Public Comments: TR546 (Sodium Dichromate Dihydrate)

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Comments: Dear Dr. Shane,

I am Silvio De Flora from the University of Genoa, Italy. For more than 30 years I have been involved in studies on chromium toxicology. As chairman of the Genetic Toxicology Group, I attended the Working Group preparing the IARC Monograph on Chromium (Vol. 49, 1990). I am the most frequently cited scientist in the IARC Monograph, with 38 of my papers cited in the references, in 36 of which I am either single author or first author or last author. Seventeen of my papers are also cited in the ATSDR Document released by the U.S. Dept. of Health and Human Services (2000). Based on the results of my studies, cited verbatim, the USEPA (1991) set up a new standard for chromium in drinking water. I am still actively involved in research on chromium, also by using genomic and postgenomic technologies.

I examined the pathology tables, the survival and growth curves, available online, as well as the NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate. I believe this is a very important, timely and well executed study. I would like, however, to make some comments on the report and interpretation of the tumor data, as available in the "Abstract" (pages 5-8 of the Technical Report) and "Discussion and Conclusions" (pages 81-90).

First of all, I am pleased to note that the general outcome of the NTP study is consistent with years of research by myself and others in that no meaningful excess of tumors occurred outside the portal of entry in the body, due to extensive reduction of Cr(VI) in blood, liver, and other body compartments. I published my first papers on this subject almost 30 years ago (Nature 271, 455-456, 1978; Mutat. Res. 54, 139-147, 1978 and 58, 167-173, 1978). These findings disprove the hypotheses raised by some authors, cited in the NTP Report discussion, who in recent years changed their opinion by claiming that Cr(VI) may cause tumors at many different sites beyond the portal of entry. Such speculations are not scientifically valid and are clearly inconsistent with the known fact about Cr(VI) kinetics and detoxification mechanisms in the body.

Second, I would like to emphasize the great tolerability of Cr(VI) even at the extremely high doses used in the present study, which at the highest concentration tested would correspond to the intake of about 1 g sodium dichromate dihydrate every day for two years in a 70 kg man. At these concentrations, the yellow color of water is so intense that nobody would drink it unless for suicidal purposes. By the way, the majority of people who acutely ingested oral doses higher than 1 g for suicidal purposes did actually survive (see my paper De Flora, Zanacchi and Bennicelli, 1995). Such a poor oral toxicity of Cr(VI) is consistent with the lack of genotoxicity of Cr(VI) when administered with the drinking water. This was demonstrated by Mirsalis et al. (1996), at concentrations up to 20 mg Cr(VI)/l, by myself, at concentrations of up to 500 mg Cr(VI)/l for up to 210 consecutive days or even in a single intragastric dose of 17.7 mg/kg b.w. (De Flora, Iltcheva and Balansky, 2006), and by the NTP genotoxicity study in various mouse strains, excepting transgenic mice.

We just finalized a study concluding that, at the concentrations of 5 or 20 mg Cr(VI)/l drinking water, given to mice for 9 consecutive months, sodium dichromate does not affect the levels of DNA-protein crosslinks or of oxidative DNA damage (8-oxo-dG) either in the forestomach or in the glandular stomach (S. De Flora et al., ready to be submitted). Indeed, the most important finding of the NTP study is that no neoplasms or nonneoplastic lesions were observed either in the forestomach or in the glandular stomach. This was probably the main goal of the study. These negative results definitively rule out the hypothesis that high dose Cr(VI) in drinking water may induce tumors in the forestomach, based on the equivocal data of the old and technically flawed study by Borneff et al. (1968). Even by taking into account my findings on Cr(VI) reduction in the gastric environment, I am surprised that no effect occurred, at least in the forestomach, at such doses. In fact, the forestomach is a vulnerable tissue, which has a neutral pH and is very sensitive to irritants. For this reason, and taking into account that no forestomach exists in humans, the WHO cautioned that neoplasia of the rodent forestomach has little relevance for regulatory decisions regarding man (IARC Sci. Publ. No. 111, 1994).

The NTP Technical Report selects as statistically significant or biologically noteworthy the increases of tumors in the rat oral cavity and in the mouse small intestine.
Mechanistically, an increase of tumors in the oral cavity may be ascribed to a local irritant and oxidizing effect of chromium(VI) at the highest dose, possibly combined with a mechanical stimulus due to the water bottle cannula. Of course, this has nothing to do with possible human exposure.
An increase of tumors in the small intestine may be ascribed to the fact that, at so high doses, some Cr(VI) may have escaped reduction and detoxification upstream in the alimentary tract. It is surprising, however, that no such effect was observed in the stomach itself. No suspicion has ever been raised that the small intestine may be a target for Cr(VI) in either humans or rodents. There are anatomical differences in the digestive system between rodents and humans, and between rats and mice, as shown by the fact that the effect was only observed in mice and not in rats, and only at very high doses, unrealistic for human exposures, which clearly imply occurrence of threshold mechanisms.

What renders the comments reported in the NTP document (pp. 81-90) not well balanced is the fact that other significant changes were completely ignored. In my opinion, in both epidemiological and experimental studies it is not correct to only select significant increases by disregarding significant decreases. Clearly, this does not imply that Cr(VI) may have protective effects in certain organs but simply demonstrates that most changes are not biologically relevant, especially when they are obtained at doses that very largely exceed drinking water standards.
It should be emphasized that no significant variation of tumor incidence was concomitant in the two rodent species, with the exception of a decrease of total benign tumors in both rats (females only) and mice (males only) treated with Cr(VI). All other changes were species-specific.
In rats all changes were detected at one concentration or seldom at two concentrations only, or simply as a trend. Apart from gender-specific tumors, such as a decrease of mammary fibroadenomas and testis adenomas or an increase of clitoral/preputial gland tumors, the only concordant changes in the two rat genders were a decrease of pituitary gland tumors and an increase of oral tumors.
In mice, the only concordant and consistent changes in the two genders were the increase of

small intestine tumors, observed at 1-2 concentrations, and a decrease of benign liver tumors, observed at 1-3 concentrations.

To be frank, I am also surprised by the fact that the data are reported and commented in a one-sided way, not only because significant decreases of tumors at certain sites were completely disregarded but also because the references are arbitrarily selected to highlight certain recent theories that do not have credit in the majority of the scientific community. Just to give one example, in the second paragraph of page 84 it is stated that "several reviews of the literature have summarized increases in the occurrence of other types of cancer attributed to chromium exposure". This is true for the cited references Costa 1997, Costa and Klein 2006, and Sedman et al. 2006, but is not true for ATSDR 2000 and Cohen et al. 1993. In particular, after having contributed to the conclusion of the IARC Working Group that "for cancers other than of the lung and sinonasal cavity, no consistent pattern of cancer risk has been shown among workers exposed to chromium compounds" (IARC Monographs, vol. 49, 1990, page 211), 3 years later M. Costa reiterated verbatim the IARC conclusion (M.D. Cohen, B. Kargacin, C.B. Klein and M. Costa, Crit. Rev. Toxicol. 23, 255-281, 1993). Thereafter, M. Costa and his colleagues changed their opinion by claiming, without any consistent scientific support, that Cr(VI) is a systemic carcinogen (M. Costa, Crit. Rev. Toxicol. 27, 431-442, 1997; M. Costa and C.B. Klein, Crit. Rev. Toxicol. 36, 155-163, 2006). Note that they published so strikingly contrasting opinions in the same journal.

I hope that these considerations may contribute to render the conclusions of this important study more objective and well balanced.

Yours sincerely,

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