Helsinki, 04 December 2013
RAC/27/2013/06 Rev.1
(Agreed at RAC-27)

APPLICATION FOR AUTHORISATION: ESTABLISHING A REFERENCE DOSE RESPONSE RELATIONSHIP FOR CARCINOGENICITY OF HEXAVALENT CHROMIUM

Background

At the 22nd meeting of the Committee for Risk Assessment (RAC) in September 2012, the ECHA Secretariat presented a proposal to set DNELs and dose response relationships for substances prior to receiving applications for authorisation (AfAs). This was approved by RAC as a trial exercise.

The DNELs and dose response relationships so derived will serve as a non-legally binding 'reference value'. They would provide applicants with a clear signal as to how RAC is likely to evaluate these important elements of the risk assessment of AfA.

This initiative is intended to improve the efficiency of the AfA process as a whole by discussing and when possible publishing reference values or dose response relationships in advance of applications, so providing greater consistency and better use of the legally defined periods of opinion-development in the RAC. The trial will be evaluated in terms of efficiency after the first applications have been discussed in the Committee.

Requested action:

Following the Committee's agreement on the document, it will be published on the ECHA website at:

http://echa.europa.eu/web/guest/applying-for-authorisation/additional-information

Annex: Reference dose response relationship for carcinogenicity of hexavalent chromium substances

Annex 1 Reference dose response relationship for carcinogenicity of hexavalent chromium substances

Table 1 Hexavalent chromium substances included in Annex XIV, the 4th recommendation for inclusion in Annex XIV and the candidate list

SUBSTANCE NAME	EC Number	Intrinsic properties specified in Annex XIV/recommendation
Ammonium dichromate	231-143-1	Carcinogenic cat 1B Mutagenic cat 1B Toxic for reproduction cat 1B
Potassium chromate	232-140-5	Carcinogenic cat 1B Mutagenic cat 1B
Acids generated from chromium trioxide and their oligomers. Names of the acids and their oligomers: Chromic acid, Dichromic acid, Oligomers of chromic acid and dichromic acid	231-801-5; 236-881-5	Carcinogenic cat 1B
Chromium trioxide	215-607-8	Carcinogenic cat 1A Mutagenic cat 1B
Potassium dichromate	231-906-6	Carcinogenic cat 1B Mutagenic cat 1B Toxic for reproduction cat 1B
Sodium chromate	231-889-5	Carcinogenic cat 1B Mutagenic cat 1B Toxic for reproduction cat 1B
Sodium dichromate	234-190-3	Carcinogenic cat 1B Mutagenic cat 1B Toxic for reproduction cat 1B
Lead sulfochromate yellow (C.I. Pigment Yellow 34)	215-693-7	Carcinogenic cat 1B Toxic for reproduction cat 1B
Lead chromate molybdate sulphate red (C.I. Pigment Red 104)	235-759-9	Carcinogenic cat 1B Toxic for reproduction cat 1B
Lead chromate	231-846-0	Carcinogenic cat 1B Toxic for reproduction cat 1B
Dichromium tris(chromate)	246-356-2	Carcinogenic cat 1B
Strontium chromate	232-142-6	Carcinogenic cat 1B
Pentazinc chromate octahydroxide	256-418-0	Carcinogenic cat 1A
Potassium hydroxyocataoxodizincatedichromate	234-329-8	Carcinogenic cat 1A

Relevance of endpoints

For applicants applying for authorisation under Article 60(2) (adequate control route), in order to conclude whether the adequate control is demonstrated, only endpoints (i.e. properties of concern) for which the substance is included in Annex XIV need to be addressed in the hazard assessment[1]. However, information on other endpoints might be necessary for comparing the risks with the alternatives.

For applicants aiming at authorisation based on Article 60(4) (socio-economic analysis route) Article 62(4)(d) also applies and the socio-economic analysis (SEA) route will as a consequence focus on the risks that are related to the intrinsic properties specified in Annex XIV. The SEA should in turn consider the impacts related to such risks. In practice the applicant is expected to provide this information in their CSR for which an update may be advisable. However, for an authorisation to be granted, the applicant should also demonstrate that there are no suitable alternatives. In this latter analysis it may be the case that other endpoints than those for which the substance was listed in 'Annex XIV' become relevant in order to demonstrate that no suitable alternative is available.

