Committee for Risk Assessment (RAC)
Committee for Socio-economic Analysis (SEAC)

Opinion on an Application for Authorisation for

Diarsenic trioxide

Formulation of diarsenic trioxide into a mixture

ECHA/RAC/SEAC: AFA-O-0000004619-65-11/D

Consolidated version

Date: 10 October 2014
Consolidated version of the

Opinion of the Committee for Risk Assessment
and
Opinion of the Committee for Socio-economic Analysis

on an Application for Authorisation

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular Chapter 2 of Title VII thereof, the Committee for Risk Assessment (RAC) and the Committee for Socio-economic Analysis (SEAC) have adopted their opinions in accordance with Article 64(4)(a) and (b) respectively of the REACH Regulation with regard to an application for authorisation for:

Chemical name(s): Diarsenic trioxide
EC No.: 215-481-4
CAS No.: 1327-53-3

for the following use:

Formulation of diarsenic trioxide into a mixture

Intrinsic property referred to in Annex XIV:

Carcinogenic (Article 57[a] of the REACH Regulation)

Applicant

Linxens France

Reference number

11-0000000334-83-0000

Rapporteur, appointed by the RAC: Sonja Kapelari
Co-rapporteur, appointed by the RAC: Marianne van der Hagen

Rapporteur, appointed by the SEAC: Stavros Georgiou
Co-rapporteur, appointed by the SEAC: Janez Furlan

This document compiles the opinions adopted by RAC and SEAC.
PROCESS FOR ADOPTION OF THE OPINIONS

On 21 November 2013 Linxens France submitted an application for authorisation including information as stipulated in Articles 62(4) and 62(5) of the REACH Regulation. On 17 January 2014 ECHA received the required fee in accordance with Fee Regulation (EC) No 340/2008. The broad information on uses of the application was made publicly available at http://echa.europa.eu/web/guest/addressing-chemicals-of-concern/authorisation/applications-for-authorisation on 12 February 2014. Interested parties were invited to submit comments and contributions by 9 April 2014.

The draft opinions of RAC and SEAC take into account the comments of interested parties provided in accordance with Article 64(2) of the REACH Regulation as well as the responses of the applicant.

The draft opinions of RAC and SEAC take into account the responses of the applicant to the requests that the SEAC made according to Article 64(3) on additional information on possible alternative substances or technologies.

The draft opinions of RAC and SEAC were sent to the applicant on 25 September 2014.

On 10 October 2014 the applicant informed that it did not wish to comment on the opinions and the draft opinions of RAC and SEAC were therefore considered as the final on 10 October 2014.

ADOPTION OF THE OPINION OF RAC

The draft opinion of RAC

The draft opinion of RAC, which assesses the risk to human health and/or the environment arising from the use of the substance – including the appropriateness and effectiveness of the risk management measures as described in the application and, if relevant, an assessment of the risks arising from possible alternatives – was reached in accordance with Article 64(4)(a) of the REACH Regulation on 12 September 2014.

The draft opinion of RAC was agreed by consensus.

The opinion of RAC

Based on the aforementioned draft opinion and in the absence of comments from the applicant, the opinion of RAC was adopted as final on 10 October 2014.
ADOPITION OF THE OPINION OF SEAC

The draft opinion of SEAC

The draft opinion of SEAC, which assesses the socio-economic factors and the availability, suitability and technical and economic feasibility of alternatives associated with the use of the substance as described in the application was reached in accordance with Article 64(4)(b) of the REACH Regulation on 13 June 2014.

The draft opinion of SEAC was agreed by consensus.

The opinion of SEAC

Based on the aforementioned draft opinion and in the absence of comments from the applicant, the opinion of SEAC was adopted as final on 10 October 2014.

THE OPINION OF RAC

RAC confirmed that it is not possible to determine a DNEL for the carcinogenic (category 1A) properties of the substance in accordance with Annex I of the REACH Regulation.

