Captafol/*o*-Nitrotoluene Expert Panel Report

Part A – Peer Review of the Background Document on Captafol

The Report on Carcinogens (RoC) expert panel for Captafol/*ortho*-Nitrotoluene met at the Sheraton Chapel Hill Hotel on October 15 & 16 2007, to peer review the draft background document on captafol and make a recommendation for its listing status in the 12th Edition of the RoC. Members of the expert panel are as follows:

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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 (8 yes/0 no) 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 captafol and for applying the RoC listing criteria.

The expert panel proposed revisions for each section of the captafol background document 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.

Section 1: Introduction

The expert panel identified additional synonyms for captafol (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 captafol

Characteristic	Information
CAS Registry number	2425-06-1
Molecular formula	$C_{10}H_9Cl_4NO_2S$
Synonyms and trade names	3a,4,7,7a-tetrahydro-2-[(1,1,2,2-tetrachloroethyl)thio]-1*H*-isoindole-1,3-(2*H*)-dione (CAS), difolatan (JMAF), 1,2,3,6-tetrahydro-N-(1,1,2,2-tetrachloroethylthio)phthalimide (IUPAC), N-(1,1,2,2-tetrachloroethylthio)cyclohex-4-ene-1,2-dicarboximide (IUPAC), 3a,4,7,7a,tetrahydro-N-(1,1,2,2-tetrachloroethanesulfenyl)phthalimide (IUPAC), Trade formulations: Alfloc 7020, Alfloc 7046, Arborseal, Captaspor, CS 5623, Difolatan, Difosan, Folcid, Foltaf, Haipen 50, Kenofol, Merpafol, Nalco 7046, Ortho Difolatan 80W, Ortho 5865, Proxel EF, Sanspor, Santar SM, Sulfonimide, Sulpheimide, Terrazol, Captafol Pestanal

Source: Agrochemicals Handbook 1991, IARC 1991, Saxena *et al.* 1997, ChemIDplus 2006, O'Neil *et al.* 2006.

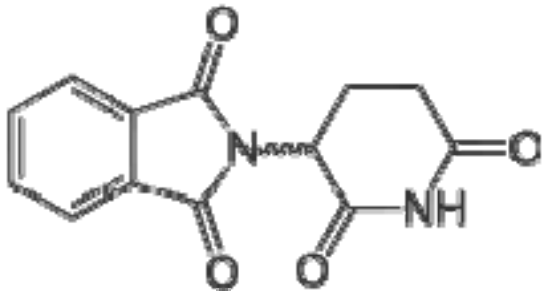
Table 1-2. Physical and chemical properties of captafol

Property	Information
Molecular weight	349.1
Melting point (°C)	160–161 (slow decomposition)[a]
Boiling point (°C)	NA
Specific gravity	NA
Density	~~NA~~1.64±0.1 g/cm^3 at 20°C[b]
Solubility water water acetone benzene dimethylsulfoxide isopropanol methyl ethyl ketone toluene xylene slightly soluble in most organic solvents	 1.4 mg/L (practically insoluble) at 20°C[a] 2.24 mg/L at 25°C[c] 43 g/kg 25 g/kg 170 g/kg 13 g/kg 44 g/kg 17 g/kg 100 g/kg
Octanol-water partition coefficient (log K_{ow})	3.8 3.183 at 25°C[c]
Dissociation constant (pK_a)	~~NA~~ 2.67±0.20 at 25°C (calculated)[b]
Hydrolysis	slowly hydrolyzed in aqueous emulsions or suspensions at room temerature but rapidly in acidic and basic aqueous media[a]
Vapor pressure (mm Hg)	8.27 x 10^{-9} at 20°C (calculated)[c]
Vapor density relative to air	12[d]
Henry's law constant	2.79 x 10^{-9} atm-m^3/mol

Source: HSDB 2006, unless otherwise noted.
[a] Source: Agrochemicals Handbook, 3rd Edition
[b] Source: Scifinder Scholar
[c] Source: Kim *et al.* 1997
[d] Source: UAkron 2004.
NA = not available

Other comments

- Add the chemical structure of the teratogen thalidomide to Figure 1-2. The chemical structure of the three fungicides is also related to the teratogenic thalidomide structure, in that it has the phthalimide group; it is most structurally similar to Folpet." However, since it does not have the chloroalkylthylthio side chain, the panel did not feel that it was necessary to describe its health effects in the background document.



