Helsinki, 04 December 2013
RAC/27/2013/07 Rev. 1
(Agreed at RAC-27)

APPLICATION FOR AUTHORISATION: ESTABLISHING A REFERENCE DOSE RESPONSE RELATIONSHIP FOR CARCINOGENICITY OF INORGANIC ARSENIC COMPOUNDS

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 inorganic arsenic compounds

Annex 1 Reference dose response relationship for carcinogenicity of inorganic arsenic substances

Table 1 Inorganic arsenic substances included in Annex XIV and the 4th recommendation for inclusion in the authorisation list

SUBSTANCE NAME	EC Number	Intrinsic properties specified in Annex XIV/recommendation
Diarsenic pentoxide	215-116-9	Carcinogenic cat 1A
Diarsenic trioxide	215-481-4	Carcinogenic cat 1A
Arsenic acid	231-901-9	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.

Diarsenic pentoxide and diarsenic trioxide were included in Annex XIV due to their carcinogenic properties. Arsenic acid was included in the 4th recommendation for inclusion in Annex XIV.

Carcinogenicity

A review was performed of the carcinogenic dose responses of three inorganic arsenic compounds (diarsenic pentoxide, diarsenic trioxide and arsenic acid). Diarsenic trioxide is a trivalent arsenic substance, diarsenic pentoxide and arsenic acid are pentavalent arsenic substances. Arsenic compounds produce lung tumours in both animals and humans, following inhalation, oral or parenteral exposures. Exposure to high levels of arsenic compounds in drinking water has been associated with skin and urinary tract / bladder cancer in humans. Tumours at sites including the adrenal glands, bladder and liver have also been reported in some studies in animals.

[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."

The cancer mode of action of arsenic and it's inorganic compounds has not been established, but it appears not to be related to direct DNA reactive genotoxicity and therefore it is possible that the arsenic carcinogenicity has a threshold exposure level. However, the available data do not allow the identification of threshold exposure levels for key events in the modes of action proposed in the scientific literature.

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.

Bioavailability

Carcinogenic potency of the three arsenic compounds following oral exposures to their solid form is expected to be similar because solubility will not be a limiting factor for human exposure levels[2].

Samples taken from the atmospheres associated with the epidemiology studies do not provide detailed information on the particle sizes contained in the atmospheres. With the systemic nature of arsenic-associated lung carcinogenicity, it is unclear whether particle size is a critical element in inhalation risks as larger particles that are deposited in the upper respiratory tract are cleared by the mucociliary escalator and swallowed present a risk of lung cancer via systemic exposure.

Dermal absorption of inorganic arsenic compounds is reported to be low (<1% – 6). However this has not been thoroughly investigated and the impact of the extensive liver metabolism (first pass-effect) on dermal risk assessment is unclear.

Data on the speciation of arsenic under different exposure conditions are inadequate to permit any differentiation, therefore the risk assessments below are considered to apply to all forms of inorganic arsenic, in the absence of data to the contrary.

Carcinogenicity risk assessment

Inhalation exposure

All of the quantitative cancer risk assessments of inorganic arsenic compounds in the available literature used the same data sets based on death certificates of exposed workers from the Tacoma (USA), Anaconda (USA) and Rönnskar (Sweden) smelting plants.

The risk of lung cancer might be reduced if the particle size of the material in air is such that a proportion cannot enter the lower respiratory tract. However, given the increased lung cancer risk from oral exposures to arsenic (see below), it seems reasonable to associate the risk estimates with all inhalable particles. The epidemiology studies contain insufficient information to discriminate between particle size and likely deposition in the respiratory tract.

Based on the DECOS (2012) risk estimates derived from an epidemiology study in the Anaconda copper smelter plant (as reported by Lubin et al., 2000), the following risk estimates were derived:

[2] The solubility of diarsenic trioxide and diarsenic pentoxide are 1.2-3.7 and 65.8 g/100 ml at 20°C, respectively. Arsenic acid is highly soluble in water.