RAC confirmed that the exposure assessment in the application is demonstrated to be appropriate and effective in limiting the risk, provided that the risk management measures and operational conditions are as described in the application.

The duration for the review period has been suggested below.

THE OPINION OF SEAC

SEAC has formulated its opinion on the socio-economic factors and the availability, suitability and technical and economic feasibility of alternatives associated with the use of the substance as documented in the application and on information submitted by interested third parties as well as other available information.

The application included the necessary information specified in Article 62 of the REACH Regulation that is relevant to the Committee’s remit.

SEAC took note of RAC’s confirmation that it is not possible to determine a DNEL for the carcinogenic (category 1A) properties of the substance in accordance with Annex I of the REACH Regulation.

SEAC confirmed that there appear not to be suitable alternatives in terms of their technical and economic feasibility for the applicant.
SEAC considered that the applicant's assessment of (a) the potential socio-economic benefits of the use, (b) the potential adverse effects to human health or the environment of use and (c) the assessment used to compare the two is based on acceptable socio-economic analysis. Therefore, SEAC does not raise any reservations that would change the validity of the applicant's conclusion that overall benefits of the use outweigh the risk to human health or the environment, whilst taking account of any uncertainties in the assessment.

The duration for the review period has been suggested below.
**Use**

The authorisation is considered for the following use:

**Formulation of diarsenic trioxide into a mixture**

**SUGGESTED CONDITIONS AND MONITORING ARRANGEMENTS**

**Conditions**

The following conditions are recommended in case the authorisation is granted:

- No additional conditions to those described in the application are proposed.

**Monitoring arrangements**

The following monitoring arrangements are recommended in case the authorisation is granted:

- No additional monitoring arrangements to those described in the application are proposed.

**REVIEW**

Taking into account the information provided in the analysis of alternatives prepared by the applicant and the comments received on the broad information on use the duration of the review period for the use is recommended to be seven (7) years.
The justifications for the opinion are as follows:

1. **The substance was included in Annex XIV due to the following property/properties:**
   - ☒ Carcinogenic (Article 57(a))
   - ☐ Mutagenic (Article 57(b))
   - ☐ Toxic to reproduction (Article 57(c))
   - ☐ Persistent, bioaccumulative and toxic (Article 57(d))
   - ☐ Very persistent and very bioaccumulative (Article 57(e))
   - ☐ Other properties in accordance with Article 57(f) [please specify]:

2. **Is the substance a threshold substance?**
   - ☐ YES
   - ☒ NO

**Justification:**

The carcinogenic mode of action of arsenic and its 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 (RAC/27/2013/07 Rev. 1; Helsinki, 4 December 2013). Therefore diarsenic trioxide is not considered to be a threshold substance.
3. Hazard assessment. Are the DNEL(s) appropriate?

Justification:

RAC has established a non-legally binding reference dose response relationship for carcinogenicity of inorganic arsenic compounds for all routes of exposure by linear extrapolation (RAC/27/2013/07 Rev. 1). 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. RAC has not derived DMEL values for inorganic arsenic compounds.

In the CSR, the applicant used a risk estimate that equals exposure of 7 µg/m³ for 40 years with a risk of 1 x 10⁻³. He pointed out that this level is a recommendation by the Dutch Health Council. In the SEA the remaining human health risks are evaluated based on the dose-response relationship adopted by RAC.

4. Exposure assessment. Is the exposure from the use adequately described?

☒ YES
☐ NO

Justification:

The applicant describes one exposure scenario:

„Formulation of diarsenic trioxide into a mixture“

This scenario covers all activities preparing a mixture containing diarsenic trioxide used for electrolytic, pure soft gold-plating on flexible etched circuitry.

