Dose-Response:
An International Journal
April-June 2018:1-2

DOI: 10.1177/1559325818777931
journals.sagepub.com/home/dos
SAGE

Commentary on New Formaldehyde Studies in Trp53 Haploinsufficient Mice: Further Support for Nonlinear Risks From Inhaled Formaldehyde

Chad M. Thompson[1]

Keywords
dose–response, risk assessment, formaldehyde, mode of action

Commentary

Formaldehyde is a widely used industrial chemical, a byproduct of combustion, and is generated endogenously. Although classified by many organizations as a carcinogen, the World Health Organization (WHO) has set an exposure guideline of 0.08 ppm based on irritant properties of formaldehyde.[1] The US Environmental Protection Agency has proposed far lower safety values based, in part, on controversial associations between formaldehyde exposure and increased risk of leukemia. Therefore, it is of interest that the National Toxicology Program (NTP), a division of the National Institute of Environmental Health Sciences, recently released an NTP Research Report that explored the potential involvement of p53 mutation in formaldehyde-induced nasal tumors as well as lymphohematopoietic cancers.[2] This study has not been published in the peer-review literature, nor is the report currently indexed in search engines like PubMed and Embase. Because the carcinogenicity of formaldehyde remains controversial and there are ongoing assessments of formaldehyde in the United States, the new NTP Research Report is an important addition to the database for informing the carcinogenicity of inhaled formaldehyde. This commentary highlights some important implications of this study for the risk assessment of formaldehyde.

In the new NTP Research Report, 2 mouse strains (note 1) haploinsufficient for TP53 were exposed to 7.5 and 15 ppm formaldehyde for 8 weeks and killed 32 weeks later at $\sim$50 weeks of age.[2] At termination, the NTP Research Report indicates that neither hematotoxicity nor lymphohematopoietic neoplasms were observed in either strain.[2] *Tp53*$^{+/-}$ mice were designed such that shortened cancer bioassays could be conducted due to their increased sensitivity to carcinogens—particularly genotoxic carcinogens.[3] These mouse strains are also reported to develop spontaneous lymphomas[3] and serve as models for lymphohematopoietic tumors in short-term studies.[2] These findings lend additional weight to the evidence that inhaled formaldehyde is not leukemogenic—including reanalysis of epidemiological studies[4] and animal studies that indicate that inhaled formaldehyde does not distribute beyond the nasal cavity or reach the blood or bone marrow.[5]

The new NTP Research Report also provides important insight into the mode of action (MOA) for nasal tumors in rodents. Formaldehyde-induced nasal tumor formation is well-documented in rats at $\geq$6 ppm,[6] and research indicates that tumors arise in nasal regions where there is cytotoxicity and regenerative hyperplasia. Research into the MOA for nasal tumors led to the development of one of the few biologically based dose–response (BBDR) models ever developed for use in risk assessment. The BBDR model and supporting research indicate that the tumor response in rats is most likely driven by increased cytotoxicity-induced regenerative hyperplasia with a negligible contribution from direct mutagenicity at noncytotoxic concentrations.[7] Subsequent in vivo genotoxicity studies have shown that exposure to up to 15 ppm for several weeks increases cell proliferation but not micronuclei or mutant frequency of *kras* or *Tp53* in the nasal cavity.[8,9] These data indicate a negligible contribution from direct mutagenicity at cytotoxic concentrations. The lack of nasal neoplasms in *Tp53*$^{+/-}$ mice considered well suited for detecting genotoxic carcinogens lends additional evidence that the MOA for

[1] ToxStrategies, Inc., Katy, TX, USA

Received 05 April 2018; accepted 24 April 2018

Corresponding Author:
Chad M. Thompson, ToxStrategies, Inc., 23123 Cinco Ranch Blvd., Suite 220, Katy, TX 77494, USA.
Email: cthompson@toxstrategies.com

formaldehyde-induced nasal tumors is unlikely to be a mutagenic MOA, as typically defined for cancer risk assessment. Importantly, the NTP study authors state that, "The primary formaldehyde-related finding was squamous metaplasia of the respiratory epithelium of the nose . . ." indicating that ". . . formaldehyde caused significant injury to the nasal mucosa and cell proliferation . . ."[2(pvi)] These observations weaken any counterargument that the exposures were too low or too short to have potentially induced nasal tumors.

