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LETTER TO THE EDITOR

Re: Seidler A, Jänichen S, Hegewald J et al. Systematic review and quantification of respiratory cancer risk for occupational exposure to hexavalent chromium

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Dear Editor,

The review of Seidler and colleagues aimed at assessing the dose–response relation for occupational exposure to hexavalent chromium (Cr (VI)) and lung cancer in order to establish a risk-based occupational exposure limit (OEL) for Germany that currently lacks a binding threshold value (Seidler et al. 2012). The authors concluded that the excess risk could be "acceptable" (<4 cases/10.000 workers assuming 40 years of exposure) at 0.1 μg Cr(VI)/m^3 or 4 μg Cr(VI)/m^3 × years as lifetime exposure and may become "intolerable" beyond 1 μg/m^3 or 40 μg/m^3 × years, respectively.

Although there are many industrial processes with exposure to Cr(VI), the assessment of Seidler and colleagues was only based on two historical cohorts in the US chromate industry (further referred to as Baltimore and Painesville cohort) (Gibb et al. 2000; Park et al. 2004; Crump et al. 2003; Luippold et al. 2003). Seidler et al. (2012) recognized this limitation but refrained from a discussion of risk estimates after major process changes and in other exposure circumstances like welding. Notably, no excess risk was observed at lower Cr(VI) concentrations in new chromate plants (Luippold et al. 2005). Welders comprise a considerably larger workforce exposed to Cr(VI) than chromate-producing workers. The excess risk presented by OSHA (U.S. Occupational Safety and Health Administration) for the IARC study in welders (Gerin et al. 1993) was lower than in chromate workers (OSHA 2006).

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These two chromate cohorts had been already subjected to previous risk assessments (e.g. (Goldbohm et al. 2006; Park and Stayner 2006)) and were preferred by OSHA in the determination of the permissible exposure limit (OSHA 2006). It is noteworthy that at least 80 % of the workers were smokers and that only four out of the 122 lung cancer cases of the Baltimore cohort were never smokers. Therefore, regression models had been applied to the individual exposure and covariate data to adjust relative risks for smoking (Gibb et al. 2000, Crump et al. 2003). OSHA's risk assessment also refers to re-analyses of the original data with attempts to adjust for smoking or to exclude short-time exposed workers (OSHA 2006). However, Seidler et al. (2012) performed a risk assessment using published standardized mortality ratios (SMRs) for these cohorts calculated for grouped exposure data. These groups span across a wide range of individual Cr(VI) levels in particular for the respective lowest class: 0–28 μg/m^3 × years in Park et al. (2004) and 0–60 μg/m^3 × years in Gibb et al. (2000). This introduces an uncertainty about the precise exposure level associated with the lung cancer risk estimated for grouped exposure data. SMRs have various additional shortcomings, as the observed cases are compared with expected cases from an external reference population without adjusting for smoking. This might at least partially explain the increased lung cancer risk of 72 cases in the lowest exposure class of the Baltimore cohort that comprised many short-term exposed workers. The average exposure duration in the whole cohort was 5 months only.

Seidler et al. (2012) performed a meta-analysis of the dose–response relation and depicted excess mortality risks in terms of additional cases per 1,000 workers for the male European population in Table 3 and 4. There is an apparent heterogeneity not only between the additional lung cancer cases per 1,000 workers in the individual studies but also

within the plants across time. Seidler et al. did not mention that fewer lung cancer cases than expected were observed after the introduction of major process changes (Luippold et al. 2005). The early process added calcium carbonate to the chromite ore before roasting. OSHA presented estimates of 1.8 (95 % 1.2–3.0) for the former cohort study of Hayes (Hayes et al. 1989) and of 9.1 (95 % CI 4–16) in the Gibb's study of the Baltimore facility per 1,000 workers with an average exposure to 1 μg/m^3 over 45 years using the US reference rates for both genders (OSHA 2006). The corresponding estimates of excess cases of the Painesville facility were 7.0 (95 % CI 4.1–11) based on the earlier study of Mancuso (Mancuso 1997a) and 2.1 (95 % CI 1.2–3.1) for the Luippold et al. (2003) study. OSHA reported the corresponding excess risk in welders of the IARC cohort with 0.9 additional cases (95 % CI 0–2.8).