The exposure of workers includes the following:

WCS1: Use in batch processes (PROC 4)
WCS2: Mixing of the substance in batch processes for formulation of preparations (PROC 5)
WCS3: Transfer of the substance from containers at dedicated facilities (PROC 8b)
WCS4: Transfer of the substance into small containers (including weighing) (PROC 9)

According to the information provided by the applicant in response to a request for additional information, none of the tasks presented in Use 1 takes longer than 5 minutes. The formulation process is carried out
twice a week, which leads to about 100 formulations per year using 0.5 kg of diarsenic trioxide each time. The maximum amount of diarsenic trioxide used is 50 kg per annum.

The conditions of use may be characterised as well controlled: according to the information provided (including a video recording of the process) the consecutive steps of the process take place under local exhaust ventilation, in a fume cabinet. Besides biomonitoring data do not contradict this statement.

**Exposure values:**

For the purpose of the exposure assessment RAC agreed to use the following exposure values:

*Inhalation exposure for workers (systemic, long-term):*

The results of the workplace monitoring indicate that the workers exposure is below \(0.3 \, \mu g/m^3\) (personal sampling and stationary measurements).

*Dermal exposure for workers (systemic, long-term):*

Due to the small quantity of diarsenic trioxide used (50 kg/year, 0.5 kg per event), none of the existing modelling tools is fully reliable to estimate the dermal exposure. However, there is a need for a starting point in order to do a risk assessment.

Therefore for the dermal exposure, the modelling tool “Riskofderm” was applied. The calculations indicate the dermal exposure level of \(0.043 \, mg/kg \, bw/day\) (according to the tool, at 90th percentile, 3 mg of the substance is deposited on the skin). However, the calculations are based on the use rate of the substance of 0.56 kg/min for 20 min (minimal use rate for which the tool is calibrated), while in reality the total use per event is 0.5 kg. If the use rate is taken into consideration – which covers more than 0.5 kg in one minute – the exposure has to be divided by 20 (\(0.043/20=2.15 \, \mu g/kg \, bw/day\)). Adjusting this exposure further for use of gloves (because their use is also not taken into consideration) brings the exposure to \(0.11 \, \mu g/kg \, bw/day\) (APF\(^1\) 20 – as presented in the exposure scenarios).

This value is used as starting point for the dermal assessment by RAC. This value is considered to represent an overestimation of the actual exposure due to the fact that the duration of the exposure is less than the 20 minutes used in the modelling. According to the applicant, the mixing of the substance, presented in the WCS 2 (PROC 5) is an automated process, not requiring involvement of workers.

**Indirect exposure of man via the environnement:**

The applicant declared that there is no direct release of diarsenic trioxide into the soil or the aquatic environment during the formulation stage. All waste water is collected from the site and treated. The final

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\(^1\) Assigned Protection Factor – an indicator of effectiveness of a RMM: APF 20= 95% effectiveness (100%/20 = 5% – level of residual risk)
concentration in the waste water before being taken from the site is given as ≤10 µg/l. Monitoring data sampled at the workplaces show concentrations in air of below 0.3 µg/m³.

5. If considered a threshold substance, has adequate control been demonstrated?

☐ YES
☐ NO

Justification:

Not relevant (non-threshold substance)

6. If adequate control is not demonstrated, is the remaining risk reduced to as low a level as is technically and practically possible?

Justification and concluding on the remaining risk:

For the purposes of this risk assessment indirect exposure to man via the environment can be considered to be negligible. In addition, as the Annex XIV substance is not present in end-products, an exposure assessment of consumers is also not necessary.

Lung cancer in workers due to inhalation and dermal exposure is considered to be the critical effect for the risk assessment. Based on the dose response relationship established by RAC, the excess lifetime lung cancer mortality risk for workers is \(1.4 \times 10^{-4}\) per µg As/m³ for the inhalable particulate fraction (based on a 40 year working life) and \(6.4 \times 10^{-6}\) per µg As/kg bw/day for the dermal route (based on a 40 years working life). The risk level for the general population according to the RAC dose-response relationship (\(1.7 \times 10^{-5}\)) was divided by 70 (years of exposure), 52 (weeks per year) and 7 (days per week) and multiplied by 40 (years of exposure), 48 (weeks per year) and 5 (days per week) resulting in a risk level of \(6.4 \times 10^{-6}\) for workers.