The hexavalent chromium compounds listed in table 1 were included on Annex XIV due to their carcinogenic (and other) properties. The reference dose response relationships proposed in the present document are only based on carcinogenicity arising from the Cr(VI) ion[2]. Applicants also need to assess other risks related to intrinsic properties specified in Annex XIV for the respective substances.

Carcinogenicity

A review was performed of the carcinogenic dose responses of 14 hexavalent chromium (Cr(VI)) compounds. The molecular entity that drives the carcinogenicity of these compounds is the Cr(VI) ion, which is released when the substances solubilise and dissociate.

Chromium(VI) causes lung tumours in humans and animals by the inhalation route and tumours of the gastrointestinal tract in animals by the oral route. These are both local, site-of-contact tumours – there is no evidence that Cr(VI) causes tumours elsewhere in the body.

A clear mode of action (MoA) for these tumours has not been established. The overall body of evidence indicates that Cr(VI) is genotoxic in vivo, resulting in the formation of DNA adducts and oxidative DNA damage. However, clear evidence of mutagenicity in vivo in the target tissues (lung and intestine) by relevant routes of exposure is lacking. This supports the contention that Cr(VI) is only weakly mutagenic in vivo and that its mutagenicity is most likely to be only one contributory factor in the carcinogenic process, together with tissue injury/irritation/inflammation and cell proliferation. However, there is insufficient evidence to exclude a genotoxic mode of action and therefore a threshold cannot be assumed.

Dose-response relationships were derived by linear extrapolation. Extrapolating outside the range of observation inevitably introduces uncertainties. As the mechanistic evidence is suggestive of non-linearity, it is acknowledged that the excess risks in the low exposure range might be an overestimate.

[1] Article 60(2) states "…an authorisation shall be granted if the risk to human health or the environment from the use of the substance arising from **intrinsic properties specified in Annex XIV** is adequately controlled."

[2] Endpoints relevant to the authorisation are also discussed in section 5 of the document: "How RAC and SEAC intend to evaluate the applications" (common approach of RAC and SEAC in opinion development on applications for authorisation, agreed RAC-20/SEAC14, 24/03/2012). Link: http://echa.europa.eu/web/guest/applying-for-authorisation/additional-information

Bioavailability

Information from epidemiological and mechanistic studies indicates that the carcinogenic potency of Cr(VI) compounds to the lung is greater for substances of high and moderate solubility in comparison to the insoluble chromates. However, quantifying any differences in lung carcinogenic potency for Cr(VI) compounds of different solubility is not possible with the currently available data. Therefore, the proposed lung cancer risk estimates should be applied to inhalation exposures to aerosols of highly soluble, slightly soluble and insoluble Cr(VI) compounds, accepting that they will perhaps overestimate risks in the case of exposure to insoluble chromates.

Inhalation exposures to Cr(VI) compounds are to a range of particle sizes. Air sampling from the plants of the cohort studies (Baltimore and Painesville) that have demonstrated a clear association between exposure to Cr(VI) and lung cancer show that workers in these cohorts were exposed to respirable-sized particles. It is therefore possible to differentiate between the risk assessments for respirable Cr(VI) particles and the non-respirable fraction of the inhalable dose, given that sufficiently detailed data on exposures is available. The "respirable fraction" ($E_{(R)}$) is defined as the portion of inhalable particles ($E_{(I)}$) that enter the deepest part of the lung, the non-ciliated alveoli. For this fraction, the particle diameter corresponding to 50% sampling efficiency (D50) is given as 4 µm (CEN, 1993).

Larger inhaled particles that are deposited in the upper respiratory tract are cleared by the mucociliary escalator and swallowed. It therefore seems reasonable to associate the "inhalable, non-respirable fraction" of Cr(VI) inhalation exposure with the potential for an increased risk of cancer of the small intestine.