Some scientists have argued that formaldehyde induces nasal tumors via a mutagenic MOA, citing evidence for labeled DNA-protein cross-links and DNA adducts in nasal tissue following inhalation of isotope labeled formaldehyde, in vitro evidence of genotoxicity, and variable evidence for genotoxicity in exfoliated nasal and buccal cells as well as lymphocytes of humans occupationally exposed to formaldehyde. Additionally, recent studies demonstrate that *endogenous* formaldehyde is genotoxic in mice genetically engineered to be susceptible to formaldehyde due to increased production, decreased detoxification, compromised DNA repair, or some combination thereof.[10] However, as Speit et al[8] have noted, the absence of genotoxicity in nasal tissue of rats following inhalation exposure suggests that inhaled formaldehyde does not readily reach basal cells lining the nasal mucosa or that formaldehyde-induced DNA adducts and cross-links are readily repaired. The lack of nasal neoplasms in $Tp53^{+/-}$ mice seems consistent with this view.

In a vacuum, the new NTP Research Report does not exclude the possibility of a mutagenic MOA for nasal tumors. However, considered along with the broader in vivo data on formaldehyde, the weight of evidence supports the use of nonlinear approaches for estimating risks from exposure to environmental levels of formaldehyde. Indeed, the WHO argues that protection against the irritant effects of inhaled formaldehyde is protective against more severe effects such as cancer.[1] The new government-funded research in $Tp53^{+/-}$ mice further supports the argument that noncytotoxic concentrations of formaldehyde pose little/no carcinogenic risk. These important new findings should be considered by regulatory agencies currently assessing the carcinogenic risk of inhaled formaldehyde.

Note

1. C3B6.129F1-Trp53^{tm1Brd} and B6.129-Trp53^{tm1Brd}.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Consulting fees received for writing might be perceived by some as a conflict.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by the American Chemistry Council.

References

1. World Health Organization. WHO guidelines for indoor air quality: selected pollutants. 2010. København, Denmark: WHO Regional Office for Europe.
2. Morgan DL, Dixon D, King DH, et al. NTP research report on absence of formaldehyde-induced neoplasia in trp53 haploinsufficient mice exposed by inhalation. *National Toxicology Program*. 2017;3:1-30.
3. Eastmond DA, Vulimiri SV, French JE, Sonawane B. The use of genetically modified mice in cancer risk assessment: challenges and limitations. *Crit Rev Toxicol*. 2013;43(8): 611-631.
4. Checkoway H, Dell LD, Boffetta P, et al. Formaldehyde exposure and mortality risks from acute myeloid leukemia and other lymphohematopoietic malignancies in the US National Cancer Institute Cohort Study of Workers in Formaldehyde Industries. *J Occup Environ Med*. 2015;57(7):785-794.
5. Swenberg JA, Moeller BC, Lu K, Rager JE, Fry RC, Starr TB. Formaldehyde carcinogenicity research: 30 years and counting for mode of action, epidemiology, and cancer risk assessment. *Toxicol Pathol*. 2013;41(2):181-189.
6. Kerns WD, Pavkov KL, Donofrio DJ, Gralla EJ, Swenberg JA. Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. *Cancer Res*. 1983;43(9): 4382-4392.
7. Conolly RB, Kimbell JS, Janszen D, et al. Human respiratory tract cancer risks of inhaled formaldehyde: dose-response predictions derived from biologically-motivated computational modeling of a combined rodent and human dataset. *Toxicol Sci*. 2004;82(1): 279-296.
8. Speit G, Schutz P, Weber I, et al. Analysis of micronuclei, histopathological changes and cell proliferation in nasal epithelium cells of rats after exposure to formaldehyde by inhalation. *Mutat Res*. 2011;721(2):127-135.
9. Meng F, Bermudez E, McKinzie PB, Andersen ME, Clewell HJ, Parsons BL. Measurement of tumor-associated mutations in the nasal mucosa of rats exposed to varying doses of formaldehyde. *Reg Tox and Pharm*. 2010;57:274-283.
10. Pontel LB, Rosado IV, Burgos-Barragan G, et al. Endogenous formaldehyde is a hematopoietic stem cell genotoxin and metabolic carcinogen. *Mol Cell*. 2015;60(1):177-188.