- 2-(2,6-dioxo-3-piperidyl)isoindole-1,3-dione
  (thalidomide)

Section 2: Human Exposure[1]

1. Introduction (Page 7)
   - P7, L9, After occurred: Insert "including exposure to spray drift, on worker reentry after spraying, and leakage into ground water from hazardous waste sites."
   - Section 2.1 Use (Pages 7 to 9)
   - P8, L14: change "tolerances, which are still in effect" to "which were still in effect until 2006"
   - P8, L17, After "captafol" Insert "In 2006, EPA revoked specific tolerances and tolerance exemptions for captafol, and stakeholders withdrew their support for import tolerances."
2. Section 2.3 Occurrence and exposure (Page 10)
   - P10, L12: Add information on FDA monitoring of byproducts of Captafol (tetrahydrophthalimide [THPI] data) residues in domestic and imported foods. Note that THPI does not provide information specific for captafol (Georgopoulos and Ziogas 1981).
   - P10, L11, After "1998": Insert "Captafol has been found as an impurity in Ridomil 25 WP, a commercial formulation of metalaxyl; exposures to captafol could occur as a result of using Ridonil 25 WP."
3. Section 2.3.1.1 Occurrence and exposure: Air (Page 10)
   - P10, L16: Delete "No information…air."
   - P 10, L18, After "HSDB 2006): Add the following information from additional studies identified by the expert panel:
     * "Captafol has been detected in air spray drift during high pressure spray boom and aerial field applications (Frank *et al.* 1994)."
     * Add results from Reddy 1988, which was an experimental study, in which sterile soil was treated with captafol. Volatiles from captafol on wet soil caused vapor phase inhibition of *Drechslera nodulosa.*
     * Vapor phase captafol caused mitotic crossing over of *Aspergillus nidulans* (Ziogas and Georgopoulus 1987).
4. Section 2.3.1.2 Occurrence and exposure: Water (Pages 10 to 11)
   - P10, L20: Delete "No information…water" Add the following information from additional studies identified by the expert panel:
     * P10, L29, After '1995': Insert "Captafol in ground water has been reported in other countries, however (Frank *et al.* 1990; Legrand *et al.* 1992)."
     * P11, L2, After "1994": Insert "Captafol has been detected in surface waters in Italy (Readman *et al.* 1997), Spain (Vioque-Fernandez *et al.* 2007) and Korea (Kim *et al.* 1997b), mostly associated with runoff after field application."
5. Section 2.3.1.3 Occurrence and exposure: Soil (Page 11)
   - P11, L5: Delete "No Information…soil.", Add (After "55 days", L11) the following information from additional studies identified by the expert panel:
     * "A nine-year study showed that captafol soil residues were not enriched in soil (Garcia e*t al.* 1990)."
     * "An Indian study showed that captafol persisted in 4 soil types for up to 60 days (Venkatramesh and Agnihothrudu 1988)."
   - L8-10: Text ("Captafol has been reported to degrade rapidly in soil with some variation based on soil type and initial concentration….") contradicts reference cited (HSDB 2006), which states

[1] Note: Section number, page numbers and line numbers refer to the location in the draft background document.

that half-life is about 11 days, independent of soil type or initial concentration. However, the text is consistent with the not-cited reference. Extoxnet 1995, which gives soil half-lives of <3 days for organic soil, 5 days for sandy soil, and 8 days for clay-loam soil. Add information from both references, and check references for lines 10 and 11 ("captafol had a half-life in three different types of soil that ranged from 23 to 55 days".)

