

NTP panel peer reviews substances for potential listing as carcinogens

By Ernie Hood

A panel of experts peer-reviewed the two most recent NTP draft Report on Carcinogens (RoC) documents, known as monographs, at a public meeting Dec. 12-13 at NIEHS.

The panel was charged with reviewing the draft monographs for [ortho-Toluidine](#)

(http://ntp.niehs.nih.gov/NTP/About_NTP/MonoPeerRvw/2013/October/oTol_PeerRevDraft_508BE.pdf)

and [pentachlorophenol and by-products of its synthesis](#)

(http://ntp.niehs.nih.gov/NTP/About_NTP/MonoPeerRvw/2013/October/PCPPeerRevDraft_508BE.pdf)

The monographs contain the rationale and background information to support NTP listing recommendations for inclusion in the RoC. The panel voted on whether the scientific evidence supports the listing recommendations, which can characterize a substance as either "known to be human carcinogens" or as "reasonably anticipated to be human carcinogens."

After thoughtful discussions, the [panel](#)

(http://ntp.niehs.nih.gov/NTP/About_NTP/MonoPeerRvw/2013/December/Roster20131212_508.pdf)

chaired by Kenneth McMartin, Ph.D., a professor in the Department of Pharmacology, Toxicology, and Neuroscience at Louisiana State University Health Sciences Center, recommended listing *ortho*-Toluidine as a known human carcinogen and pentachlorophenol and by-products of its synthesis as reasonably anticipated to be a human carcinogen.

Monograph on *ortho*-Toluidine

The substance *ortho*-Toluidine is used to make dyes, rubber chemicals, herbicides, and the local anesthetic prilocaine. It has been listed in the RoC since 1983 as reasonably anticipated to be a human carcinogen. Since then, several cancer studies have been published in peer-reviewed literature, and the [International Agency for Research on Cancer](#) (<http://www.iarc.fr/>)

(IARC) has concluded that the compound is carcinogenic to humans. For these reasons, it was selected for a reevaluation and a possible change in RoC listing status.

NTP staff highlighted studies, presented in the draft monograph, showing credible evidence of an association between urinary-bladder cancer and exposure to *ortho*-Toluidine, based on consistent findings across human studies. Evidence from studies in experimental animals and on mechanisms of carcinogenicity also supports that finding. The peer-review panel unanimously concurred with the NTP's preliminary listing recommendation that *ortho*-Toluidine is known to be a human carcinogen.

Monograph on pentachlorophenol and by-products of its synthesis

Studies evaluating the carcinogenicity of pentachlorophenol and by-products of its synthesis were discussed in great length and detail among the peer-review panel and RoC staff, to determine if there was sufficient evidence to support NTP's preliminary listing recommendation of known to be a human carcinogen, with non-Hodgkin lymphoma as the primary cancer endpoint of concern in these studies.



Ruth Lunn, Dr.P.H., director of the Office of the Report on Carcinogens, briefed the peer review panel on the process for preparing the draft monographs, and presented much of the information on *ortho*-Toluidine. (Photo courtesy of Steve McCaw)



NTP Health Scientist Gloria Jahnke, D.V.M., presented most of the information on pentachlorophenol and by-products of its synthesis to the panel. (Photo courtesy of Steve McCaw)

Pentachlorophenol is a chlorinated aromatic compound that was used in the U.S. as a commercial and residential wood preservative and multipurpose biocide, until it was restricted in the mid-1980s to non-residential use. Today, it is limited to commercial wood preservation in items such as utility poles, fence posts, and railroad ties.

The panel members stated that overall the evidence of carcinogenicity from the studies in human cancer was limited. They agreed that there was one very good study that found an association between exposure to pentachlorophenol and by-products of its synthesis, but thought the evidence from the other studies was much more limited, due to their small size and potential for confounding factors.

The panel also struggled over whether the candidate substance should be pentachlorophenol itself or pentachlorophenol and the byproducts of its synthesis. Technical-grade pentachlorophenol is a mixture, with up to 10 percent of the substance being by-products of its synthesis, many of which are dioxin-like compounds that may contribute to its carcinogenicity.

At the end of the day, the panel voted to recommend changing the NTP preliminary listing decision of known to be human carcinogen, to reasonably anticipated to be a human carcinogen, based on limited evidence from studies in humans. The listing recommendation also took into consideration the sufficient evidence of carcinogenicity of pentachlorophenol, and pentachlorophenol and by-products of its synthesis, from studies in experimental animals and supporting mechanistic evidence.



Following the robust discussion of pentachlorophenol and the by-products of its synthesis, NTP Associate Director John Bucher, Ph.D., right, praised the panel's work. "This has been one of the more detailed and very careful reviews that I've seen any of our expert panels engage in," he said. "The effort you've put in on this is quite remarkable." Next to Bucher is Mary Wolfe, Ph.D., director of the NTP Office of Liaison Policy and Review, who briefed the panel on the scientific issues raised by public comments regarding both substances under review. (Photo courtesy of Steve McCaw)

Next Steps

The NTP will consider the panel's comments and public comments, as it makes revisions to the draft monographs. The updated monographs will be presented to the NTP Board of Scientific Counselors at the next meeting in April 2014.

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)



Panel member Laura Beane Freeman, Ph.D., tenure track researcher at the National Cancer Institute, agreed with the panel's recommendation to change the pentachlorophenol and the by-products of its synthesis listing. "I don't view the whole body of epidemiologic evidence as being supportive of pentachlorophenol being listed as a carcinogen," she said. (Photo courtesy of Steve McCaw)



Peer-review member Gabriele Sabbioni, Ph.D., of Tulane University, asked several pointed questions during the course of the proceedings on the review of ortho-Toluidine. (Photo courtesy of Steve McCaw)



Panelist Allan Smith, M.D., Ph.D., of the University of California, Berkeley, center, contributed many thoughtful remarks during the discussions about the two draft monographs. Lisa Peterson, Ph.D., of the University of Minnesota, right, attended the meeting as the liaison to an NTP Board of Scientific Counselors member. (Photo courtesy of Steve McCaw)



Stephen Nesnow, Ph.D., a retired senior scientist at the National Health and Environmental Effects Research Laboratory at the U.S. Environmental Protection Agency in Research Triangle Park, N.C., paid close attention to the data being presented on the two substances under review. (Photo courtesy of Steve McCaw)

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