**Captan 2004 Peer Review Charge Questions**

Overall, the document was fairly complete, including most of the available studies. However, the panel did suggest several additional studies and sources of information that should be considered.

- Include a description of the literature search and the criteria used to determine which studies would be included in the analysis.
- Include more detail in the study summaries.
- For human data, add a description of the Mills (1998) study. Also consider the available human data on acute toxicity and data available from health studies of pesticide applicators.
- For tumor data, add a discussion of Antony et al. (1994), as well as describing any other data for inhalation or dermal routes, to support WOE statements regarding those routes of exposure.
- Include data on GI tract pathogenesis for other agents, as well as data on GI tract pathogenesis and physiology in general.
- Use updated references for tumor incidence for historical controls.
- For mechanistic data, add a discussion of studies that support the MOA such as GSH depletion studies and rat kinetic studies.

The panel reached unanimous consensus that the only available epidemiological study is insufficient to contribute to conclusions regarding the carcinogenicity of captan. In general, the panel agreed with the conclusions of the document regarding this study. However, the panel unanimously agreed that the summary statement should be clarified to read "Based on this limited study, there is no evidence of an increase in deaths by cancer or for death by duodenal tumors as reported in death certificates." As above, the panel suggested that the Mills study and information on the acute effects of captan in humans should be included in the discussion of the proposed MOA.

The panel reached unanimous consensus that the kidney and uterine tumors observed in rats are not biologically relevant or treatment related and that the mouse small intestine tumors are biologically relevant and treatment related. However, the rationale for these conclusions needs to be strengthened in the document to reflect the balance and totality of the data.

For rat kidney tumors, enhance the argument that tumors are spontaneous based on the observation of a lack of increased atypical hyperplasia, and possible observation of chronic renal nephropathy as indicated by increased BUN levels. Address the contribution of, or rule out, other possible MOAs such as alpha-2-microglogulin or beta-lyase activation of thiols. Use structure activity relationship information to strengthen arguments.

For uterine tumors, it is appropriate to evaluate stromal sarcomas separately from other undifferentiated or unclassified sarcomas. This is consistent with NTP guidelines. In addition, it is appropriate to also evaluate stromal sarcomas combined with uterine polyps as a secondary measure.

There appears to be no apparent explanation for the species differences between rats and mice in the development of small intestine tumors. The panel speculated on two explanations that should be explored: mouse has a higher background rate and so may have more pre-initiated cells which give rise to more spontaneous lesions; for a given concentration in feed, rats which eat more food, reach the MTD earlier than mice, and develop systemic toxicity prior to doses that induce tumors.

For mouse data, acknowledge and discuss the observation of effects (both non-neoplastic and tumors) in the stomach and jejunum and the contribution of these effects to the overall proposed MOA. The document should change focus from "duodenal tumors" to "small intestinal tumors, primarily of the duodenum." The higher incidence of small intestine tumors in the Wong et al. (1981) study can be attributed to the sensitive sectioning technique and the long study duration. The document should show the incidence of hyperplasia in the tables in addition to tumor incidence and also clarify the underlying cell type and region of the small intestine of tumors, if presented in the study. (However, the panel noted that the tumor studies themselves do not identify which region of the small intestine is the location of the tumors, nor do they identify the tumors as crypt cell adenomas.) The panel recommended adding discussion of the Pavkov (1985) study to the discussion of tumor studies as well as the Antony et al. (1994) study of tumor promotion following dermal treatment.

The panel noted that the kinetic data are not well developed. They reached unanimous consensus that the kinetic data do not completely support the MOA, but they do not detract from it either. The mechanistic studies are confounded by methodological issues related to the high reactivity of the metabolites, and because the studies do not show the pattern of localization that matches with the histopathology.

The panel reached unanimous consensus that the histopathology data are very supportive of the MOA. They noted that the cell proliferation data are not robust, but that they are not inconsistent given the limited sensitivity of this measure in tissue with a high background proliferation rate. Other mechanistic data for captan, including the $S^{35}$ binding studies, have limited interpretation due to methodological issues. Other suggestions by the panel are to include information on the pathogenic mechanisms for other gastrointestinal toxicants and including a discussion of the THPI toxicity data.

The panel reached unanimous consensus that, based on the weight of evidence, captan genotoxicity does not contribute significantly to human carcinogenic potential at environmentally relevant doses (note that a formal exposure assessment was not reviewed by the panel). Overall, the panel concluded that captan is probably not a genotoxic carcinogen; although there are some limitations in the existing data regarding thiophosgene. Based on the weight of evidence, captan is a weak mutagen in the *in vitro* bacterial studies and a very weak mutagen in the *in vitro* eukaryotic cell studies. Captan is negative in *in vivo* assays. The panel recommended that the document be revised to include a detailed evaluation of the genotoxicity studies using standardized study quality criteria to aid in weighing conflicting results and to explain questionable studies. Also,

the document should expand discussion of the genotoxicity data on THPI and its close analogues. If additional data were to be generated, an *in vivo* mutagenicity study, for example Big Blue or MutaMouse, would be useful.

The panel reached unanimous consensus that the proposed MOA was adequately supported by the weight of evidence and that the proposed MOA was relevant to humans at environmentally relevant doses. (However, the panel noted that they did not conduct a thorough exposure analysis.) However, there are some remaining uncertainties regarding the cellular mechanisms and the cell of origin involved. There was a suggestion that the document draw comparisons to U.S. EPA's chloroform assessment for similarities in arguments regarding the rapidity of the reaction of thiophosgene. The panel noted that there are no known explanations for the species specificity of the small intestine tumors, nor are there data to demonstrate if humans would respond more like rats (non-responsive) or mice (responsive) for this tumor type. The panel suggested that the document include a discussion of the susceptibility of children under this proposed MOA, and noted several lines of evidence that could be considered in this type of evaluation.

The panel did not vote on consensus regarding the weight of evidence narrative because the panel felt that the document would need to be revised to incorporate the suggestions and scientific points summarized throughout the course of the meeting before an accurate WOE narrative could be prepared. Therefore, the panel did not provide specific wording changes for the WOE narrative, but did agree that the science supports the statement that captan is "likely to be carcinogenic only following prolonged oral exposures at doses causing cytotoxicity and regenerative hyperplasia in the gastrointestinal tract (primarily duodenum)" and that captan is "not likely to be carcinogenic at doses that do not result in cytotoxicity and regenerative hyperplasia." The panel suggested that the authors follow examples from the EPA's (2003) Draft Cancer Guidelines and current EPA cancer assessments (e.g., chloroform and atrazine) when revising the WOE narrative for captan.