6. Section 2.3.1.4 Occurrence and exposure: Food (Pages 11 to 13)
   - P11 L18-19: Delete sentence "Captafol is non-systemic…animals". It is inaccurate and unnecessary.
   - P11, L19-23: "residues would be easily removed…in animals.)", If it can not be confirmed that residues are easily removed, then delete text.
   - P11 L27: The tolerances statement needs to be modified in light of Federal Register (2006), 71(80); e.g., change "United States still has tolerances" to "the United States had tolerances until 2006…".
   - P12, L5-7: Change text to "Based on these analyses, captafol was detected in domestic apples in only 5 of 2,464 samples (highest level 0.13 ppm [below the EPA tolerance level of 0.25 ppm]) analyzed..."
   - P12, L10-11: Change text to "In 1996, detectable levels of captafol were found in only 3 of over 5,000 samples."
   - P12, lines 23-24. Delete "No further information…United States", because it is not accurate. The USDA Pesticide Data Program, managed by the Agricultural Marketing Service is also another U.S. government-funded food residue monitoring program (in addition to FDA). Insert "Captafol was not detected in orange juice, canned spinach, or tomatoes in 2005 according to USDA 2006. The degradation product THPI has been detected in foods [but may also come from captan degradation or metabolism]."

7. Section 2.3.2 General Population exposure (Pages 13 to 14)
   - P13, L21-22, After "ingestion of foods that had been treated with captafol": Add a new paragraph. "Populations that drink contaminated ground water from landfills with wastes containing captafol and from contaminated top soils can also be exposed."
   - P13, L30: Replace "widespread" with "potential"; note that the authors of that study are quite careful about referring to their exposure measure (Zip code-level pesticide usage data) as "potential" for exposure.
   - P14, L17-25, Whyatt *et al.* (2003) study:
     * Review this study to see whether captafol was detected in the air.
     * Review other studies on the cohort from the Columbia (NY) Center for Children's Environmental Health to see whether there is any air sampling data on phthalimides.
     * P14, L25, After "captafol": Insert as bracketed comment "[THPI in both plasma and urine reflects exposure from all routes of exposures.]"
   - P14, After L25: Add a new paragraph with new information identified by the expert panel:
     * "The toxicity potential in the nested multi-media fate, exposure and effects model USES-LCA has been estimated for captafol using 6 environmental impacts after initial emission to the 5 compartments air, freshwater, seawater, industrial soil, and agricultural soil (Huijbregts *et al.* 2000)."

8. Section 2.3.3 Occupational Exposure (Pages 14 to 17)
   - P14, L29, After "fungicide": Insert "or after reentry of a sprayed field"
   - P15, L6, After "use", insert Monge *et al*. (2005) estimated an 'exposure intensity' based on retrospective exposure assessment using interviews and application rate (L/ha) estimates at regional levels as a proxy for potential exposure level." (Additional study identified by the expert panel.)

- Search the literature for additional occupational studies of captafol exposure, such as production, or among farm workers.
- P14, L29: Delete "however, no data…in the literature" and insert "Daily absorbed doses for mixers, loaders, and applicators of captafol were compared with acute human LD_{50} values, and lifetime absorbed daily doses were compared with Reference doses and carcinogenic thresholds developed by EPA (Woodruff *et al.* 1994)."
- P14, After above: Insert "The threshold concentrations for dermatitis effects of captafol have not been determined."