Based on the exposure data described above, the excess lung cancer risk via the inhalation route is therefore about \(0.3 \times 1.4 \times 10^{-4} = 4.2 \times 10^{-5}\) (40 years exposure) and \(0.11 \times 6.4 \times 10^{-6} = 7.0 \times 10^{-7}\) via the dermal route (40 years exposure).

For the purposes of the SEA, RAC calculated an illustrative estimate of the presumed lung cancer cases for four workers caused by exposure of 40 years of \(4 \times 4.2 \times 10^{-5} \times 100/240 = 7.0 \times 10^{-5}\) (inhalation route) and \(4 \times 7.0 \times 10^{-7} \times 100/240 = 1.2 \times 10^{-6}\) (dermal route). This takes into account that formulation only takes place 100 times per year and the number of working days per year is 240.
The RMMs described in the application are considered to be appropriate by RAC in reducing the exposures and the risk (local exhaust ventilation, job rotation, training, PPE, periodic check-ups of collective PPE and monitoring of the quality, cleaning and renewal of collective equipment. There is periodic workplace concentration measuring and biomonitoring (urine tests) to control the effectiveness of the RMMs.

### 7. Justification of the suitability and availability of alternatives

The applicant has considered 11 alternative substances. Further investigations on some of these alternatives are being done by the applicant. According to the applicant’s statement there are currently no suitable alternatives.

#### 7.1 Would the alternatives lead to overall reduction of risk?

- [ ] YES
- [ ] NO
- [x] NOT APPLICABLE

**Justification:**

It is not clear to RAC if the alternatives would result in a lower risk to workers. There is insufficient information presented on hazards and potential exposure.

However, as the applicant has presented arguments that there are no useable alternatives at the moment which guarantee the required quality for the plating process, the risk assessment on alternatives is not assessed further by RAC.

#### 7.1.1 Are the risks of alternatives adequately described and compared with the Annex XIV substance?

- [ ] YES
- [x] NO
- [ ] NOT APPLICABLE

**Justification:**

11 potential alternative substances are identified. All of them contain the same salt (potassium gold cyanide) but the additives are different.

_Hazard profile_
It is not possible to give detailed information about the hazard profile because the exact composition of alternatives is not known by the applicant. The additives range from Antimony, Bismuth to Lead and Thallium.

### 7.2 Are the alternatives technically and economically feasible for the applicant?

- [ ] YES
- x NO

**Justification:**

According to the applicant, diarsenic trioxide does not have any functionality in use 1 (the formulation stage), other than as a prerequisite stage for use 2 (Industrial use of diarsenic trioxide as a processing aid in electroplating). The assessment of the analysis of alternatives is thus only meaningful in the context of use 2 – see opinion justification for use 2 (AFA-O-0000004619-65-12/D).

### 7.2.1 Are the technical and economic feasibility of alternatives adequately described and compared with the Annex XIV substance?

- x YES
- [ ] NO

**Justification:**

According to the applicant, diarsenic trioxide does not have any functionality in use 1 (the formulation stage), other than as a prerequisite stage for use 2 (Industrial use of diarsenic trioxide as a processing aid in electroplating). The assessment of the analysis of alternatives is thus only meaningful in the context of use 2 – see opinion justification for use 2 (AFA-O-0000004619-65-12/D).

### 7.3 If alternatives are suitable, are they available to the applicant?

- [ ] YES
- [ ] NO
- x NO SUITABLE ALTERNATIVES EXIST
**Justification:**

According to the applicant, diarsenic trioxide does not have any functionality in Use 1 (the formulation stage), other than as a prerequisite stage for use 2 (Industrial use of diarsenic trioxide as a processing aid in electroplating). The assessment of the analysis of alternatives is thus only meaningful in the context of use 2 – see opinion justification for use 2 (AFA-O-0000004619-65-12/D).

