis et al. 1984 (Additional study identified by the expert panel)
     These studies showed that sulfotransferase inhibition in vivo decreased the covalent binding of the hepatocarcinogen 2,6-dinitrotoluene to hepatic DNA by >95%. These results indicate that sulfation is involved in the bioactivation of 2,6-dinitrotoluene. These studies, along with the in vitro studies of N-oxidation cited above, helped clarify the complex bioactivation mechanisms of the dinitrotoluenes (Kedderis et al. 1984).
   - P72 L9, After Kedderis et al. 1984, summarizes the findings of Kedderis et al. 1985 mentioned above (5.1.3)
   - P72 L19 to p73 L6: Move description of human epidemiological studies to the new Section 3.2  (See comments on Section 3:  Human Cancer Studies, above)

8. Section 5.5.3 o-Toluidine hydrochloride (Pages 73-74)
   - P73, L25-29 to P74, L1-4); Move description of human epidemiological studies to the new Section 3.2  (See comments on Section 3:  Human Cancer Studies, above)

9. Summary (Pages 74-77)
   - Section 5.1, P74, L18, Delete “indirect” before evidence.
   - P75, After 17: Add a summary of the in vivo studies summarized in Table 5-6
   - P75, L 28-29 to P76, L 1-2: Delete text related to the statement that female rats should be more resistant to the hepatocarcinogenic effects of o-nitrotoluene if only the bioactivation factors were considered. Remove “In addition" on line 2.


12. Jones CR, Sepai O, Liu YY, Yan H, Sabbioni G. 2005a. Hemoglobin adducts in workers exposed to nitrotoluenes. *Carcinogenesis* 26(1): 133-143. (Supported by the European Commission. Author affiliations: Institute of Environmental and Occupational Toxicology, Switzerland; University of Newcastle upon Tyne, UK; Ludwig-Maximilians-Universität München, Germany; Chinese Academy of Preventative Medicine, China.)

13. Kedderis GL, Dyroff MC, Rickert DE. 1984. Hepatic macromolecular covalent binding of the hepatocarcinogen 2,6-dinitrotoluene and its 2,4-isomer in vivo: modulation by the


