Pulmonary toxicity, genotoxicity, and carcinogenicity evaluation of molybdenum, lithium, and tungsten

A review

Hadrup, Niels; Sørli, Jorid B.; Sharma, Anoop K.

Published in:
Toxicology

Link to article, DOI:
10.1016/j.tox.2022.153098

Publication date:
2022

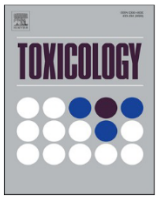
Document Version
Publisher's PDF, also known as Version of record

Toxicology 480 (2022) 153323

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol



Response to commentary on "Pulmonary toxicity, genotoxicity, and carcinogenicity evaluation of molybdenum, lithium, and tungsten: A review"

1. Response

Dear authors,

Thank you for the interest in our article (Hadrup et al., 2022). You suggest that doses higher than what are observed in humans with pharmaceutical use of lithium are irrelevant. We think that studies with higher doses are important too. Generally in toxicological experiments doses applied are higher than those seen in humans. One argument for this is differences in toxico-dynamics and –kinetics between humans and animals. Hence, the adjustment (safety) factors applied when converting dose descriptors from animal studies into dose levels safe for humans. Moreover, in some intoxications higher exposures than those seen with normal pharmacological doses can be foreseen. This is for example in blood, and in lung cells after inhalation.

You cite a number of past reviews with publication years 1976, 1980, 1995, 2002, 2008, and 2009. Notably five studies in our article are from 2009 or later (Akbaba et al., 2016; Çelikezen et al., 2016; Pastor et al., 2009; Sironval et al., 2020; Turkez et al., 2016). Thus, we provide an evaluation that takes all studies up to 2022 into account. You suggest that some in vitro study concentrations were too high to be human-relevant. We disagree, actually most often in vitro studies are conducted with concentrations above what is seen in bodily fluids. This for example accounts for accumulation of the substance in lung lining upon inhalation exposure. You disagree with our sentence: "a clastogenic effect cannot be excluded after intraperitoneal and oral exposure". While Pastor et al. (2009) points to an aneugenic effect, the studies by King et al. (1979) and Sobti et al. (1989) support a possible clastogenic effect. You suggest that materials used for batteries are not relevant for oral exposure. In the article we take into account genotoxicity studies with all exposure pathways, and in vitro studies. This is because genotoxicity most often occurs inside cells irrespective of exposure pathway.

Concerning the in vitro part of De La Torre (De La Torre et al., 1976), you suggest that the effect is not a dose-response relation, as there is a higher effect at the lowest dose than in the middle dose. The total numbers of chromosome abnormalities in Table 1 of the De La Torre article are: in the control group: 6 of 246 counted (2.4 %), in the lowest concentration: 51 of 202 counted (25 %), middle concentration: 39 of 179 counted (22 %) and highest concentration: 102 of 239 counted (43 %). Taking the highest concentration into account we consider it a concentration-related increase. Next you suggest that some studies are not important as they do not adhere to current OECD guidelines, or that some information is missing in the original research papers. We note that we have not stated to only take studies that are performed according to OECD guidelines into account. In the overall conclusion, which is cautious, we take into account that some studies have limitations.

In the study in which lithium is given in combination with benzodiazepine we clearly write that "it is unknown if the effect is caused by any of the two non-lithium substances (Bigatti et al., 1998)." Concerning the in vivo part of the De La Torre experiment, we write: "Lymphocytes were isolated from 10 psychiatric patients who were taking Lithium carbonicum. The lymphocytes showed elevated chromosomal abnormalities as compared to cells from three control persons (De La Torre et al., 1976)." Notably, satellite associations are statistically significantly different (t test: controls vs. treated: $P < 0.0001$) in that study, justifying the sentence. Concerning the study by Freiderich and Nielsen: we write: "Three psychiatric patients under treatment with lithium had increased breaks and hypo-diploid cells in leukocytes compared to a control group (11 persons) (Friedrich and Nielsen, 1969)." Friedrich and Nielsen themselves write: "There was a significantly higher frequency of breaks ($P < 0.001$) and hypodiploid cells ($P < 0.001$) in these three patients than in a control group of the same age." Thus, we convey this finding.

You write: "In some studies, SCE frequencies were found to be higher than in control. These data are disregarded since SCE frequency does not appear to have cancer predictive value." We are aware that there are concerns about interpretation and relevance of SCE results. However, we are of the opinion that SCE frequency is an indicator of DNA repair. A firm conclusion about in vitro genotoxicity of a substance cannot be based solely on SCE results and we have not done so.

You highlight the negative studies in humans, and those we indeed mentioned in the article (Banduhn et al., 2008; Jarvik, 1971; Matsushima et al., 1986). Finally you mention one study by Murbach et al. that we had not identified in our literature search. The study finds no in vitro or in vivo genotoxicity of lithium orotate (Murbach et al., 2021). The study is relevant and should have been included, but does not change our conclusions.

The potential genotoxicity of lithium substances might have a threshold. We acknowledge that in case of a threshold, exposures that are low enough will not exert genotoxicity. Yet we believe more well-designed studies are needed to make a firm conclusion on this.

