Comments on DECOS draft document on Tin and selected inorganic tin compounds

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PAGE NUMBER, LINE NUMBER	COMMENT
General Comments	I support the conclusions in the draft and find the Committee's recommendations appropriate for fertility, development, and lactation. Please see below for minor, specific comments on the document. At the end of the document, I've included a list of additional literature that may warrant inclusion or consideration in the final document.
Specific Comments	
(Table) Page 36, under 'General toxicity'	The second bullet down, "…survival of the control group was significantly ($p<0.05$) lower in the treatment groups in males" should be changed to "…survival of the control group was significantly ($p<0.05$) lower *compared* to the treatment groups in males."
Page 42, lines 13-16	From the report summary, the absolute weight of the pituitary gland was statistically significantly increased; however, there were no changes of microscopic structure of the pituitary gland so the effect could be considered not to be of toxicological significance. This may not need to be mentioned and may confuse significant findings.
Page 44, lines 18-19	Suggest making it clearer or stating explicitly that the nanosize of the SnS2 flowers appears to matter when it comes to penetrating the blood-testis barrier and inducing testicular tissue injury (*e.g.*, no effects were seen at exposure to 200 nm).
(Table) Page 47, under 'Results on sexual function and fertility', last bullet	Would help to clarify that the median value of T (389 ng/dL) was the total T for the study population.
(Table) Page 48, under 'Results on sexual function and fertility', last bullet	Would help to clarify that the total T/LH ratio of 3.5 was the total T/LH ratio for the study population.
Page 53, line 3	Might be helpful to include the dose in parentheses for quick reference point (38 mg/kg).
(Table) Page 68, under 'Results on developmental toxicity'	Would help to clarify that these are birth weight for gestational age (GA) z-scores.
(Table) Page 73, under 'Bias and confounding'	Suggest mentioning there were major differences in mode of delivery between base population and sample population (i.e., 65.1% vs. 99%, respectively). This discrepancy may be—in part—explained by other factors (maternal age, parity, gestational length, etc.) that should be considered when interpreting the findings.

(Table) Page 74, under 'Exposure assessment and statistical analyses'	Should be corrected to state that for both paternal and maternal urine tin concentrations, the values are the percent *above* the LOD and not below.
(Table) Page 74, under 'Bias and confounding'	Suggest removing that the "…sample size was quite low." Though they included several covariates in their adjusted models, the sample size was similar or larger than other studies where limited sample size was not mentioned.
Page 86, lines 16-17	Suggest adding here that Sn levels appeared to be highly correlated with other metals (e.g., arsenic, antimony, bismuth), so co-exposure was a major study limitation (see Figure 1).
Page 88, lines 22-23	Suggest emphasizing that tin levels in breastmilk were lower compared to *both* water and soil levels—add soil median value of 3.10 µg/L here as well.
Page 89, lines 3-4	Suggest mentioning the potential for selection bias in this study, as volunteers were recruited (i.e., could lead to women enrolling who were already concerned about potentially high environmental contaminants, including tin).
Page 91, line 32	Reference for #13 is a link to the main page on 'Tin' and not directly to the study it is intended to reference. The direct link is Registration Dossier - ECHA (europa.eu)
Page 92, line 5	Reference for #15 is a link to the main page on 'Tin' and not directly to the study it is intended to reference. The direct link to that study is here Registration Dossier - ECHA (europa.eu)
Human studies that were in the data collection range that were not included, but may be relevant or worth consideration in final report	