9. Section 2.4 Regulations and Guidelines (Page 15)
   - P15, L15: Change to "Tolerance levels have been revoked for all foods thereby making it illegal to import or introduce into commerce any foods with captafol residue." Need to verify whether tolerances were regulated under the Federal Insecticide, Fungicide, and Rodenticide Act.
   - P15, L18: Check whether the OSHA regulation still exists, if not, delete air concentration and replace with "none" (result of being vacated June 1993).
   - P15, L21 After "mg/m^3": Insert "(skin; not classifiable as a human carcinogen)"
   - P15, L24, After "mg/m^3": Insert "(skin)"
10. Section 2.5 Summary (Page16)
   - P16, L6 After "tomatoes": Insert the 2006 EPA Federal Register details
   - Revise to reflect peer-review comments of the expert panel listed above.

Section 3: Human Cancer Studies

1. Section 3.1.1 Human exposure to captafol: Statistical analysis (Page 18)
   - P18, L9: Replace "prevalence odds ratios" with "mortality odds ratios"
2. Section 3.1.4 Human exposure to captafol: Results (Page 18)
   - P18, L18: Insert "The main statistically significant finding was for 1.3-dichloropropene, for which the OR was 1.89 (95% CI; 1.13-3.15) for residence in the county for over 20 years."
   - P18, L 24, after "cases)." Insert "The first three quartiles of captafol usage were combined as the reference category. Dose response relationship between pancreatic cancer mortality incidence and captafol potential exposure was not evaluated."
3. Section 3.1.4 Human exposure to captafol: Strengths and limitations (Pages 18 to 19)
   - The limitations that were acknowledged by the authors should be attributed to them: These include: misclassification of disease; incompleteness of pesticide usage data; lack of complete residential history; and migration of resident.
   - Add to the text on the authors' discussion of limitations: "The authors believe that the direction of distortion of odds ratios would be towards the null. Failure to adjust for smoking could have led to bias away from the null."
   - Add text to note the following additional limitations or modify the text:
   - P19, L1-4, After "assigned.": Insert, "Given the ecological study design, the direction of bias due to misclassification of exposure is not predictable, since so much exposure data is lacking." Also, at L3 replace "which will tend towards null findings, and a lack of precision" with "…misclassification of exposure….,which limited the precision with which different dose levels."
   - P19 L5: "Eighteen compounds were studied, and there was no accounting for multiple statistical tests (comparisons)."
   - P19, L13-15: Delete ("It is not clear…combined") and replace with "Missing information about captafol usage and failure to specify actual distributions within quartiles do not permit evaluation of this potential effect. It is not always clear when levels are zero, or whether the information is missing."
   - P19, L 15, Insert "The authors did not examine correlations between captafol and each of the three components that showed elevated ORs (1,3-dichloropropene, dieldrin and pentachloronitrobenzene). Correlations between one or more of these compounds could contribute to the elevated ORs for captafol."
   - P19, L23: Delete, " and no information…confounders." and replace with "for example, correlation data between the pesticides usage was not presented."
4. Section 3.2 Human exposure to captan
   - Add an introduction to this section that states that studies on captan are less informative for review of captafol but are included because (1) captan is closely related chemically to captafol, and (2) to understand the studies in Section 3.3 that include exposure to captan.
5. Section 3.2 Human exposure to captan: McDuffie *et al.* 2001 (Pages 19 to 20)
   - P20, L4, Note that increased risk was noted for both exposure categories.
   - P20, L6 to 11 (controlling for other pesticide), Delete (1) "When exposure to other pesticides was controlled for in a multivariate logistic model, captan did not contribute significantly to the risk of non-Hodgkins" and (2) bracketed comment about the multivariate model ("[Because…overcontrolling].") because this information was not verified.
   - P20, last statement in paragraph: Add that "The findings of multiple elevated odds ratios for various pesticides and the exposure of subjects to multiple pesticides suggest that finding for captan could be non-specific."

- Add comments as additional limitations: (1) “Response rates were low overall, and lower among controls versus cases. This could have contributed to recall bias.”; (2) “No dose response relationships were identified.”; and (3) “The authors did not address multiple comparisons.”