Overall, we retain our conclusion: "The data on lithium in vitro are equivocal; there are several negative studies; however, there are also positive studies indicating a clastogenic effect. In vivo studies in animals show a similar number of negative and positive results. The studies showing a positive effect measure damage on chromosomes. Therefore, a clastogenic effect cannot be excluded after intraperitoneal and oral exposure. Some human studies show an association between lithium substances exposure and genotoxicity; however, it remains unknown if the effect was due to lithium substances, and better-designed human studies are required to make firm conclusions."

https://doi.org/10.1016/j.tox.2022.153323
Received 12 August 2022; Received in revised form 9 September 2022; Accepted 13 September 2022
Available online 14 September 2022

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

Akbaba, G.B., Turkez, H., Sönmez, E., Tatar, A., Yilmaz, M., 2016. Genotoxicity in primary human peripheral lymphocytes after exposure to lithium titanate nanoparticles in vitro. Toxicol. Ind. Health 32, 1423–1429. https://doi.org/10.1177/0748233714562624.

Banduhn, N., Obe, G., Müller-Oerlinghausen, B., 2008. Is lithium mutagenic in man? Pharmacopsychiatry 13, 218–227. https://doi.org/10.1055/s-2007-1019634.

Bigatti, M.P., Corona, D., Munizza, C., 1998. Increased sister chromatid exchange and chromosomal aberration frequencies in psychiatric patients receiving psychopharmacological therapy. Mutat. Res. Toxicol. Environ. Mutagen. 413, 169–175. https://doi.org/10.1016/S1383-5718(98)00028-X.

Çelikezen, F.Ç., Toğar, B., Özgeriş, F.B., İzgi, M.S., Türkez, H., 2016. Cytogenetic and oxidative alterations after exposure of cultured human whole blood cells to lithium metaborate dehydrate. Cytotechnology 68, 821–827. https://doi.org/10.1007/s10616-014-9833-x.

De La Torre, R., Krompotic, E., Kowlessard, L., 1976. The in vivo and in vitro effects of lithium on human chromosomes and cell replication. Teratology 13, 131–138. https://doi.org/10.1002/tera.1420130203.

Friedrich, U., Nielsen, J., 1969. Lithium and chromosome abnormalities. Lancet 294, 435–436. https://doi.org/10.1016/S0140-6736(69)90143-3.

Hadrup, N., Sørli, J.B., Sharma, A.K., 2022. Pulmonary toxicity, genotoxicity, and carcinogenicity evaluation of molybdenum, lithium, and tungsten: A review. Toxicology 467, 153098. https://doi.org/10.1016/j.tox.2022.153098.

Jarvik, L.F., 1971. Chromosome examinations in patients on lithium carbonate. Arch. Gen. Psychiatry 24, 166. https://doi.org/10.1001/archpsyc.1971.01750080070011.

King, M.-T., Beikirch, H., Eckhardt, K., Gocke, E., Wild, D., 1979. Mutagenicity studies with X-ray-contrast media, analgesics, antipyretics, antirheumatics and some other pharmaceutical drugs in bacterial, Drosophila and mammalian test systems. Mutat. Res. Toxicol. 66, 33–43. https://doi.org/10.1016/0165-1218(79)90005-3.

Matsushima, Y., Hazama, H., Kishimoto, A., 1986. Chromosome examination of patients under lithium therapy. Psychiatry Clin. Neurosci. 40, 625–630. https://doi.org/10.1111/j.1440-1819.1986.tb03177.x.

Murbach, T.S., Glávits, R., Endres, J.R., Hirka, G., Vértesi, A., Béres, E., Szakonyiné, I.P., 2021. A toxicological evaluation of lithium orotate. Regul. Toxicol. Pharmacol. 124, 104973 https://doi.org/10.1016/j.yrtph.2021.104973.

Pastor, N., Kaplan, C., Domínguez, I., Mateos, S., Cortés, F., 2009. Cytotoxicity and mitotic alterations induced by non-genotoxic lithium salts in CHO cells in vitro. Toxicol. Vitr. 23, 432–438. https://doi.org/10.1016/j.tiv.2009.01.009.

Sironval, V., Scagliarini, V., Murugadoss, S., Tomatis, M., Yakoub, Y., Turci, F., Hoet, P., Lison, D., van den Brule, S., 2020. LiCoO2 particles used in Li-ion batteries induce primary mutagenicity in lung cells via their capacity to generate hydroxyl radicals. Part. Fibre Toxicol. 17, 6. https://doi.org/10.1186/s12989-020-0338-9.

Sobti, R.C., Sharma, M., Gill, R.K., 1989. Frequency of sister chromatid exchanges (SCEs) and chromosome aberrations (CAs) caused by three salts of lithium (in vivo). Cytologia 54, 245–248. https://doi.org/10.1508/cytologia.54.245.

Turkez, H., Sönmez, E., Di Stefano, A., Mokhtar, Y.I., 2016. Health risk assessments of lithium titanate nanoparticles in rat liver cell model for its safe applications in nanopharmacology and nanomedicine. Cytotechnology 68, 291–302. https://doi.org/10.1007/s10616-014-9780-6.

Niels Hadrup[a,*], Jorid B. Sørli[a], Anoop K. Sharma[b]

[a] *National Research Centre for the Working Environment, Lersø Parkallé 105, DK-2100 Copenhagen, Denmark*

[b] *Division for Risk Assessment and Nutrition, Group for Chemical Risk Assessment and GMO, National Food Institute, Technical University of Denmark, Kemitorvet, 201, 031, 2800 Kgs. Lyngby, Denmark*

[*] Corresponding author.

E-mail addresses: nih@nfa.dk (N. Hadrup), jbs@nfa.dk (J.B. Sørli), aksha@food.dtu.dk (A.K. Sharma).