	1. Frye, R.E., Cakir, J., Rose, S. et al. Early life metal exposure dysregulates cellular bioenergetics in children with regressive autism spectrum disorder. Transl Psychiatry 10, 223 (2020). https://doi.org/10.1038/s41398-020-00905-3 2. Howe, C. G., Claus Henn, B., Farzan, S. F., Habre, R., Eckel, S. P., Grubbs, B. H., Chavez, T. A., Faham, D., Al-Marayati, L., Lerner, D., Quimby, A., Twogood, S., Richards, M. J., Meeker, J. D., Bastain, T. M., & Breton, C. V. (2021). Prenatal metal mixtures and fetal size in mid-pregnancy in the MADRES study. Environmental research, 196, 110388. https://doi.org/10.1016/j.envres.2020.110388 3. Wang, Yi-Xin, et al. "Association of urinary metal levels with human semen quality: A cross-sectional study in China." Environment international 91 (2016): 51-59. https://doi.org/10.1016/j.envint.2016.02.019 4. Kot, Karolina, et al. "Interactions between 14 elements in the human placenta, fetal membrane and umbilical cord." International Journal of Environmental Research and Public Health 16.9 (2019): 1615. https://doi.org/10.3390/ijerph16091615 ***of note, that this article is closest related to reference #8 in the draft, in which maternal blood, cord blood and placenta were examined for Sn exposure*** 5. Ovayolu, Ali, et al. "Amniotic fluid levels of selected trace elements and heavy metals in pregnancies complicated with neural tube defects." Congenital Anomalies 60.5 (2020): 136-141. https://doi.org/10.1111/cga.12363 6. Cabrera-Rodriguez, Raul, et al. “Occurrence of 44 elements in human cord blood and their association with growth indicators in newborns.” Environment international 116 (2018):43-51. https://doi.org/10.1016/j.envint.2018.03.048 7. Wang, Ruixia, et al. "Elevated non-essential metals and the disordered metabolism of essential metals are associated to abnormal pregnancy with spontaneous abortion." Environment International 144 (2020): 106061. https://doi.org/10.1016/j.envint.2020.106061 8. Shirai, Sayaka, et al. "Maternal exposure to low-level heavy metals during pregnancy and birth size." Journal of Environmental Science and Health Part A 45.11 (2010): 1468-1474. https://doi.org/10.1080/10934529.2010.500942

	9. Goodrich, Jaclyn M., et al. "First trimester maternal exposures to endocrine disrupting chemicals and metals and fetal size in the Michigan Mother–Infant Pairs study." Journal of developmental origins of health and disease 10.4 (2019): 447-458. https://doi.org/10.1017/S204017441800106X 10. Wu, Y.; Zhang, J.; Peng, S.; Wang, X.; Luo, L.; Liu, L.; Huang, Q.; Tian, M.; Zhang, X.; Shen, H. Multiple elements related to metabolic markers in the context of gestational diabetes mellitus in meconium. Environ. Int. 2018, 121, 1227–1234. https://doi.org/10.1016/j.envint.2018.10.044. ***worth noting that this study was focused on gestational diabetes, a condition during pregnancy, and not a pregnancy outcome; however, gestational diabetes is associated with select adverse birth outcomes among infants, so it may be loosely relevant under, 'Effects of Development'.***
	11. Björklund KL, Vahter M, Palm B et al (2012) Metals and trace element concentrations in breast milk of first time healthy mothers: a biological monitoring study. Environ Health 11:92 40. https://doi.org/10.1186/1476-069X-11-92
Human studies published since March of 2021 that may warrant consideration if/when an update is performed	Important to note that none of the evidence provided in the studies below changes the overall agreement with the Committee's current recommendations in this draft.

	1. Zhang, Ludi, et al. "Factors Influencing Trace Element Levels in the Blood of Tin Smelting Workers." Journal of Occupational and Environmental Medicine (2022). https://doi.org/10.1097/JOM.0000000000002554 2. Xu, Song, et al. "Environmental metal exposure, seminal plasma metabolome and semen quality: Evidence from Chinese reproductive-aged men." Science of The Total Environment 838 (2022): https://doi.org/10.1016/j.scitotenv.2022.155860 3. Dórea, José G. "Neurodevelopment and exposure to neurotoxic metal (loid) s in environments polluted by mining, metal scrapping and smelters, and e-waste recycling in low and middle-income countries." Environmental Research 197 (2021): https://doi.org/10.1016/j.envres.2021.111124 4. Huang, Hui, et al. "Cord serum elementomics profiling of 56 elements depicts risk of preterm birth: evidence from a prospective birth cohort in rural Bangladesh." Environment International 156 (2021): https://doi.org/10.1016/j.envint.2021.106731 5. Wang, Xin, et al. "Urinary metals and adipokines in midlife women: The Study of Women's Health Across the nation (SWAN)." Environmental research 196 (2021): 110426. https://doi.org/10.1016/j.envres.2020.110426 6. Shi, Xiao, et al. "Associations between blood metal/metalloid concentration and human semen quality and sperm function: A cross-sectional study in Hong Kong." Journal of Trace Elements in Medicine and Biology 65 (2021): 126735. https://doi.org/10.1016/j.jtemb.2021.126735