Major uncertainties were recognized by Seidler and colleagues, such as the high fractions of smokers or short-term exposed workers in the Baltimore cohort, as well as general uncertainties in exposure assessment and model building. However, they did not consider these uncertainties in their analyses and presented the acceptable and tolerable excess risks as point estimates without confidence intervals or sensitivity analyses to explore the influence of these uncertainties on the risk assessment. Due to the prominent role of these cohorts in deriving occupational exposure limits for Cr(VI), it is important to detail these uncertainties.

The dose–response relation was established at historically high levels of Cr(VI) exposure and then extrapolated by Seidler et al. (2012) into the low-dose range by assuming linearity due to potential genotoxic effects. This procedure then results in an "acceptable risk" at exposure levels below 0.1 μg/m^3 or 4 μg/m^3 x years, respectively. However, no lung cancer cases were observed up to 60 μg/m^3 × years in the Painesville cohort (Crump et al. 2003). In contrast, 60 % of the Baltimore cases were found at the lowest level of cumulative exposure (up to 15 μg Cr(VI)/m^3 × years) due to a very short exposure time (Park et al. 2004). About 65 % of the Baltimore workers were exposed shorter than one year. This heterogeneity in risk estimates impairs to set a point of departure. Hence, no sound epidemiological data are available to determine the point of departure. Epidemiological data are also lacking for working at very low Cr(VI) concentrations for 40 years. A linear extrapolation into the low-dose range is thus not supported by data. OSHA recognized that the statistical power is not sufficient to detect small increases in risks in the low-dose range of both cohorts (OSHA 2006). OSHA further noticed that neither the Painesville nor the Baltimore cohort provides ideal information with which to identify a threshold or to detect nonlinearities in the relationship between Cr(VI) exposure and lung cancer risk, and that it is important to consider other sources of information about the exposure–response relationship at very low levels of Cr(VI) exposure. Hence, also alternative exposure metrics or threshold models may be considered (Proctor et al. 2004). The shape of the dose–response function at very low Cr(VI) concentrations can therefore not only be based on statistical modelling but rather on the biological understanding of disease development. This includes not only just one mode of action, but also a wider range of possible toxic effects in adjunct with defence mechanisms. So far, the specific molecular targets and precise mechanisms for metal toxicity are not yet fully understood (Chervona et al. 2012).

An uncertainty with great impact on risk estimates relates to the assessment of exposure to Cr(VI). Methods for determining airborne Cr(VI) have been changed, and OSHA as well as the U.S. National Institute for Occupational Safety and Health (NIOSH) identified a need to characterize Cr(VI) exposure with state-of-the-art methods. NIOSH conducted a field study in anticipation of OSHA's regulatory action on Cr(VI) (Blade et al. 2007). Whereas a concentration of 5 μg Cr(VI)/m^3 was assumed to calculate the exposure when welding stainless steel with tungsten inert gas welding (TIG) in the IARC cohort (Gerin et al. 1993), the shift concentrations of TIG welders measured in the NIOSH survey were actually lower than 1 μg Cr(VI)/m^3. Uncertainties in the measurements in the two chromate cohorts have been described by Proctor et al. (2004) and OSHA (2006). A proper sampling and sample processing are necessary to avoid underestimation of Cr(VI) exposure due to reduction to Cr(III) or to the extraction of water-soluble Cr(VI) only (Unceta et al. 2010). The redox conversions of chromium species can be influenced by iron or manganese oxide, for example, in welding fume. Challenging is in particular the precision of measurements in the low-dose range. Even with current methods, 0.1 μg/m^3 may be lower than the analytical limit of quantitation. Reliable analytical methods are necessary to monitor Cr(VI) at very low levels in the breathing zone of occupationally exposed workers.