<table>
<thead>
<tr>
<th>8. For non-threshold substances, have the benefits of continued use been adequately demonstrated to exceed the risks of continued use?</th>
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<tbody>
<tr>
<td>☑ YES</td>
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<tr>
<td>☐ NO</td>
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<tr>
<td>☐ NOT RELEVANT</td>
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**Justification:**

According to the applicant, diarsenic trioxide does not have any functionality in use 1 (the formulation stage), other than as a prerequisite stage for use 2 (Industrial use of diarsenic trioxide as a processing aid in electroplating). The benefits of continued use cannot therefore be considered in isolation of use 2. Because of this, the benefits are considered as one and the same as for use 2 and hence only summarised in this chapter. More details are reported in the opinion justification for use 2 (AFA-O-0000004619-65-12/D). Although RAC estimated the remaining risks for uses 1 and 2 separately (i.e. only the risk from use 1 is presented in this opinion justification), the cancer estimates for both uses are presented in the opinion justification for use 2 of SEAC. This is to allow a meaningful comparison of benefits of authorisation (costs of non-use) with risks, as the costs of non-use cannot be allocated between the uses.

The assessment of impacts associated with this authorisation application and which has been undertaken by the applicant is based on a quantitative monetary assessment of the societal costs and benefits associated with the “non-use” of diarsenic trioxide. As such the perspective of the analysis is such that it aims to provide net cost estimates as the necessary corollary that the benefits of continued use exceed the risks of continued use. The net cost estimates are assessed on an annualised basis for the “non-use” scenario. Although this is not ideal from the point of view of transparency given the asymmetrical time profiles associated with cancer burdens with long exposure and latency periods as compared to the investment and operative costs time profile associated with “non-use”, the approach is acceptable in the context of...
estimating the impacts across different authorisation review. The analysis of the economic costs of the “non-use” scenario follows established procedures for the calculation of financial costs of switching to an alternative substance. The analysis of human health benefits is based on established procedures for the calculation of economic welfare changes as a result of human health risk reductions. An acceptable general methodological approach thus underpins the assessment of impacts. Moreover, the analysis is proportionate, taking into account the likely magnitude of risks.

Given the very small level of risks associated with the applicants use of diarsenic trioxide, the benefits of the “non-use scenario are negligible, whilst the additional costs (associated mainly with the increase in materials used) associated with the use of any alternative substance are relatively substantial, such that the benefits of continued use of diarsenic trioxide exceed the risks of continued use. Any uncertainties are relatively minor and would in any case tend to magnify the magnitude by which the benefits exceed the risks. The total net cost of the “non-use” scenario (and hence the net benefits from granting the authorisation) are estimated at €4,654,137 per year. Although this does not take into account the re-estimation of cancer cases by RAC, SEAC concludes that the effect on the total net cost estimate of the “non-use scenario” is negligible in any case.

9. Do you propose additional conditions or monitoring arrangements

☐ YES
☒ NO

Justification for additional conditions and monitoring arrangements:

Considering that the implemented risk management measures and existing operational conditions appear to be appropriate in reducing the exposures and the risk, additional conditions or monitoring arrangements are not considered necessary.
10. Proposed review period:

- Normal (7 years)
- Long (12 years)
- Short (.... _years)
- Other:

Justification for the suggested review period:

According to the applicant, diarsenic trioxide does not have any functionality in use 1 (the formulation stage), other than as a prerequisite stage for use 2 (Industrial use of diarsenic trioxide as a processing aid in electroplating). The consideration of a proposed review period is thus only meaningful in the context of use 2 – see opinion justification for use 2 (AFA-O-0000004619-65-12/D).