6. Section 3.2 Human exposure to captan: Mills 1998 (Page 20)
   - Add to results: “Captan was associated with a decreased statistically significant risk of testicular cancer.”
   - Add that “The author reported that Hispanic and African American men may have been the most highly exposed.”
   - Line 21, Insert “Sample sizes were not given, but differences in population size probably explained why the correlation coefficient of 0.46 was statistically significant while 0.49 was not.”
7. Section 3.2 Human exposure to captan: Engel *et al.* (2005) (Pages 20 to 21)
   - P 21 L14-15: Insert “exposed” before “cases”
   - Add the following comments:
     * “The study did not have power to examine dose-response relationships.”
     * “Overall response rates were low, and were not reported for cases and controls separately.”
     * “There was a considerable amount of missing data, both on the primary exposures and covariates.”
8. Section 3.3 Human exposure to phthalimides and fungicides as a class: Miligi (2003) (Pages 21-22)
   - Add the following comments or information:
     * The effects of various crops were examined. But there was no evaluation of the risk from ingestion of specific food items.
     * Add number of cases and controls.
9. Section 3.3 Human exposure to phthalimides and fungicides as a class: Schroeder *et al*. (2001) (Page 22)
   - P22, L5: Change “marginally” to “approaches” significance.
   - P22, L11: Delete “[it is not clear whether this was an adjusted OR]”; the ORs are adjusted for age, state, vital status (footnote to Table 5 in Schroeder *et al.* 2001).
   - Add the following comments:
     * “Only a small portion of cases (29%) were evaluated for the molecular marker.”
     * “ORs could not be estimated for phthalimides and translocation negative NHL.”
10. Section 3.4 Discussion and summary (Pages 22 to 23)
    - P23, L5-8: Rewrite to discuss the following 3 major areas of bias:
      * Exposure assessment – likely bias towards to null
      * Residual confounding – likely bias away from null
      * Correlation of exposure – bias towards or away from the null
    - P23, L5-8: After the discussion of the 3 biases, add “In addition, the studies had small numbers of exposed cases leading to imprecise risk estimates.”
11. Tables.
    - Add the results for testicular cancer to the entry for Mills 1998.

Section 4: Studies of Cancer in Experimental Animals

2. General comment:
   - The description of each study should include the age of the animals at start of the study.
   - Statistics: The NTP should calculate and/or report (1) Statistics on combined incidence, according to current NTP practice and scientific rationale, and (2) pair-wise comparisons and trend tests, when study authors fail to report them. If data are available from the Cancer Potency Data Base (CPDB) that provide combined incidence information and statistics they should be included in the report. NTP could use the trend values from the CPDB or calculate the values and report them. (3) For sites that are targets of tumorigenesis, report additional statistics even if the study author has not done so when a relevant tumor type is of marginal statistical signficance. For example, in Table 4-5 exact p-values for the ✓/x case could be given instead of reporting them as non-statistically significant; the exact p-values for these sites would also be reported in Table 4-2.

12. Section 4.1 Mice: Quest et al (Page 27-28)
   - P28, L4, After "Excessive toxicity was indicated by poor survival": Insert "[survival and body weight data not provided]."
   - P28, L5, After Lymphosarcoma: Insert "[This does not impact on the overall evaluation/interpretation of the carcinogenicity results for this study. While the authors indicate the early deaths were attributed to lymphosarcomas and while this may be true for those cases with a known cause of death this could not explain the degree of reduced survival in this case.]"
   - P28, L10: Bracketed statement should be included to indicate site-specific tumor incidence was not reported.
   - P28 L11: Bracketed statement should be included to indicate historical control ranges for tumors were not given.
   - P 29 L27 to 28: Discussion regarding chronic nephropathy should be moved to the toxicity section.
   - Table 4.1: Several inconsistencies in the statistical results from Quest *et al.* review were noted in the draft background document as [bracketed] footnotes for this table. In addition to those footnotes, the expert panel identified other consistencies or errors:
     * The NTP expresses skepticism in footnote b about the reporting of statistical significance for one finding. By Fisher Exact, the finding is significant (p = 0.016), contrary to the Quest *et al.* reporting of their findings.
     * The trend test for vascular neoplasms in females (0-1-3-6) was not significant while the incidence for males (1-0-5-6) was significant (the trend in females appears to be as strong as in males).
     * The trend test in males for lymphosarcoma (0-3-4-13) was not significant while the vascular tumor trend test (1-0-5-6) was significant.
     * The trend test findings for lymphosarcoma in both males and females and for hemangiosarcoma in females show them as not significant in the draft report. However, they all appear to be significant (e.g., with positive hazard function slopes reported in the CPDB of $P < 0.006$ for female hemangiosarcoma and $P < 0.004$ and $P < 0.0005$ for female and male lymphosarcoma).