For exposure by the oral route, tumours of the small intestine were observed in animals dosed with soluble Cr(VI) compounds. There is no information on the oral carcinogenic potential of chromates of lower solubility, but it is expected that these will be less bioavailable. As noted above, and in the absence of further information, the proposed small intestine cancer risk estimates should be applied to exposures to highly soluble, slightly soluble and insoluble Cr(VI) compounds, accepting that they will perhaps overestimate risks in the case of exposure to slightly soluble and insoluble chromates.

Carcinogenicity risk assessment

Inhalation exposure

Risk assessments for the inhalation route should, as a default, use the risk estimates for inhalation given below. In case an applicant provides data on exposure via inhalation to the fraction of inhalable, but not respirable, particles ($E_{(I)}$-$E_{(R)}$), the risk arising from exposure to this fraction will be assessed assuming exposure via the gastro-intestinal tract and thus using the risk estimates for that exposure route. In cases where the applicant only provides data for the exposure to the inhalable particulate fraction, as a default, it will be assumed that all particles where in the respirable size range.

Based on human epidemiology data for the respirable particulate fraction and linear extrapolation, using the analyses by Seidler et al. (2012) on the literature from the Baltimore cohort (Park et al., 2004) and the Painesville cohort (Crump et al., 2003; Luippold et al., 2003), and against a background, cumulative lifetime lung cancer risk of 48 per 1000 for the EU male population, and an 89-year life expectancy, the following risk estimates are used for workers and the general population.

Workers

Based on a 40 year working life (8h/day, 5 days/week), the following risk estimates are used:

An excess lifetime lung cancer mortality risk = 4 x 10^{-3} per µg Cr(VI)/m^3

Table 2 Excess lifetime (up to age 89) lung[$] cancer risk estimates for workers exposed at different 8h-TWA concentrations of Cr(VI) for 40 years

TWA Cr(VI) exposure concentration (µg/m^3)	Excess lung cancer risk in EU workers (x10^{-3})
25	100
12.5	50
10	40
5	20
2.5	10
1	4
0.5	2
0.25	1
0.1	0.4
0.01	0.04

[$] Background cumulative lifetime risk of dying from lung cancer between ages 0 and 74 in EU males is 48/1000 (Globocan, 2008)

This excess risk linear function was derived from a RR (relative risk) of about 2 at the cumulative exposure of 0.5 mg Cr(VI)/m^3/year, equivalent to a RR of 2 for exposure to 12.5 µg Cr(VI)/m^3 for 40 years. The associated excess lifetime risk (ELR) at this cumulative exposure for a RR of 2 was determined by multiplying the excess RR (RR – 1) by the background lung cancer risk in the EU population (Po) according to the equation: ELR(x) = Po(RR-1), where Po = 0.05. This resulted in a ELR of 50 x10^{-3} at 12.5 µg Cr(VI)/m^3 for 40 years (equivalent to a ELR of 4 x10^{-3} at 1 µg Cr(VI)/m^3 for 40 years).

General population

Based on an exposure for 70 years (24h/day, every day), the following risk estimates are used:

An excess lifetime lung cancer mortality risk = 2.9 x 10^{-2} per µg Cr(VI)/m^3

Table 3 Excess lifetime lung[$] cancer risk estimates for the general population exposed at different ambient concentrations of Cr(VI) for 70 years

Ambient Cr(VI) exposure concentration (µg/m^3)	Excess lung cancer risk in the general population (x10^{-3})
10	290
5	145
2.5	72
1	29
0.5	14
0.25	7
0.1	2.9
0.01	0.29
0.001	0.029
0.0001	0.0029

[$] Background cumulative lifetime risk of dying from lung cancer between ages 0 and 74 in EU males is 48/1000 (Globocan, 2008)

Dermal exposure

There are no data to indicate that dermal exposure to Cr(VI) compounds presents a cancer risk to humans.

Oral exposure & inhalation exposure from the non-respirable fraction

The risk estimates presented in this section cover oral exposure for the general population, as well as for cases where the fraction of inhalable non-respirable particles is characterised, thus allowing an estimate of the resulting exposure via the gastro-intestinal tract (both for the general population and for workers, see above).