Workers

Based on a 40 year working life (8 h/day, 5 days/week):

An excess lifetime lung cancer mortality risk = 1.4 x 10^{-4} per µg As/m^3

(derived for the inhalable particulate fraction)

Table 2 Excess lifetime (up to age 89) lung cancer risk estimates for workers exposed at different 8h-TWA concentrations of inorganic As (inhalable particulate fraction) for 40 years

Inorganic Arsenic exposure concentration –inhalable fraction (µg/m^3)	Excess lung cancer risk in EU workers (x10^{-3})
10	1.4
5	0.71
2.5	0.36
1	0.14
0.5	0.07
0.25	0.036
0.1	0.014
0.01	0.0014

General population

Based on an exposure for 70 years (24 h/day every day) and an 89-year life expectancy and extrapolating from the occupational excess risks given in the analyses by DECOS (2012) above the following risk estimates were derived:

An excess lifetime lung cancer mortality risk = 1.0 x 10^{-3} per µg As/m^3

(derived for the inhalable particulate fraction)

Table 3 Excess lifetime lung cancer risk estimates for the general population exposed at different ambient concentrations of As (respirable particulate fraction) for 70 years

Ambient As exposure concentration – inhalable fraction ($\mu g/m^3$)	Excess lung cancer risk in the general population ($x10^{-3}$)
10	11
5	5.5
2.5	2.7
1	1.1
0.5	0.55
0.25	0.27
0.1	0.11
0.01	0.01
0.001	0.001
0.0001	0.0001

Dermal exposure

There is no evidence that dermal exposure to inorganic arsenic compounds has caused skin or other tumours in humans. The epidemiology studies of the smelter plants included investigations of general health and tumours at a wide range of sites. Hence, it would be anticipated that, had there been any significant increases in skin tumours, these would have been noticed and recorded. No adequate studies investigating the carcinogenicity of inorganic arsenic compounds in experimental animals exposed via the dermal route are available.

For a dermal assessment of systemic cancer risk it is considered appropriate to extrapolate from the oral risk estimates below.

The following dose-relationship for the dermal route was derived:

Starting point for the assessment: $BMDL_{0.5}$ = 3 µg As/kg/day (0.5% excess risk of cancer)

Excess lifetime risk of lung tumours = 1.7 x 10^5 per µg As/kg bw/day

(as a dermal exposure)

For further details on the assessment see 'Oral exposure (general population)' below.

Table 4 Cancer risk estimates for persons with dermal exposure of inorganic arsenic compounds, for an average follow-up period of 11.5 years

Daily dermal exposure of As (µg/kg bw/day)	Excess lung cancer risk ($x10^{-5}$) (assuming 100% oral absorption and 1% dermal absorption)
10	17
5	8
2.5	4
1	1.7
0.5	0.8
0.25	0.4
0.1	0.17
0.01	0.017

Oral exposure (general population)

Based on human epidemiology data WHO/FAO (2011) derived a $BMLD_{0.5}$, by applying a number of models to lung and bladder cancer mortality data from the Taiwanese drinking water cohorts, using data from the most recent publications of Chen et al (2010a, 2010b). The four models with a good fit to the data were gamma, log-logistic, multistage and quantal linear. The $BMLD_{0.5}$ does not describe the shape of the dose response curve, but because a quantal linear model has a good fit to the data, a linear dose response relationship can be assumed.

The WHO/FAO risk estimates for the oral route are recommended over the other published cancer risk estimates for several reasons. The assessment was well described and used a variety models to find the best fit to the data from a number of studies, in order to find the most conservative cancer risk estimates using the defined approach. This assessment used the most up-to-date data from the Taiwanese drinking water cohort. Although this does not produce the greatest excess risk per unit exposure, it is considered to be the most robust assessment for oral arsenic exposure available at the present time.

The following relationship for the oral route, which assumes linearity, was derived:

Starting point for the assessment: $BMDL_{0.5}$ = 3 µg As/kg/day (0.5% excess risk of cancer)

Excess lifetime risk of lung tumours = 1.7 x 10^{-3} per µg As/kg bw/day (as a systemic exposure)

Because there are inadequate data to support a threshold value for cancers associated with oral exposure, the dose response relationship can be regarded as linear and therefore, the oral exposure level associated with any chosen risk level can be calculated by simple arithmetic, as shown in Table 5.

Table 5 Cancer risk estimates for the general population exposed to different oral daily doses of inorganic arsenic compounds, for an average follow-up period of 11.5 years

Constant average oral daily dose of As (µg/kg bw/day)	Excess lung cancer risk in the general population ($x10^{-3}$)
10	17
5	8
2.5	4
1	**1.7**
0.5	0.8
0.25	0.4
0.1	0.17
0.01	0.017

References

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