     The expert panel recommends that pair-wise and trend tests be checked and reported correctly for all sites and tumor types. Corrected values and the type of statistical test should be reported in the NTP report. If the survival data on individual animals is not available to perform the poly-3 tests, the Fisher Exact test could be performed. The NTP should perform and include trend tests for these sites or report CPDB statistics. Given the low survival it would have been preferable to perform the statistical tests on an individual animal basis had such data been available, since dose related mortality biases the statistics toward the null. Thus, the actual

significance of the finding may be higher than that calculated. If NTP does not have access to the individual animal data (with time of observation recorded) this should be noted as a limitation.

13. Section 4.1 Mice: Ito *et al.* (Page 28 to 29)
    - P29, L4 to 5: Add to the description of the study, "The decrease in body weight gain exceeded 10% for all dose-groups in both sexes."
    - P29, L16. The document states that "[Some of the *P* values reported as less than 0.05 by the authors…were recalculated and found…]" Clarify in a footnote that values were recalculated by authors of the background document.
    - P29, L27: Indicate that the "endothelial hyperplasia" was in the heart where the hemangiosarcomas also occurred. Add to text, the hyperplasia in the small intestine (0-0-0-3; 0-1-0-2; males and females, respectively); while not statistically significant, they seem to be relevant to the neoplastic effect (progression) at that site.
    - Table 4-2:
        * As per NTP practice, the combined incidence of liver adenoma (hyperplastic nodules) and carcinoma for the $B6C3F_1$ mouse for data should be reported in Table 4-2. The CPDB reports the combined incidence as 4/48, 27/50, 22/49 and 0/51 for female control, low, mid and high dose groups, and 22/47, 41/51, 31/46 and 8/47 for the same dose groups in males.
        * The combined incidence of forestomach (benign and malignant) tumors and small intestine tumors (benign and malignant) should be reported.
        * Resolve the discrepancy (from the review of Ito *et al.* or by contacting Dr. Lois Gold) for male $B63F_1$ mice liver tumors between the result reported Ito *et al.* and the CPDB
    - The data in the report suggests that combined incidence of vascular tumors at multiple sites could be highly significant for the B6C3F1 mice of both sexes but incidence data may not be available. Analysis of vascular tumors combined across multiple sites should be performed and reported if data are available.

14. Section 4.2.1 Rats: Nyska *et al.* study: (Pages 31 to 32)
    - P 32, L3 to 4, "Cortical tubular cysts, a known pre-neoplastic lesion, …": Delete "known pre-neoplastic lesion". If the cortical tubular cysts are "known preneoplastic lesions" in the kidney of rats, the relationship of this finding to tumors is not evident in females that had the same cyst incidences as males but no renal tumors. The 'tubular epithelial nodular hyperplasia' that occurred primarily in males is a more appropriate non neoplastic finding associated with the tumor response in this study and should be included in the draft text.

15. Section 4.2.1: Tamano *et al.* 1990 (Page 32)
    - Add in brackets [ ] "Chronic progressive nephrotoxicity was observed but there appears that there is no relationship with tumor findings.]"