The authors discussed only a potential confounding by asbestos due to chrysotile fibres found in the lung of a Baltimore case (Mancuso 1997b). The interstitial tissue of the investigated lungs showed large amounts of amorphous black pigments and fibrotic changes. The embedded particulate matter may originate from the processing of chromite ore. Furthermore, calcium carbonate was added to produce chromium in early years, for example, in the Painesville facility, whereas the lung cancer mortality after major process changes was not elevated any more (Luippold et al. 2005). Particulate matter can impair the defence mechanisms of the lungs. Former surveys collected total particulate matter but not selectively the respirable particles, which can reach the alveoli and are thus of specific concern for the development of lung cancer. Particles larger than the respirable size fraction may be removed from

the inhaled air stream by mucociliary clearance. The concentrations of metals are commonly lower in respirable than in inhalable particles as already shown for welding fume (Weiss et al. 2013).

A study in two German chromium-producing plants in which exposure was assessed with urinary chromium (Birk et al. 2006) was not included in this risk assessment. More than 12,000 individual concentrations of urinary chromium were available since 1958. Concentrations in the range of 12–40 μg/L in earlier years would correspond to 16–52 μg Cr(VI)/m^3 according to "exposure equivalents for carcinogenic materials" (EKA) (DFG 2012). This conversion describes the association between airborne concentrations of a carcinogen at the workplace and the concentrations of the carcinogen or its metabolites in biological material. Airborne concentrations deduced from the study by Birk et al. are considerably lower than the average concentration of 270 μg Cr(VI)/m^3 reported for the Painesville plant in early years (Proctor et al. 2004). Although this conversion may also be subjected to drawbacks, a linear extrapolation into the low-dose range yields 0.075 μg Cr/L at 0.1 μg Cr(VI)/m^3, which is even lower than the geometric mean of 0.17 μg/L in the German population (Krause et al. 1996). This may also demonstrate that an extrapolation into the low-dose range without data support should be done with great caution.

In summary, the authors did not consider uncertainties in exposure and risk assessment. They presented point estimates of acceptable and tolerable excess risks for lung cancer at 0.1 μg/m^3 and 1 μg/m^3, respectively, by extrapolation into the low-dose range. These risk estimates were based on two historical cohorts but without showing confidence limits or other means to explore the heterogeneity between these studies or the various uncertainties in risk assessment. The apparent lack of data about lung tumours in workers exposed to 0.1 μg/m^3 over 40 years does not justify a statistical modelling with grouped exposure data into very low doses that are challenging to measure even with current analytical methods. We share OSHA's conclusion that the statistical power is not sufficient to identify the shape of the dose–response relation or to detect the small increases in risk in the low-dose range of these cohorts. The observation of a lower excess risk in welders and of fewer lung cancer cases than expected after major process changes in the US chromate plants than in these historical cohorts indicates a need for research under recent exposure circumstances as well as in other, more prevalent exposure circumstances settings like welding.

References

Birk T, Mundt KA, Dell LD, Luippold RS, Miksche L, Steinmann-Steiner-Haldenstaett W, Mundt DJ (2006) Lung cancer mortality in the German chromate industry, 1958 to 1998. J Occup Environ Med 48:426–433

Blade LM, Yencken MS, Wallace ME, Catalano JD, Khan A, Topmiller JL, Shulman SA, Martinez A, Crouch KG, Bennett JS (2007) Hexavalent chromium exposures and exposure-control technologies in American enterprise: results of a NIOSH field research study. J Occup Environ Hyg 4:596–618

Chervona Y, Arita A, Costa M (2012) Carcinogenic metals and the epigenome: understanding the effect of nickel, arsenic, and chromium. Metallomics 4:619–627