The risk estimates are based on the analyses by USEPA (2012). The USEPA selected the NTP bioassay in rats and mice (NTP, 2008) for dose-response assessment because it was a well-conducted lifetime animal study of Cr(VI) carcinogenicity via ingestion, and no other adequate studies of Cr(VI) carcinogenicity by the oral route were available.

In the mouse study, exposure to sodium dichromate dihydrate in drinking water for 2 years resulted in significant increases in the incidences of neoplasms of the small intestine in males and females at doses ≥ 2.4 and ≥ 3.1 mg Cr(VI)/kg bw/day, respectively. The mouse was determined to be the most sensitive because tumor incidences were statistically significantly elevated at lower doses and a greater response was exhibited by the mice at the two highest doses.

In order to derive an oral cancer slope factor[3] (CSF), BMD (benchmark dose) modelling was carried out using USEPA's BMDS (USEPA, 2000). The multistage model was fitted to the data and the $BMDL_{10}$ (lower 95% confidence bound of the dose corresponding to a BMR of 10% extra risk) was estimated. The CSF was then calculated by dividing the BMR_{10} (0.1) by the $BMDL_{10}$ and then converting this slope value to human equivalents.

A $BMDL_{10}$ of 0.9 mg/kg bw/day was identified in males, leading to a CSF of 0.09 (mg/kg bw/day)$^{-1}$ in males. The animal CSF values were then converted in human CSF values by multiplying them for the mouse allometric scaling factor (~ 6), resulting in a human oral CSF

[3] The CSF represents the excess cancer risk at a dose of 1 mg/kg bw/day.

values for tumours of the small intestine of 0.5. These CSFs were further adjusted by applying age-derived assessment factors (assuming higher sensitivity during childhood) resulting in an average lifetime CSF of 0.8 per mg/kg bw/day for the general population.

Based on the analyses outlined above, against a human background cumulative lifetime intestinal cancer risk of 9 – 16 per 1000 for the German population and an 89-year life expectancy, the following risk estimates are used for workers and the general population:

Workers

Based on a 40 year working life (8h/day, 5 days/week) and an age-derived assessment factor of 1, the following risk estimates are used:

An excess lifetime intestinal cancer risk = 2.0 x 10^{-4} per µg Cr(VI)/kg bw/day

Exposure to inhalable, non-respirable particles is first converted into oral doses by applying the standard worker breathing rate of 1.25 m^3/hour, 8h per day, and the standard worker body weight default value of 70 kg. It is assumed that there is 100% retention of particles that are inhaled (the gastro-intestinal absorption is not 100% and is reflected in the oral risk estimates).

Table 4 Excess lifetime (up to age 89) small intestine[$] cancer risk estimates for workers exposed at different oral daily doses of Cr(VI) for 40 years

Oral daily dose of Cr(VI) (µg/kg bw/day)	Excess small intestine cancer risk in EU workers (x10^{-4})
10	20
5	10
2.5	5
1	2
0.5	0.5
0.1	0.2

[$] Background cumulative lifetime risk of dying from intestine cancer between ages 0 and 74 in Germany is 9/1000 in females and 16/1000 in males (IARC, 2008)

General population

Based on an exposure for 70 years (24h/day, every day) and an 89-year life expectancy and against a human background cumulative lifetime intestinal cancer risk of 9 – 16 per 1000 for the German population, the following risk estimates are used:

An excess lifetime intestinal cancer risk = 8 x 10^{-4} per µg Cr(VI)/kg bw/day

Exposures to inhalable, non-respirable particles are first converted into oral doses by applying the standard human resting breathing rate of 0.8 m^3/hr and the standard average human body weight default value of 60 kg.

Table 5 Excess lifetime (70 yr) small intestine[$] cancer risk estimates for the general population exposed to different oral daily doses of Cr(VI)

Constant average oral daily dose of Cr(VI) (µg/kg bw/day)	Excess small intestine cancer risk in the general population ($x10^{-4}$)
10	80
5	40
2.5	20
1	8
0.5	4
0.1	0.8

[$] Background cumulative lifetime risk of dying from intestine cancer between ages 0 and 74 in Germany is 9/1000 in females and 16/1000 in males (IARC, 2008)

References

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