16. Table 4.3 Neoplastic lesions observed in rats
    - Quest *et al*. 1993. Report the trend test for the (1) combined kidney (renal cell adenoma and carcinoma) tumor incidence in males (which is significant) and (2) for the combined liver (neoplastic nodule adenoma and carcinoma) tumor incidence for females. (While it makes little difference in inferences for the liver, not doing so can be questioned.)
    - *Nyska et al.*1989. Report the pair-wise test findings for the combined kidney (renal cell adenoma and carcinoma) tumor incidence for male F334 rats. Although not reported by the authors, the CPDB reports the combined incidence for kidney for F344 males as 0/50, 1/49, 5/49 ($P = 0.027$), 12/49 ($P < 0.0001$). The trend is significant as are pair-wise Fisher Exact tests for the mid and high dose groups.
    - Tamano *et al.* 1990. Trend tests should be provided for Tamano *et al.* liver and kidney findings.

17. Summary

- State in the text which tumors were seen in both genders or seen in a single gender (This information is provided in the summary table and the Executive Summary).
- Table 4-5 (summary table) should report where possible and appropriate combined incidence results and note where trend tests show significant findings. Thus, as one example the combined forestomach tumors for male B6C3F_1 mice would be reported as having significant dose related trend, as noted above. Also for the Nyska *et al.* study, combined incidence for kidney tumors for F344 males should be taken from the CPDB and reported as significant. The table should take care to note positive trend tests for sites with approaching significant/insignificant pair-wise comparisons.

Section 5: Other Relevant Data

1. Section 5.2 Metabolism (Pages 40-41)
   - P40, L16, After "N-S": Insert "and C-S bonds in captafol are" instead of "bond in captafol is".
   - P40, L18: Delete "at N-S bond"
   - P40, L20, After "1990a)": Insert "and the major degradation product in water hydrolysis and from heating (Table 1-2)."
   - P41, L10, After "captafol": Insert "Evidence also exists for conjugates for all the Phase I intermediates."
2. Section 5.3 Toxicity (Pages 42 to 44)
   - P42, L3 or so: Summarize several studies on the dermal effects in Japanese workers noted in Hayes, 1982 (P583) including the findings of Groundwater (1977).
   - P42, L7, After farmers: Insert findings from an additional study, "Lisi *et al.* (1986,1987) also reported on patch test results for captafol."
   - P42 L10, After "1975,": Insert the following reference "Matsushuta *et al.* 1980"
   - P42 L11, After "1984)": Insert new references, "Cushman *et al.* 1990, and Guo *et al.* 1996
   - P43, L26: Correct the IC_{50} reported for captafol in the Janik and Wolf paper; it was 2 µmol/L, not 300 (See Table 1 and Figure 3).
   - P43: Provide the IC_{50} for captafol inhibition reported by Di Ilio, *et al.* 1996 study; "The IC_{50} values for captan and captafol were 5.8 µM and 1.5 µM, respectively."
3. Section 5.4 Genetic damage and related effects (Pages 44-54)
   - P48, and Table 5-4, Add a description of an additional study identified by the expert panel (Ziogas and Georgopoulus, 1987): "Captafol caused mitotic crossing over of *Aspergillus nidulans*" Also add results to Table 5.4
4. Section 5.6 Structural analogues, etc. (pages 56 to 62)
   - Table 5-9 (page 61) compares the carcinogenic effects of captafol and analogues. The listed tumor effects in this table do not include the forestomach site for captafol neoplasms, which was not statistically significant after statistical re-evaluation. Re-evaluate this endpoint after the additional statistics suggested in section 4 are completed.
   - Sections 5.6.3 and 5.7.6 (Summary): Include a brief summary of non-mutagenic mode of action for captan's duodenal tumors using Bernard and Gordon (2000) and Gordon (2007) as source material.

Report Approved _____ Date _____
Lauren Zeise, Ph.D. (Chair)

References

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