Crump C, Crump K, Hack E, Luippold R, Mundt K, Liebig E, Panko J, Paustenbach D, Proctor D (2003) Dose-response and risk assessment of airborne hexavalent chromium and lung cancer mortality. Risk Anal 23:1147–1163

Gerin M, Fletcher AC, Gray C, Winkelmann R, Boffetta P, Simonato L (1993) Development and use of a welding process exposure matrix in a historical prospective study of lung cancer risk in European welders. Int J Epidemiol 22(Suppl 2): S22–S28

Gibb HJ, Lees PS, Pinsky PF, Rooney BC (2000) Lung cancer among workers in chromium chemical production. Am J Ind Med 38:115–126

Goldbohm RA, Tielemans EL, Heederik D, Rubingh CM, Dekkers S, Willems MI, Dinant KE (2006) Risk estimation for carcinogens based on epidemiological data: a structured approach, illustrated by an example on chromium. Regul Toxicol Pharmacol 44: 294–310

Hayes RB, Sheffet A, Spirtas R (1989) Cancer mortality among a cohort of chromium pigment workers. Am J Ind Med 16: 127–133

Krause C, Babisch W, Becker K, Bernigau W, Hoffmann K, Nöllke P, Schulz C, Schwabe R, Seiwert M, Thefeld W (1996) Umwelt-Survey 1990/92, Studienbeschreibung und Human-Biomonitoring: Deskription der Spurenelementgehalte in Blut und Urin der Bevölkerung der Bundesrepublik Deutschland. Umweltbundesamt, Germany. WaBoLu Hefte 1/1996

Luippold RS, Mundt KA, Austin RP, Liebig E, Panko J, Crump C, Crump K, Proctor D (2003) Lung cancer mortality among chromate production workers. Occup Environ Med 60:451–457

Luippold RS, Mundt KA, Dell LD, Birk T (2005) Low-level hexavalent chromium exposure and rate of mortality among US chromate production employees. J Occup Environ Med 47:381–385

Mancuso TF (1997a) Chromium as an industrial carcinogen: Part I. Am J Ind Med 31:129–139

Mancuso TF (1997b) Chromium as an industrial carcinogen: part II. Chromium in human tissues. Am J Ind Med 31:140–147

Occupational Safety and Health Administration (OSHA) (2006) Occupational exposure to hexavalent chromium; final rule. United States Department of Labour. Federal Register 71(39):10099-10385

Park RM, Stayner LT (2006) A search for thresholds and other nonlinearities in the relationship between hexavalent chromium and lung cancer. Risk Anal 26:79–88

Park RM, Bena JF, Stayner LT, Smith RJ, Gibb HJ, Lees PS (2004) Hexavalent chromium and lung cancer in the chromate industry: a quantitative risk assessment. Risk Anal 24:1099–1108

Proctor DM, Panko JP, Liebig EW, Paustenbach DJ (2004) Estimating historical occupational exposure to airborne hexavalent chromium in a chromate production plant: 1940–1972. J Occup Environ Hyg 1:752–767

Seidler A, Jahnichen S, Hegewald J, Fishta A, Krug O, Ruter L, Strik C, Hallier E, Straube S (2012) Systematic review and quantification of respiratory cancer risk for occupational exposure to hexavalent chromium. Int Arch Occup Environ Health 1–13. doi 10.1007/s00420-012-0822-0

Unceta N, Seby F, Malherbe J, Donard OF (2010) Chromium speciation in solid matrices and regulation: a review. Anal Bioanal Chem 397:1097–1111

Weiss T, Pesch B, Lotz A, Gutwinski E, Van Gelder R, Punkenburg E, Kendzia B, Gawrych K, Lehnert M, Heinze E, Hartwig A, Käfferlein HU, Hahn JU, Brüning T (2013) Levels and predictors of airborne and internal exposure to chromium and nickel among welders-Results of the WELDOX study. Int J Hyg Environ Health 216:175–183